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Genicular nerves anatomy

From accuracy of anatomical landmarks to the treatment of knee osteoarthritis pain by genicular nerve blockade and radiofrequency ablation

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DEDICACE

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List of abbreviations

AB	Osteo-articular branch of the descending genicular artery
AT	Adductor tubercle
CFN	Common fibular nerve
CSI	Central sensitization inventory
CT	Classical targets
DGA	Descending genicular artery
GNB	Genicular nerve blockade
GN-RFA	Genicular nerve radiofrequency ablation
GPES	Global perceived effect scale
GT	Gerdy's tubercle
LRN	Lateral retinacular nerve
ILGN	Inferior-lateral genicular nerve
IMGA	Inferior-medial genicular artery
IMGN	Inferior-medial genicular nerve
IPBSN	Infrapatellar branch of saphenous nerve
MB	Muscular branch of the descending genicular artery
NRS	Numeric rating pain scale
NVL	Nerve to the vastus lateralis
NVM	Nerve to the vastus medialis
PA	Popliteal artery
SN	Saphenous nerve
OA	Osteoarthritis
OKS	Oxford knee score
QAQ	Quantitative analgesic questionnaire

RF	Radiofrequency
RFA	Radiofrequency ablation
RFN	Recurrent fibular nerve
RT	Revised targets
SB	Saphenous branch of the descending genicular artery
SLGN	Superior-lateral genicular nerve
SLGA	Superior-lateral genicular artery
SMGN	Superior-medial genicular nerve
SMGA	Superior-medial genicular artery
TKA	Total knee arthroplasty
TT	Tibial tuberosity
WOMAC	Western Ontario and McMaster Universities osteoarthritis index score

Summary

The treatment of chronic knee pain from osteoarthritis (OA) remains a challenge for physicians. When conservative therapies fail to provide pain relief, total knee arthroplasty (TKA) is the gold standard treatment. However, a large proportion of patients continue to experience intractable pain after common conservative therapies or TKA. In recent years, radiofrequency denervation has emerged as a promising alternative in the treatment of chronic knee pain, as it has several advantages over other conservative therapies. However, knowledge of anatomy is critical in order to ensure a successful outcome. Despite the recent popularity of genicular nerve radiofrequency ablation (RFA), there are many discrepancies between authors on the innervation of the knee joint capsule, and some authors have suggested that the anatomical targets that are currently used are somewhat inaccurate or incomplete. The objectives of this PhD thesis were to investigate the anatomical distribution of the nerve supply to the knee joint capsule in order to determine the neural targets and anatomical landmarks for genicular nerve blockade (GNB) and RFA, to develop and validate accurate anatomical targets for fluoroscopic and ultrasound-guided GNB and RFA, and to compare the accuracy of the technique that is currently most popular, which uses classical anatomical targets to the above developed technique that uses revised targets, on cadavers first, then in patients suffering from chronic knee pain.

To this end, systematic anterograde dissections of fresh frozen lower limbs were performed, with fixation of consistent nerves with radiopaque material

and imaging of the knee. We found major differences in the anatomical foundations of GNB and RFA and identified five consistent neural targets for these procedures. These revised targets were experimentally validated for GNB and RFA, and they were compared with the classical targets on the cadaveric model. The revised targets were found to be much more accurate than the classical targets, and they also targeted more nerves (five versus three). To explore the feasibility and effectiveness of the revised procedure, and to compare it to the standard procedure, a double-blind randomized control trial was conducted on patients suffering from chronic knee pain. This demonstrated that the GNB with a mixture of 2mL of 1% lidocaine plus 20mg of triamcinolone per target site was more effective for pain relief and functional improvement with the revised procedure. However, this difference was only statistically and clinically significant one-hour post-injection. The difference between the two techniques is expected to be clearer with RFA, where the precision of anatomical targets is more crucial.

Keywords: genicular nerves, anatomical landmarks, knee osteoarthritis, genicular nerve blockade, radiofrequency ablation

General introduction

Context

Knee osteoarthritis (OA) is a leading cause of chronic knee pain that affects more than a third of the population that are over 65 years of age [1-4]. Many conservative therapies or minimally invasive treatments are available in the early stages of the disease [5-7]. However, if these conservative treatments fail, prosthetic knee replacement remains the gold standard treatment. Yet, not all the patients are appropriate candidates for this surgery because of comorbidities, surgical contra-indications, or refusal of the surgery. Moreover, in several regions of the world, knee replacement surgery is not accessible to most patients. Furthermore, total knee arthroplasty (TKA) is not a guarantee of knee pain remission, given that up to 44% of patients present with persistent pain and functional limitations after the surgery, 15% report severe persistent pain, and 7% report post-TKA pain that is worse than before the surgery[8, 9]. Therefore, regardless of the global region, the problem of chronic knee pain remains a topical challenge for physicians and researchers. This highlights the need to develop alternative therapies to control chronic knee pain.

In the past decade, genicular nerve blockade (GNB) and radiofrequency ablation (RFA) have emerged as novel alternative therapies to control knee OA pain [10]. Both techniques have been shown to consistently provide some pain relief in patients with chronic knee pain that is related to knee OA or following TKA [11]. These procedures are based on the principle that selective disruption of the sensory nerves that supply a painful structure alleviates pain

and restores function [10]. These therapies have a wide variety of indications that concern a large number of patients, including painful early-stage knee OA that has failed to respond to other conservative treatments, late-stage knee OA without the possibility of performing TKA (due to poor medical conditions, patients who wish to avoid surgery, and regions of the world with limited access to knee arthroplasty), and persistent pain after TKA. Several reasons explain the emergence of these procedures. First, the main articular branches that innervate the knee joint capsule, which are known as genicular nerves, are described to be adjacent to the periosteum with constant bony landmarks, and running alongside the genicular vessels [10]. Therefore, they could be targeted using indirect anatomical landmarks under fluoroscopic or ultrasound guidance [12]. Secondly, since their targets are purely sensitive branches at their distal courses, before entering the knee capsule, RFA of the genicular nerves is not likely to provoke motor dysfunction. In addition, it is a minimally invasive, outpatient, medication-free therapeutic procedure. A single treatment session provides relatively long pain relief, and the treatment can be repeatedly administered [11]. It is accessible and suitable for elderly patients, who are mainly affected by knee OA [10]. Complications and adverse effects have only rarely been reported in the literature [10, 13, 14] and, if present, are minor [15]. However, as these procedures are more invasive than some other conservative treatments, they should preferably be used for patients who have not responded to these first-line treatments [10].

The success of these treatments relies on the targeted nerves being included in the tissue volume that has been moistened by local anesthetic or thermocoagulated by radiofrequency (RF). Given the small volume that is injected and the limited size of the RF lesions, a successful outcome relies on

the proximity of the needle or cannula tip being close to the nerve. Optimizing the effectiveness of knee denervation relies on the precise localization of the consistent articular nerves that supply the knee joint [16]. Since the genicular nerves are very small, and as their direct visualization during image-guided procedures is difficult, GNB and RFA rely on the accuracy of the anatomical landmarks for needle or cannula placement. However, described and popular anatomical foundations are confusing. There is a lack of consensus about the anatomy of the sensory branches that supply the knee joint capsule [17-23], and some authors suggest that the current anatomical targets for GNB and RFA appear to be inaccurate, unclear, and incomplete [14, 24]. Recent systematic reviews have concluded that more research is needed to better identify neural targets [14, 24, 25]. Notwithstanding these findings, clinical studies on GNB/RFA and practical guides to these procedures [11] still currently use the original classical anatomical targets. This may explain their relative efficacy on chronic knee pain, with variability in clinical outcomes among studies. We can therefore hypothesize that an improved technique that targets consistent nerves with accurate anatomical landmarks would probably lead to better clinical outcomes.

This PhD thesis aims to address this knowledge gap by performing a detailed anatomical study of the innervation of the knee joint capsule, identifying the neural targets for GNB and RFA based on sound anatomical foundations, developing and validating a revised technique with precise anatomical targets to capture the genicular nerves under fluoroscopic and ultrasound guidance, and comparing its accuracy to that of the current technique, first in a cadaveric model and then in patients. To introduce our topic, we will briefly review knee

OA and its treatments, the sources of pain in knee OA, GNB and RFA for the treatment of chronic knee pain and their anatomical foundations.

Knee osteoarthritis

Osteoarthritis (OA) is a degenerative disease of the joints that results from an imbalance between the breakdown and repair of cartilage in joints [26]. It occurs as a result of several factors, including trauma, overuse, and genetic predisposition. There are two types of OA: primary, which develops from an unknown cause, and secondary, for which a specific cause can be determined (such as trauma, rheumatologic conditions, congenital deformities, endocrine or metabolic abnormalities) [7].

Prevalence of OA increases with age, especially in women. It has been estimated that OA causes disabling knee symptoms in 10% of people aged >55 years [7]. OA is the most common source of knee pain, and it is associated with stiffness, loss of movement and function, muscle atrophy, instability, depression, limitations in day-to-day activities, and diminished quality of life [27, 28]. However, pain is the leading cause of seeking medical care, and it has the greatest impact on patients' quality of life [14, 28].

Three treatment modalities can be combined to treat OA: non-pharmacological, pharmacological, and surgical [28]. No single modality has been shown to be completely effective [27]. As there is no curative treatment for OA, the main goal of these therapeutic modalities is to reduce pain and improve the patient's overall functional ability [7].

With regards to pharmacological treatments, paracetamol (acetaminophen) is the first choice, but patients have often used this with little effect before visiting their physician. Non-steroidal anti-inflammatory drugs (NSAIDs) may be more effective than acetaminophen in terms of pain control, but they are associated

with significant risks and should be used at the lowest effective dose for the shortest duration. NSAIDs should also be prescribed with caution in elderly patients. Gastrointestinal undesirable effects are fairly common, and patients with cardiovascular or renal impairments may better avoid using NSAIDs [7]. Weak opioids and narcotic analgesics, which are indicated if previous drugs have been ineffective or contraindicated, do not provide a real improvement in OA pain that has failed to respond to NSAIDs [28]. Strong opioids can relieve the persistent pain, but there is a high withdrawal rate among treated patients because of undesirable effects, and there are concerns about the risk of dependence on or addiction to opiates [28]. The effectiveness of glucosamine and chondroitin on pain and function is still conflicting. While some authors have reported optimistic results [29], a robust randomized controlled clinical trial on 1,583 patients with symptomatic knee OA did not find that glucosamine and chondroitin sulfate alone or in combination were effective for knee OA pain, compared to placebo [30]. Many injectable agents have been proposed for the treatment of knee pain, whose efficacy is supported by varying levels of evidence [27]. Long-acting corticosteroid injections and viscosupplementation have been widely used and studied, but there is still no consensus about their effectiveness [27]. A meta-analysis involving 28 trials showed that intra-articular steroid injections of the knee effectively provided pain relief but only up to three weeks post-injection, compared to placebo [31]. The American Academy of Orthopedic Surgeons (AAOS) recently changed its clinical practice guidelines to no longer recommend the use of viscosupplementation for symptomatic knee OA [7, 32]. Other injectable agents include platelet-rich plasma (PRP), stem cells, ozone [27], and dextrose (prolotherapy) [33].

There are several conservative non-pharmacological treatments. Weight loss is quite effective but not easy to achieve, and patients with severe pain require approaches that provide immediate relief in order to improve their quality of life[25]. Activity modification and physical therapy, which aim to strengthen the supporting muscle groups and improve flexibility, can prove beneficial [7]. However, patients with moderate and severe knee OA may experience minimal benefit from physical therapy, and there are concerns about patient compliance [25]. Measures like braces, cranes, and other forms of joint protection might have a slight effect and are generally cost-effective [27, 28]. Other minimally invasive alternatives to surgery include thermal ablation (RFA and cryotherapy), which is promising [27], and genicular artery embolization [27].

If conservative treatments fail, surgical intervention should be considered. Surgical options include arthroscopic debridement, high tibial osteotomy, unicondylar or bicompartmental knee arthroplasty, and total knee arthroplasty [34]. Surgical lavage and debridement in knee OA showed no benefit in the short or long term, compared with placebo [35]. TKA is the gold standard option once knee pain is no longer responsive to pharmacologic and non-pharmacologic treatments. However, TKA does not address all the components of pain (*e.g.*, central pain, impaired mechanics despite arthroplasty, secondary neuropathic pain). Therefore, it is ineffective for chronic knee pain in a significant proportion of patients.

This large variety of treatment options with controversial outcomes and ongoing research into therapeutic alternatives clearly show that chronic OA knee pain remains a challenge for physicians and researchers.

In sub-Saharan Africa, the burden of knee OA is increasing because of the population's progressive aging and the progression of obesity. The prevalence of OA is high in this region and is up to 33% of the population aged over 35 years in some communities [36, 37]. The main struggle is patients' limited access to effective treatments. Locally available and accessible treatment include oral analgesics, NSAIDs (which are dispensed without a medical prescription and patient consumption is not controlled), chondroitin and glucosamine, physical therapy, orthotics, and intra-articular infiltration of long-acting corticoids. Viscosupplementation is available but not affordable for the large majority of the population. Among surgical treatments, osteotomies to correct axial deformities of the knee are the most frequently performed procedures. In these places, this is considered the "arthroplasty for the poor." TKA, which is the gold standard treatment for the advanced stages of knee OA, is performed only in few urban cities of some sub-Saharan African countries, and it is extremely expensive (*e.g.*, 110 times the guaranteed minimum wage in Cameroon). Since there is no health coverage, TKA is completely unaffordable for the countless patients who are in great need, so they are usually condemned to consume NSAIDs throughout their lives, with all the known consequences. The advantages of alternatives therapies like GNB and RFA over locally available therapeutic possibilities could have a prominent place in these settings.

The source of pain in knee osteoarthritis

Pain is the most prominent and disabling symptom of OA. Optimal treatment of OA knee pain requires an understanding of the causes of pain. Pain has many components, including psychological aspects. However, most knee pain, including that observed in OA, is mechanically-based [38]. Nociception in the knee is complex as it is produced by tissue that contains nociceptors, which primarily includes the joint capsule, ligaments, synovium and outer edge of the menisci [38, 39]. There are no pain fibers in the cartilage, cortical bone, or subchondral bone of the normal joint. In people with knee pain, nociceptive stimuli are produced by stimulation of unmyelinated and small myelinated fibers in one or more of these tissues. Inflammation lowers the threshold for nociception. There is evidence that patients with OA have abnormal sensitivity to pain and noxious stimulation and that their threshold for pain induction is lower. Factors triggering articular nociceptors include activities, loading, and knee pain [38].

The knee joint is innervated by four types of nerves: large Type 1 and Type 2 fibers, smaller myelinated Type 3 fibers, and tiny and slowly conducting non-myelinated Type 4 fibers (C-fibers). Types 3 and 4 are the primary nociceptors, which have a high threshold. There are four categories of joint receptors: Type I (Ruffini), Type II (Pacini), Type III (Golgi), and Type IV (free nerve endings). The free nerve endings (FNE) transmit information about pain and inflammation (Type IVa) [18, 40]. They also function as mechanoreceptors and thermoreceptors, and they are important for proprioception [41]. As nociceptors, free nerve endings can be sensitized or activated both mechanically and chemically. The sources of knee pain have been investigated

using anatomical, immunohistochemical, exploratory, and MRI studies. Anatomical studies reveal that Type 3 and 4 fibers are consistently found in most joint structures, except for the inner avascular portion of the meniscus and the hyaline cartilage [42]. The branches, which are divided from the nerves innervating the knee capsule, are distributed to different tissues inside the knee [18]. Immunohistochemistry staining has shown that fibers containing substance P (the nociceptive neurotransmitter found in afferent nerve fibers) are present in the retinaculum, fat pad, periosteum, and subchondral bone that are affected by degenerative disease, as well as in the marrow underneath them, the synovial membrane, and the outer part of the menisci [43-45]. The highest FNE count was found in capsuloligamentous complexes [41]. The presence of nociceptive fibers in the soft tissues around the knee reinforces the important pain producing role played by these tissues [44]. Nociceptive stimulation of awake subjects whose knees were anesthetized during knee surgery have suggested that the most pain sensitive structures in the knee are the fibrous ligaments, joint capsule, and the fat pad deep to the patella [38, 46]. These studies also suggest that bone pain in OA may be caused by increased bone pressure. Cartilage is not tender. Studies comparing MRI findings in people with and without joint pain have suggested the role played by bone marrow lesions in joint pain. However, bone marrow lesions' association with pain remains an enigma [47-49]. Other MRI features that were found to be linked to pain were the presence and size of knee effusion, synovial thickening, and small amounts of peri-articular lesions, such as tendonitis or bursitis [50].

From the knee nociceptor to the spinal cord, two different functional types of peripheral neurons, which are contained in the nerves that supply the knee joint, produce nociception. The first are nociceptive-specific neurons, which

have relatively small receptor fields in the periphery that bridge the joint and the deep soft tissue and extend to the spinal cord. The second type is a wide- or dynamic-range neuron that fires in response to both innocuous and noxious pressure. This neuron's receptor fields include both the joint and the overlying skin, and these neurons cover a wide territory of skin and joint. When nociceptive sensory neurons are excited, they conduct neural input through afferent nerves. The production of the sensation of pain requires both temporal and spatial summation in a population of nerve fibers, and there is a correlation with its magnitude. These fibers release nociceptive neuropeptides in the dorsal horn of the spinal cord, predominantly calcitonin gene-related peptide (CGRP) and substance P [38].

The processing of nociceptive input in the spinal cord is complex and not completely understood. In the spinal cord, nociceptive stimuli are subject to two inhibitory effectors: interneurons and descending central neurons. The amount of signal reaching the central nervous system is therefore modulated. Impairment of this tonic inhibition of nociceptive input is thought to play a role in chronic pain syndromes, but its role in pain from OA is unknown.

RFA to periarticular afferent nerves of the knee creates focal lesions on the anatomical course of the nerves, interrupting the conduction of nociceptive input, which subsequently leads to the alleviation of knee pain that is of peripheral origin. When pulsed RF was applied to the afferent axon of the sciatic nerve in rats, it damaged the unmyelinated C-fibers more than myelinated A-delta and A-beta fibers. This suggests a predominant effect on neuropathic knee pain over other sensory inputs *(e.g.,* proprioception) [51]. The distribution of substance P nerve fibers in the soft tissue around the knee

suggests that the denervation may be the mechanism by which surgical procedures for anterior knee pain produce favorable results [44].

Genicular nerve blockade and radiofrequency ablation for the treatment of chronic knee pain

RFA is a technique used to treat numerous conditions, such as cancers and cardiac arrhythmia, but it has also gained popularity in alleviating chronic musculoskeletal pain [25]. RFA to treat knee OA pain was first introduced by Choi et al. in 2011 [10]. Following this first report, multiple publications have suggested that RFA provides some analgesic benefits for patients with knee OA [52-57] or persistent pain after TKA [4, 54, 55, 58]. However, researchers express both optimism and concern [14] because many questions remain regarding anatomical targets, selection criteria, and evidence of effectiveness [24]. A recent review concluded that the quality of evidence is low, and there are several concerns regarding procedural aspects in these publications [14]. There is also a lack of clarity regarding clinical protocols, anatomical targets, and the real benefit of genicular nerve RFA procedures [14].

RFA relieves knee pain through the thermal ablation of some of the articular nerves that supply the knee joint capsule [59, 60]. RFA's postulated mechanism of action for clinical benefit involves heat production, which results in thermocoagulation that generates a well-delineated tissue lesion and localized destruction of neuronal tissue that is included in the thermocoagulated tissue. The thermal energy is produced by an alternating high-frequency electrical current that is generated in an electrode tip, which creates an electromagnetic field at the tip of the electrode. This causes high-frequency ionic vibrations, resulting in frictional heat at the cellular level surrounding the electrode tip. The delineated area of tissue that is thermocoagulated depends on the temperature, duration of RFA, and electrode size [59, 60]. These lesions

demonstrate the characteristics of scar formation, including an acute inflammatory response, cell necrosis, and fibrosis, which occur during the three weeks following the procedure. The basal lamina of Schwann cells may be preserved, which could allow nerve regeneration [25]. Lesions of the neural tissues degrade their ability to conduct pain signals [59]. In addition, RFA produces a local electrical field, which may lead to neuromodulation by inhibition of the C-fibers [25, 61, 62].

RFA dates as far back as 1931, when it was used for ablation of the Gasserian ganglion to treat trigeminal neuralgia [60]. It has evolved into a therapy that is currently predominantly used for mechanical joint pain [24]. RFA has been used to treat pain arising from the spinal facet joints since the 1970s and to treat chronic knee pain since the 2010s. The intra-articular delivery of RF energy (non-ablative pulsed RF) for treatment of OA knee pain was first described [63], followed by periarticular thermal ablation of the genicular nerves [10].

The classical procedure targets the superior-medial, superior-lateral, and inferior-medial genicular nerves at their periosteal location, where the femoral and tibial shafts meet their condyles [10, 60, 64]. Needle placement is guided by fluoroscopy [10, 53, 55, 57, 60, 64-66] or ultrasound [54, 67-71], or both. Some authors have performed RFA without image guidance [52, 72].

Figure 1: RFA of the genicular nerves (*Picture adapted from Sinclair et al.[4], 2017).*

Genicular nerve RFA is a two-step procedure. Prior to RF treatment, a prognostic genicular nerve block with local anesthetic is administered to predict the analgesic response to the RFA. The response is considered positive if the patient reports a decrease in pain score of at least 50% for more than 24 hours [10, 11]. Patients with positive response to GNB are elective for RFA.

Under sterile conditions, the patient is placed in a supine position with a pillow under the popliteal fossa. The skin and soft tissues are anesthetized with

lidocaine. Under fluoroscopic or ultrasound guidance, a RF cannula is inserted, and percutaneously advanced toward the anatomical target of the corresponding nerve (figure 1). After verification of the correct cannula placement, sensory stimulation (50 Hz) is performed to identify the nerve position. In order to avoid ablating motor nerves, motor stimulation (2.0 V at 2 Hz) is performed to verify the absence of fasciculation in the corresponding area of the lower limb. Then, one RF lesion is made for each selected genicular nerve. The electrode tip heats up the targeted local tissue within a few millimeters, at a temperature generated through an electromagnetic field with a frequency of 250 kHz.

Several modes of RFA exist, with different lesioning temperatures and durations, and different volumes and shapes of the thermocoagulated tissue. There is only low-level certainty to support the superiority of any specific RFA procedure modality over the others [25]:

- Monopolar RFA [10, 60] (ablative) involves continuous application of energy for 90 seconds, resulting in temperature of 70°C–90°C. Monopolar RF refers to the current flow between a probe electrode and a large-area ground pad that is placed on the skin's surface [73]. Monopolar lesions are egg-shaped (figure 2), the largest volume of which has been experimentally found to be 360 mm^3 *ex vivo* [74].

- Bipolar RFA refers to the current flow between two probe electrodes without a grounding pad [73]. Bipolar lesions have a rounded brick shape when the tips of both probes are close and parallel.

- Cooled RF [64-66, 75] (ablative) is a novel technology that uses circulating water inside the probe to reduce the temperature to around + 60°C, so that lesioning can be performed for a longer duration (150–180 s). The shape of the lesion is quasi-spherical (figure 2) and affects a greater volume of tissue with less risk of thermal injury. Experiments have found the mean lesion volume with cooled RF to be 595mm^3 *ex vivo* [74]. By creating a greater volume of tissue lesion, cooled RFA increases the chances of effective denervation [25, 76]. To date, this is the most common mode of RFA used in studies of RFA to treat knee pain.

- In pulsed RF [63, 72, 77-79] (non-ablative), the generator produces a high voltage in short bursts with an intercalated rest period (45V lasting 20 ms every 500 ms), resulting in a maximum temperature of +42°C. Pulsed RF has been proven to improve neuropathic pain by down-regulating the expression of calcitonin gene-related peptide (CGRP) in the dorsal root ganglion [80]. As with monopolar RF and cooled RF, pulsed RF has been demonstrated to exhibit similar effects on neuronal conduction, the disruption of which is often reversible [25]. However, pulse RF is less neuro-destructive. Patients experience less pain during the procedure, whereas the duration of pain relief is shorter [25].

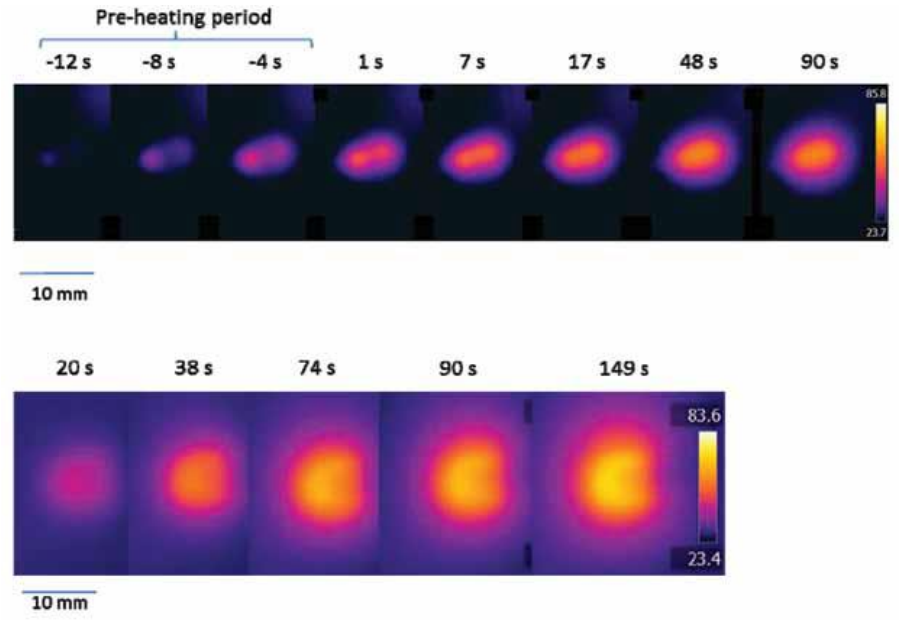


Figure 2. Thermographic sequences of the formation of a lesion, which is generated with RF using a monopolar 18-gauge, 10-mm active tip probe (top panel) and a cooled 17-gauge, 4-mm active tip probe (bottom panel). Adapted from Cedeno et al. [74]

There is promising evidence to support the use of RFA for OA knee pain [10, 64, 65]. However, a recent systematic review that included 429 patients from 17 studies concluded that, although RFA is promising, there is a lack of consistency with regards to study quality, which prevents stronger conclusions being drawn [25].

Nerve supply to the knee joint capsule, and the anatomical foundation of GNB and RFA

Before the first description of RFA of the genicular nerves to treat chronic knee OA pain [10], there were only few cadaveric studies found describing the anatomical distribution of sensory nerves to the knee joint [18, 19, 21, 22, 81-83]. It is surprising that, in most anatomical textbooks, the anatomical distribution of nerve branches innervating the knee joint lacks detail, is imprecise, or is not described at all. The anatomical foundation of these techniques was based on the literature review and observations from the dissection of two cadavers by Choi et al. [10]. The term genicular nerve was initially only used to define the main innervating articular branches of the knee joint, rather than all of them. Since then, this term has been widely used and generalized to apply to the afferent nerves supplying the knee joint capsule. Based on these descriptions, branches of the femoral, common fibular, and saphenous nerves innervate the anterior aspect of the knee, whereas the posterior aspect is innervated by branches of the obturator, sciatic, and tibial nerves. The tibial nerve projects articular branches in the popliteal fossa, including the SMGN, middle GN, and IMGN [10]. The common fibular nerve projects articular branches into the posterior-lateral aspects of the knee, specifically the SLGN, ILGN, and recurrent tibial genicular nerve [10]. The SLGN, SMGN, and IMGN that accompany the genicular vessels pass close to the metaphysis of the femur and the tibia, except for the ILGN. Therefore, the SLGN, SMGN, and IMGN were chosen for RFA because of their relatively precise anatomical landmarks and their proximity to bony structures [10]. The target points were identified as periosteal areas that connect the shaft of the femur to the bilateral condyles and the shaft of the tibia to the medial condyle

[10]. So, only three of the genicular nerves were targeted in the original procedure, and not all of them.

Since then, RFA of the genicular nerves has found some clinical success, as evidenced by a hundred publications on the topic over ten years. In parallel, anatomical study of innervation of the knee joint capsule has aroused great interest among researchers, leading to novel anatomical studies that are specifically dedicated to image-guided interventions [16, 17, 20, 23, 84]. However, there is no consensus about the origin, course, distribution, and nomenclature of sensory nerves that supply the knee joint capsule. There has been much discussion about the anatomical foundations and accurate targets for RFA to treat chronic knee pain. The most striking remark is that, although the results of some studies' dissections were not consistent with the original description, these studies concluded that the original target points for RFA of the genicular nerves were sound [16, 23]. Therefore, the original anatomical targets and classical procedure continue to be widely used.

Recent systematic reviews have found that justification for choosing target points for the placement of RFA cannulas was unclear [14, 24]. These reviews found that, although studies reported improvements in knee pain and function, the quality of evidence was low [14]. Moreover, there was considerable variation in the neuroanatomy described, and the neural targets were not always precise [24]. In many studies, the description of the targets was different from the illustration provided. This is annoying because the very small size of RF lesion means capturing the genicular nerves during RFA requires infra-centimetric precision. This is not currently the case, as we can see when analyzing protocols in different studies (figure 3).

Thus, the complexity of the knee joint's innervation has resulted in disparate procedural techniques among studies, which describe the following varying anatomical targets:

- The SLGN, SMGN, and IMGN, which pass periosteal areas that connect the shaft of the femur to bilateral epicondyles and that connect the shaft of the tibia to the medial epicondyle [10, 53, 55, 58, 60].

- The SLGN at the confluence of the lateral femoral shaft and condyle in the anteroposterior (A-P) plane and at the midpoint of the femur in the lateral plane, the SMGN at the confluence of the medial femoral shaft and the condyle at the midpoint of the femur in the lateral plane, and the IMGN at the confluence of the medial tibial shaft and the tibial flare in the A-P plane and the midpoint of the tibia in the lateral plane [64, 66, 75, 85].

- The infrapatellar branch of the saphenous nerve (IPBSN) [54, 72], either alone or in combination with the SMGN [52].

- The SLGN, SMGN, IMGN, and the suprapatellar genicular nerve [86].

- The SMGN, SLGN, middle GN, ILGN, IMGN, lateral retinacular nerve (LRN), and posterior articular plexus [67].

However, the three original targets that are described by Choi et al. are used in the vast majority of studies, as well as in the procedural guides provided by the firms. No protocol included targeting of the RFN, with all authors stating the reason as their close proximity to the CFN.

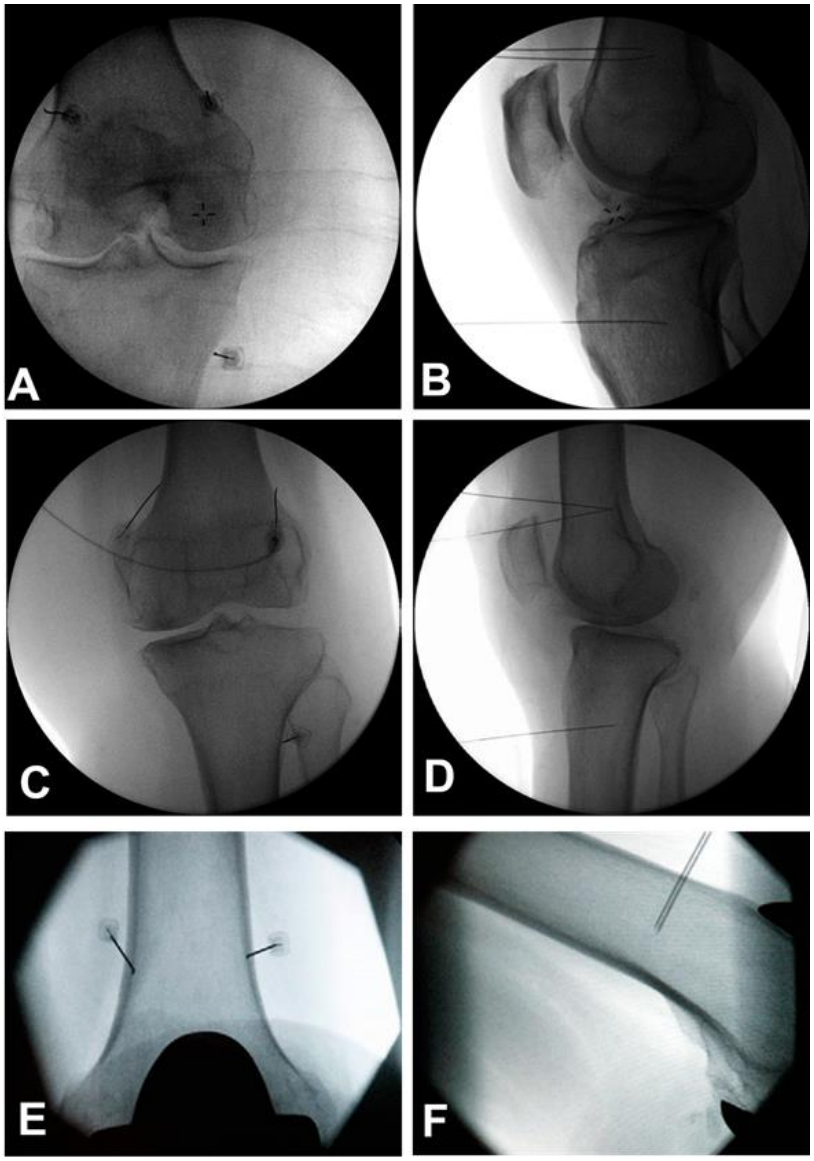


Figure 3. Illustration of the disparities in the targets points for the RFA of SMGN, SLGN, and IMGN, from three differents studies. A-B: *Mc cormick et al.[64];* C-D : *Sari S et al.*[87]; *E-F: Kidd VL et al.*[11]

It has also been suggested that genicular nerves accompany small arteries that can be used as an aid to identify the nerves under ultrasound guidance [14, 58], provided having the correct pattern of arteries with corresponding nerves. Analysis of the literature once again reveals discrepancies concerning the artery accompanying some of the targeted genicular nerves, despite this being the key to this method. Supplementary sonoanatomical landmarks (including tendons, their insertions, and ligaments) and bony landmarks can also be used to improve the precision of cannula positioning during ultrasound-guided procedures, given the complex innervation of the knee. Yet, the majority of publications do not utilize this combination of anatomical landmarks to improve precision.

Therefore, there is a need for precise and validated anatomical landmarks for GNB and RFA, based on updated anatomical knowledge of knee joint innervation.

Aims of this thesis

Given the need for precise and validated anatomical targets for GNB and RFA, in order to improve these promising techniques to treat chronic knee pain, this constitutes the main topic of this thesis. The main goal is to provide a sound anatomical basis for these procedures. It thus provides insight into the nerve supply to the knee joint capsule and the development and validation of accurate anatomical targets for GNB and RFA, as well as providing an anatomical comparison with currently used targets and a clinical comparison of their effectiveness on OA knee pain.

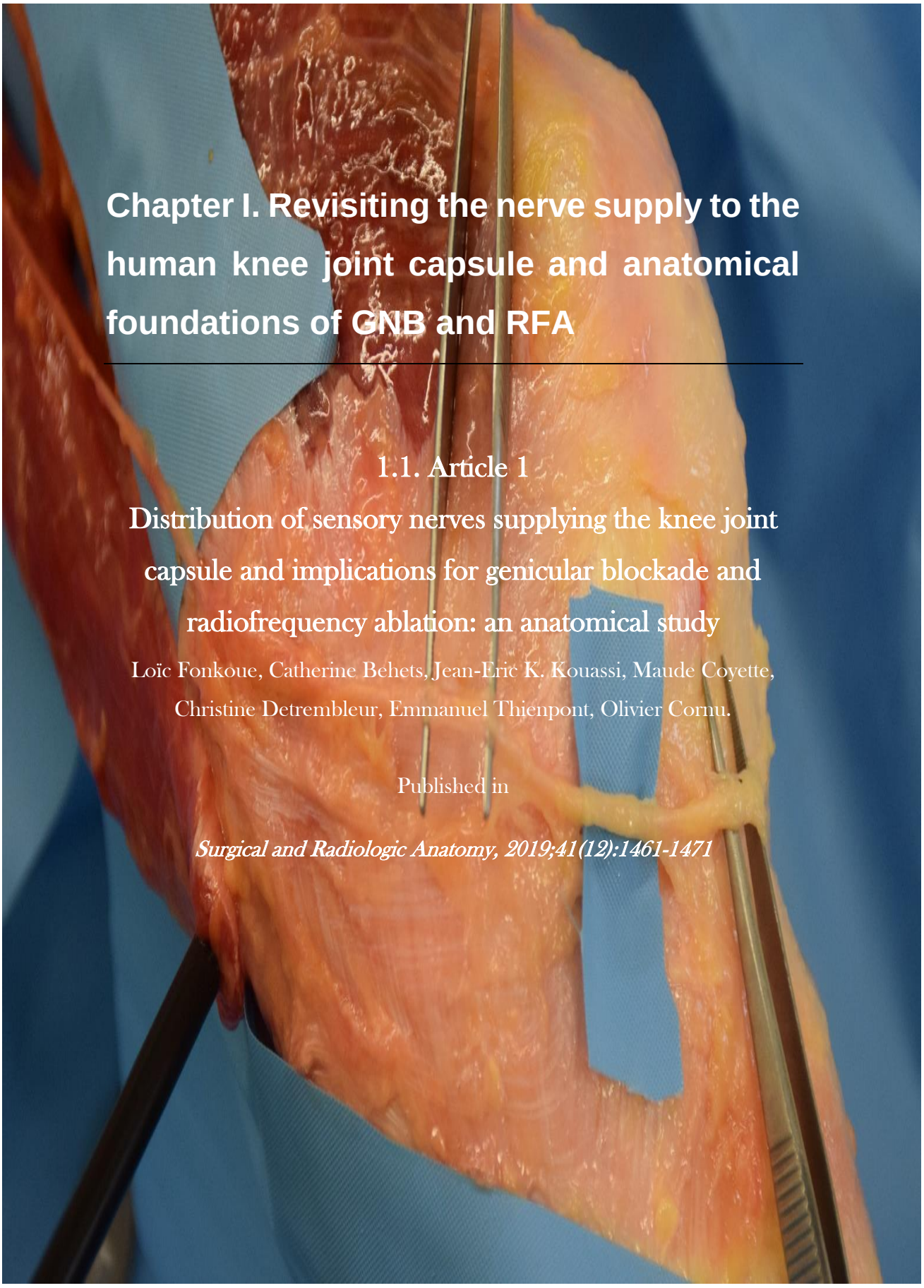
All the studies in this thesis focus on the same final objective. The thesis is divided into four parts that illustrate the research process, from the anatomy laboratory to the pain clinic.

Chapter I investigates the anatomical distribution of the nerve supply to the knee joint capsule and determines the neural targets and anatomical landmarks for GNB and RFA. Based on systematic anatomical dissections of cadaveric lower limbs, imaging of the dissected knees, and a literature review, **Article 1** describes the anatomical distribution of nerves supplying the knee joint capsule, identifies the consistent articular nerves to be targeted, and determines their anatomical targets for fluoroscopic-guided GNB and RFA. **Article 2** examines the anatomical distribution of the descending genicular artery, with regards to its application to target genicular nerves during interventional procedures for medial knee pain. This article also clarifies the origin and course of the vessels accompanying genicular nerves at the medial aspect of the knee, which has important implications for GNB and RFA.

Chapter II focuses on validating the accuracy and safety of the revised anatomical targets for GNB and RFA. **Article 1** investigates the accuracy and safety of the identified anatomical landmarks for fluoroscopic-guided GNB. An experimental validation study with clinical conditions was performed on cadavers to assess the effective capture rate of the genicular nerves. **Article 2** proposes and validates revised anatomical targets and a new technique for ultrasound-guided GNB and RFA. An experimental study was carried out to identify anatomical landmarks for ultrasound-guided procedures and assess the capture rate of the genicular nerves with the new technique. **Article 3** outlines the discrepancies among authors about the anatomical landmarks used in these procedures. Although an editorial by a famous author of the most recent review of the innervation of the knee joint agreed with the need to revisit the anatomical targets, as we had just demonstrated, the authors of one the most recent anatomical studies on the innervation of the knee joint capsule disagreed with this need, despite evidence that is based on their own study. In response, our paper highlights anatomical evidence that justifies the need to revisit the original targets for the SMGN and SLGN, based on anatomical updates on the innervation of knee joint.

Chapter III compares the accuracy of the currently most used technique, which uses classical anatomical targets, with the new technique that uses revised targets. An experimental anatomical study on cadavers, under clinical conditions, was performed to compare the effective capture rate of genicular nerves using the classical technique vs the revised technique. This chapter also clarifies some of the anatomical discrepancies raised by some authors.

Chapter IV assesses the clinical effectiveness of the revised technique for fluoroscopic-guided GNB in patients with painful knee OA, in comparison with the classical technique. A double-blind randomized control trial was conducted for this purpose.



Chapter I. Revisiting the nerve supply to the human knee joint capsule and anatomical foundations of GNB and RFA

1.1. Article 1

Distribution of sensory nerves supplying the knee joint capsule and implications for genicular blockade and radiofrequency ablation: an anatomical study

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1.1.1 Abstract

Background: Despite their emerging therapeutic relevance, there are many discrepancies in anatomical description and terminology of the articular nerves supplying the human knee capsule. This cadaveric study aimed to determine their origin, trajectory, relationship and landmarks for therapeutic purpose.

Methods: We dissected 21 lower limbs from 21 cadavers, to investigate the anatomical distribution of all the articular nerves supplying the knee joint capsule. We identified constant genicular nerves according to their anatomical landmarks at their entering point to knee capsule and inserted Kirshner wires through the nerves in underlying bone at those target points. Measurements were taken, and both antero-posterior and lateral radiographs were obtained.

Results: The nerve to vastus medialis, saphenous nerve, anterior branch of obturator nerve and a branch from sciatic nerve provide substantial innervation to the medial knee capsule and retinaculum. The sciatic nerve and the nerve to the vastus lateralis supply sensory innervation to the supero-lateral aspect of the knee joint while the fibular nerve supplies its infero-lateral quadrant. Tibial nerve and posterior branch of obturator nerve supply posterior aspect of knee capsule. According to our findings, five constant genicular nerves with accurate landmarks could be targeted for therapeutic purpose.

Conclusion: The pattern of distribution of sensitive nerves supplying the knee joint capsule allows accurate and safe targeting of five constant genicular nerves for therapeutic purpose. This study provides robust anatomical foundations for genicular nerve blockade and radiofrequency ablation.

Key words: genicular nerve, knee innervation, anatomical landmarks, genicular blockade, radiofrequency ablation.

1.1.2 Introduction

The sensory innervation of the human knee joint has risen an interest in the last decade due to the emergence of new tools to control severe chronic knee pain [10, 12, 16, 17, 20, 23, 64, 88, 89]. These alternative procedures such as radiofrequency denervation, genicular blockade and cryoneurolysis are all based on the theory that cutting the nerve supply to a painful structure may alleviate pain and restore function [4, 10, 90]. Many studies have shown the relatively significant efficacy of this technique in several chronic knee pain conditions such as osteoarthritis and persistent pain after a total knee arthroplasty [4, 10, 64, 90]. However, a more precise anatomical knowledge of sensory nerve distribution and constant branches to the knee capsule, allowing more accurate treatment targets, would certainly lead to better analgesic effects [17, 20, 23].

Unfortunately, many discrepancies exist in the anatomic description and terminology of the nerves supplying the knee capsule. The term « genicular nerves » has been introduced by *Choi et al* [10] to refer to the sensory nerves of the knee and, since then, this appellation is widely used. Despite the evidence that the technique described by Choi relieves chronic knee osteoarthritis pain to a certain amount, justifying the recent popularity of the genicular radiofrequency ablation, its anatomical foundations are somewhat inappropriate and confusing [23, 24]. Therefore, this anatomical basis currently

used among interventional practitioners has to be evaluated and eventually revised.

Innervation of the human knee is complex and variable [18, 19, 22, 23, 81]. Although the nerves to the knee are known to originate from the lumbar (femoral and obturator nerve) and sacral (sciatic nerve) plexus, there is no consensus in the literature on the number, origin, trajectory, landmarks and importance of the nerve branches supplying the knee capsule [10, 17, 19, 20, 22, 23]. However, accurate anatomical description of the sensory innervation of the knee is mandatory regarding its emerging therapeutic relevance.

Therefore, we conducted this comprehensive cadaveric study to (1) investigate the distribution of nerves supplying the human knee capsule, (2) assess the constant branches that could be targeted during genicular nerve blocks (GNB) or radiofrequency ablation (RFA), and (3) define their anatomical landmarks and compare them with previous reports.

1.1.3 Materials and methods

We dissected 21 lower limbs (10 right and 11 left) from 21 cadavers (14 men and 7 women, aged 85.9 ± 15.6 years) donated to the Pole of Morphology of UCLouvain. This sample consisted of 20 fresh frozen limbs and a well-conserved embalmed (with zinc chloride solution) specimen donated during our study period. Specimens showed no sign of previous lower limb surgery or pathology. All dissections were performed using standard instruments.

Before dissection, a special preparation was performed in the first 10 specimens:

- After flushing with lukewarm normal saline, red coloured latex was injected in the femoral artery under continuous manual pressure. This aimed to clearly discriminate small nerve branches from vessels, and to analyse whether the nerve distribution to the knee follows the vascular pattern. The dissection was performed after latex setting, 48 hours after vascular injection.

- Intra-articular injection of 20 ml of 0.1% methylene blue was performed in order to highlight the knee capsule and then, to clearly identify the nerves reaching it.

In the femoral triangle, we first identified the femoral nerve and its branches. We carefully dissected each one of them to isolate the articular nerves penetrating the knee capsule. Secondly, we identified the anterior and posterior branches of the obturator nerve at the obturator foramen and followed their course distally to document any genicular branches. Then, in prone position, we carefully dissected the sciatic nerve and its terminal branches (tibial and common fibular nerves) from the upper thigh to the upper leg to highlight all the articular branches to the knee.

The origin and course of each articular nerve were photographed and documented. Articular nerves whose the distal anatomical trajectory, at their entry point to the knee capsule, followed the same pattern in all the specimens, were considered constant. We precisely identified their constant location on the periosteum just before their distribution to the knee capsule, which is theoretically admitted to be their best target area during GNB and RFA [10]. Then, each constant nerve was fixed, at its target point, by a 1.5 mm Kirshner wire inserted through the nerve in the underlying bone. In a full extension

position, measurements were taken from this target point to the articular line and surrounding anatomical bony landmarks using a sliding digital calliper in order to determine clinical landmarks (Table 1).

Then, antero-posterior (A-P) and lateral radiographic images of the knees were made using a C – arm in order to highlight accurate geniculate landmarks under fluoroscopy, as it would customarily be used for the precise needle placement during an image-guided RFA procedure.

Table 1 Different parameters measured on each specimen for each constant genicular nerve

Genicular nerve	Axis of measurement	From target point of the genicular nerve to:
SMGN	Longitudinal	Medial femoral epicondyle
		Femoro-tibial articular space
IMGN	Longitudinal	Femoro-tibial articular space
	Transversal	Tibial tuberosity
ILGN	Longitudinal	Gerdy tubercle
	Transversal	Tibial tuberosity
SLGN	Longitudinal	Lateral femoral epicondyle
		Femoro-tibial articular space
		Apex of the fibular head
IPBSN[a]	Transversal	Midpoint of the medial patellar margin
		Apex patellae

[a]We measured the transversal distance from the midpoint of the patella medial edge to the trunk of IPBSN. We also measured the transversal distance from the apex of the patella to the IPBSN. SMGN superior medial genicular nerve, ILGN inferior lateral genicular nerve, IMGN inferior medial genicular nerve, SLGN superior lateral genicular nerve, IPBSN infra-patellar branch of saphenous nerve

1.1.4 Results

The Table 2 summarizes the nerves supplying the knee joint capsule.

Articular branches from the femoral nerve

We observed that the femoral nerve innervates the knee capsule through branches from the saphenous nerve (SN), the nerve to the vastus medialis (NVM), the nerve to the vastus lateralis (NVL) and the nerve to the vastus intermedius (NVI).

Articular branches from the saphenous nerve (SN)

We observed two articular branches from SN:

- The infrapatellar branch of saphenous nerve (IPBSN) was present in 100% of specimens. In most of them (18 of 21), it branched off distally, after the SN emerged from the adductor canal (AC) at the medial aspect of the distal third of the thigh (figure 1a). In three specimens, we observed an important variation of its origin: the IPBSN was detached from the SN in the proximal third of the thigh, above the AC and was running outside it (figure 1.b). However, its distal trajectory at the level of the knee was constant. The IPBSN emerged variably in relation to the sartorius (anterior border, trans-muscular, or posterior border), curved in the subcutaneous layer from postero-medial to anterior, towards the infero-medial aspect of the knee. The main trunk of the IPBSN was located 58.2 ± 7.1 mm posterior to the midpoint of the medial patellar margin and 51.3 ± 7.3 mm medially to the apex patellae. It divided into one to four ending branches some of which were

Table 2 Summary of the nerve supplying the knee joint capsule

Original nervous trunk	Branches from the original trunk carrying knee nerves	Nerves to the knee capsule (Genicular Nerves)	Constant landmarks for genicular blockade?	Supplied part of the knee capsule
Femoral	Nerve to the VM	1 Direct branch (SMGN)	Yes	Supero-medial
		0 to 3 Indirect branches (trans-muscular)	No	Superior medial
	Nerve to the VL	1 or 2 branches	No	Supero-lateral
	Nerve to the VI	Intermedium GN	No	Anterior Supra-patellar zone
	Saphenous nerve	IPBSN	Yes	Infero-medial
		1 small branch in the AC	No	Supero-medial
Obturator	Anterior branch	1 branch to the popliteal fossa via adductor hiatus	No	Postero-medial
	Posterior branch	1 trans-muscular branch to the popliteal fossa	No	Posterior
Sciatic	SLGN	Superior lateral GN	Yes	Supero-lateral
	Posterior articular nerve	Infero-medial GN	Yes	Infero-medial
	Common fibular nerve	Lateral recurrent GN	No	Inferior lateral
		Inferior lateral GN	Yes	Inferior lateral
	Tibial nerve	1 to 2 direct articular nerves	No	Posterior

VM vastus medialis muscle, VL vastus lateralis muscle, VI vastus intermedium muscle, SMGN superior medial genicular nerve, SLGN superior lateral genicular nerve, IPBSN infra-patellar branch of saphenous nerve, GN genicular nerve

ascending towards the patella, some crossed towards the patellar ligament and others descended towards the tibial tuberosity (figure 1c-d). Some of these branches crossed the mid-line of the knee to innervate its antero-lateral aspect.

- In four specimens, a small branch from the SN detached within the AC and joined the descending genicular artery and, a few centimeters lower, the articular nerve from the NVM. They ran together towards the medial aspect of the knee capsule.

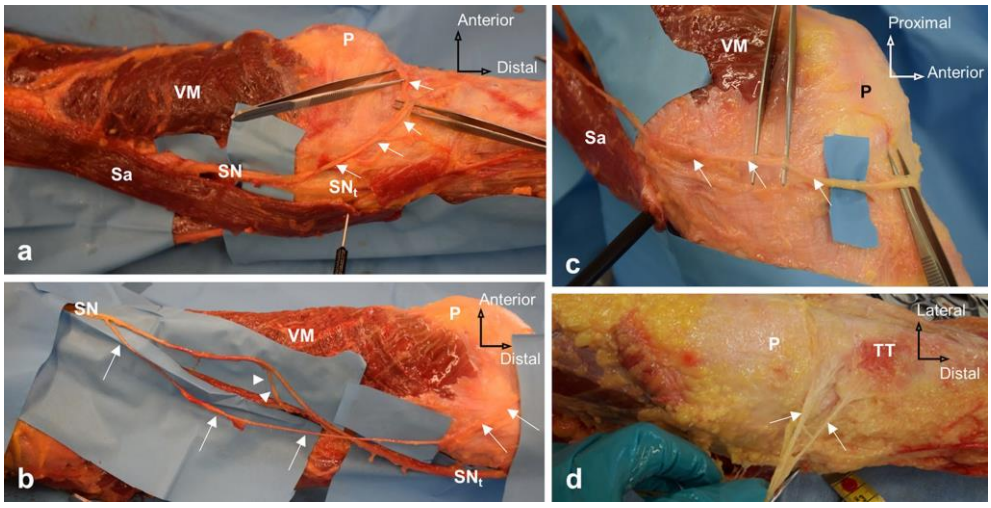


Fig. 1 Articular branches of the saphenous nerve. **a** Infra-patellar branch of saphenous nerve (IPBSN) detached distally after the emergence of SN from the adductor canal. **b** Important anatomical variation of the origin of the IPBSN, detached proximally to the adductor canal (opened). c, d Ending branches of IPBSN penetrating the knee capsule. SN saphenous nerve, Thin arrows IPBSN, Arrowheads posterior branch of SN, SN_t tibial branch of the saphenous nerve running toward the medial aspect of the leg, Sa Sartorius muscle, VM vastus medialis muscle, P patella, TT tibial tuberosity

Articular branches from the nerve to the vastus medialis (NVM)

The NVM was found running in a short distance with the SN in the proximal third of the thigh, then pierced the fascia of the VM muscle to continue its course between the muscle and its fascia. The NVM was not found within the adductor canal. It divided into three to five muscular rami and one constant articular branch. We observed two types of articular branches from the NVM:

- A constant direct (intra-fascial) articular branch, present in all specimens (figure 2a-b): the supero-medial genicular nerve (SMGN). This was the distal branch of the NVM, originating at the union between the middle and distal third of the thigh. After a short distance, it entered a tunnel within the fascia of the VM and ran in this intra-fascial trajectory for 5 to 8 cm. Then, it joined the descending geniculate artery and they descended together in the same bundle on the adductor magnus tendon towards the adductor tubercle. Just in front of the adductor tubercle, this nerve established a bony contact with the medial condyle 48.4 ± 8.9 mm above the femoro-tibial (FT) space; it divided into three or more branches entering the knee capsule.

- Indirect (trans-muscular) branches: after ramifying into the VM, some muscular branches of the NVM ended in the supero-medial aspect of the anterior knee capsule. They were inconstant in number (zero to three) and anatomic location.

Articular branch of the nerve to the vastus lateralis (NVL)

After giving off all the muscular branches, the NVL was found at the deep surface of the distal third of this muscle and ran obliquely close to the

periosteum near the metaphysis towards the antero-lateral aspect of the knee (figure 3). It ended by giving one or two articular branches: a superficial retinacular branch running transversally forward, and a deep capsular branch descending longitudinally. The anatomical location of this nerve was variable in our specimens.

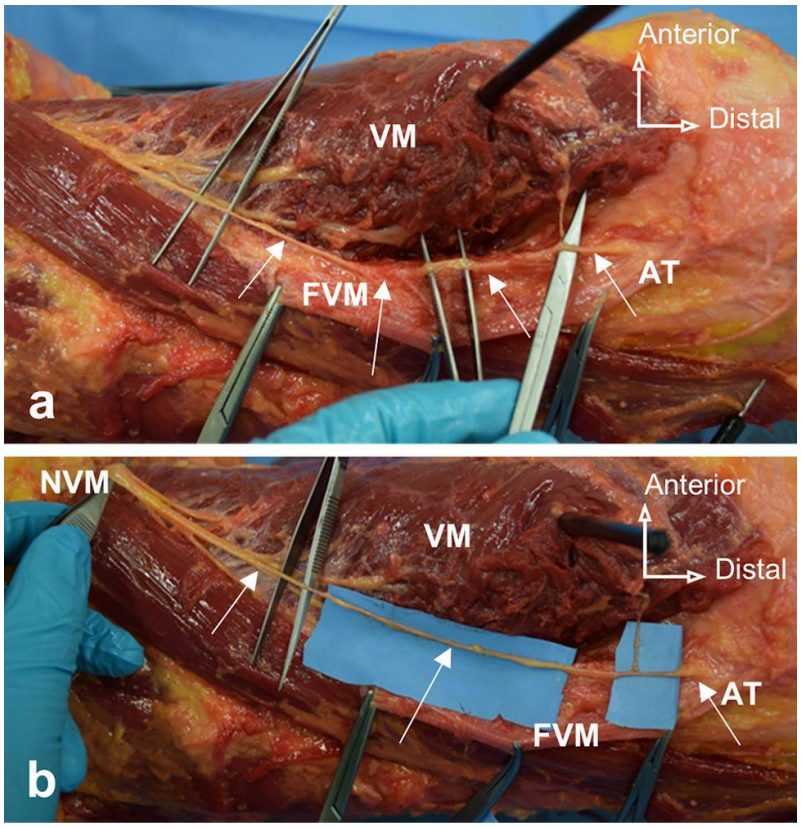


Fig. 2 Supero-medial genicular nerve (SMGN) from the Nerve to the Vastus Medialis (NVM). a Trajectory of the SMGN in a fascial tunnel (partially dissected) in the thick vastus medialis fascia which belongs to the medial intermuscular septum. b Complete view of the SMGN after delicate dissection from the fascial tunnel. Thin arrows SMGN, NVM nerve to the Vastus Medialis, FVM fascia of the Vastus medialis muscle, AT adductor tubercle, VM vastus medialis muscle

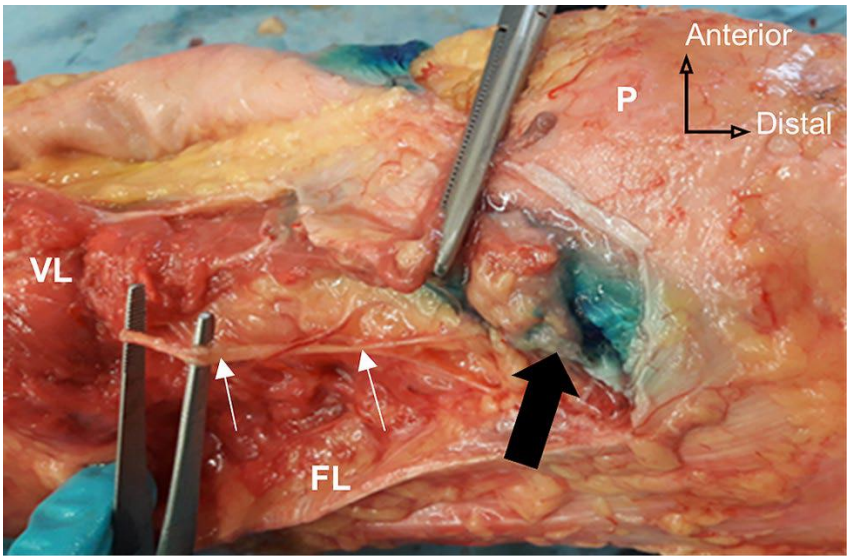


Fig. 3 Articular branch from the nerve to the vastus lateralis penetrating the knee capsule. The knee capsule is highlighted (*thick arrows)* due to infiltration of methylene blue in the knee joint before dissection. *Thin arrows* indicate articular branch from the Nerve to the Vastus Lateralis at the deep aspect of the VL muscle*, VL* vastus lateralis muscle (retracted), *FL* fascia lata*, P* patella

Articular branch of the nerve to the vastus intermedius (NVI)

The ending branch of the NVI was found at the anterior aspect of distal femur, deep to the VI muscle, running towards the supra-patellar pouch of the knee capsule (figure 4).

Articular branches of the obturator nerve

The obturator nerve emerges from the pelvis by the obturator canal and divides into two branches that descend together between the obturator externus and the pectineus muscles.

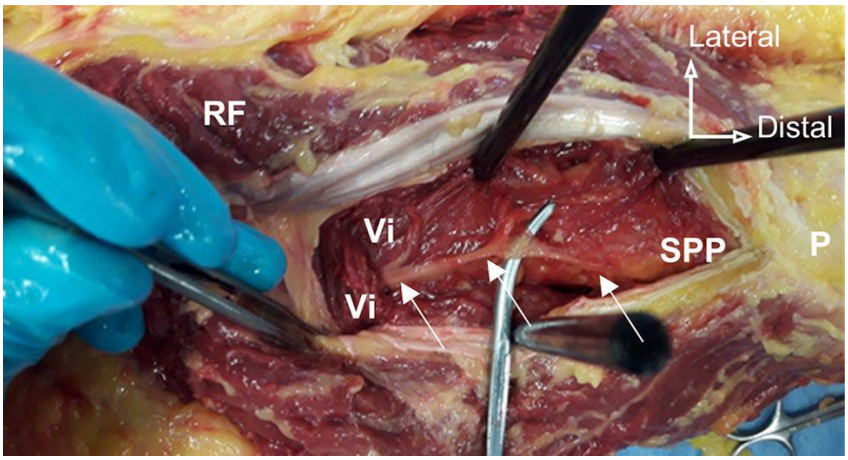


Fig. 4 Anterior view of the supra-patellar region, with the rectus femoris and the vastus intermedium muscles dissected and retracted. See the middle genicular nerve (MGN), terminal branch of the nerve to the vastus intermedium, running toward the supra-patellar pouch. *Thin arrows* indicate MGN emerging at the deep surface of the Vi muscle, *Vi* vastus intermedium muscle, *P* patella, *RF* rectus femoris muscle, *SPP:* supra-patellar pouch

- The anterior branch: descended between the adductor longus and brevis muscles, then on the posterior side of the adductor longus. It turned round anteriorly along the free edge of the adductor longus muscle, pierced the vasto-adductorum membrane (VAM) to enter the AC. It ran in a short distance in the proximal part of the AC and gave two branches. One branch anastomosed with a posterior branch from the SN and pierced the VAM to exit from the AC above the emergence of the SN, descended between the sartorius and gracilis muscles to innervate superficially the medial aspect of the knee and distal thigh (Figure 5 a). The second branch joined a thin descending artery in the

AC and entered in the adductor hiatus with the femoral vessels towards the popliteal fossa (figure 5b).

- The posterior branch of the obturator nerve was found running between the external obturator and the pectineus muscles, then between the adductor brevis and the adductor magnus muscles (AM). It divided proximally into many muscular branches supplying the AM. One of those branches pierced obliquely through the AM and emerged at its posterior surface to enter the popliteal fossa. We were not able to follow the distribution of this branch to the posterior capsule of the knee, as we could not demonstrate its participation in a popliteal plexus innervating the knee capsule like previously described.

Articular branches of the sciatic nerve

We observed that the sciatic nerve gives two constant branches to the knee capsule before its bifurcation:

- The supero-lateral genicular nerve (SLGN) detached from the sciatic nerve in 19 specimens. It ran down laterally under the biceps femoris muscle towards the postero-superior angle of the lateral femoral condyle where it reached the periosteum (figure 6), 40.1 ± 10.7 mm above the FT space. It then divided into two branches: a transversal branch running forward to the lateral retinaculum (lateral retinacular nerve) and a longitudinal branch descending towards the FT space.

- The posterior articular nerve detached from the tibial part of the sciatic nerve before its bifurcation in 19 of the specimens. It descended

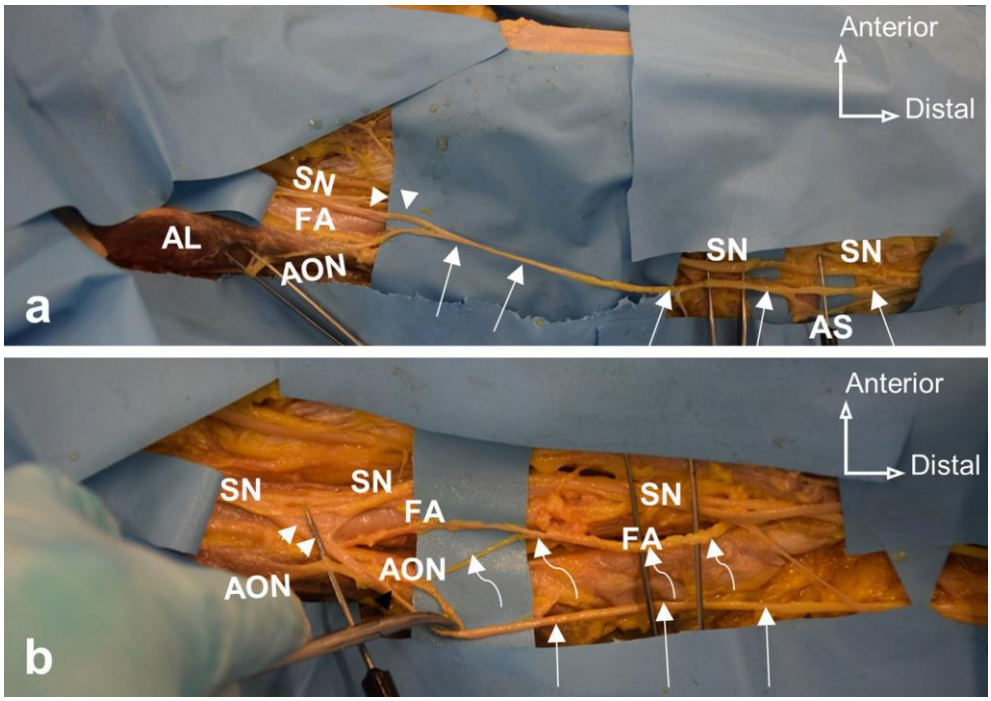


Fig. 5 Branches of the obturator nerve running toward to the knee. a: anterior branch (AON) turning round the medial edge of adductor longus (AL) and branches with a branch (arrowhead) of saphenous nerve in the adductor canal (opened) to supply the medial aspect of the distal thigh and the knee. b: bifurcation of AON in the adductor canal, one branch joins a branch of SN like described above (thin arrow), the second branch (spiral arrow) joins a small vessel and enters the adductor hiatus with femoral vessels. *(AON* anterior branch of the obturator nerve, *SN* saphenous nerve*, Arrowhead* branch from saphenous nerve anastomosing with a branch of AON, *Thin arrows* ending branch from the AON and SN running to the knee*, Spiral arrow* ending branch of AON penetrating the adductor hiatus with the femoral vessels*, AL* adductor longus muscle*, AS* articular (femoro-tibial) interspace (black tip inserted into))

towards the popliteal vessels and divided into two branches. The distal branch passed between the popliteal artery and vein, crossed obliquely the deep surface of the popliteal artery and joined the infero-medial genicular vessels (figure 7a-b). Both turned around the medial tibial

5condyle, from posterior to anterior, following a recurrent trajectory. They coursed beneath the deep surface of the collateral tibial ligament, and then ascended anteriorly towards the antero-medial part of the knee capsule. We found this nerve constant in 100% of specimens and it corresponded to the infero-medial genicular nerve (IMGN).

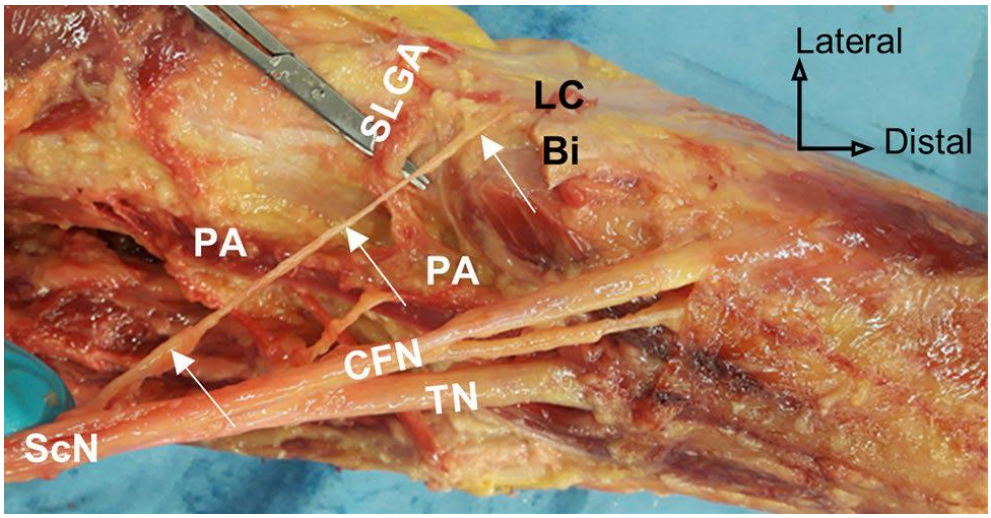


Fig. 6 Articular branches from sciatic nerve: supero-lateral genicular nerve (SLGN). Postero-lateral view of the knee, biceps femoris (Bi) removed. Note that the SLGN (thin arrows) do not run in the same bundle with SLGA. *Thin arrows* SLGN, *ScN* sciatic nerve, *TN* tibial nerve, *CFN* common fibular nerve, *SLGA* supero-lateral genicular artery from popliteal artery *(PA); Bi* biceps femoris tendon (sectioned*); LC* lateral femoral condyle

Articular branches from the tibial nerve (after bifurcation)

The tibial nerve released inconstantly one to two branches, which dived towards the posterior knee capsule. In the two specimens with proximal sciatic bifurcation, the posterior articular nerve was detached directly from the tibial nerve, and the SLGN detached from the common fibular nerve (CFN). In 11

specimens, we did not identify any articular branch directly arising from the tibial nerve.

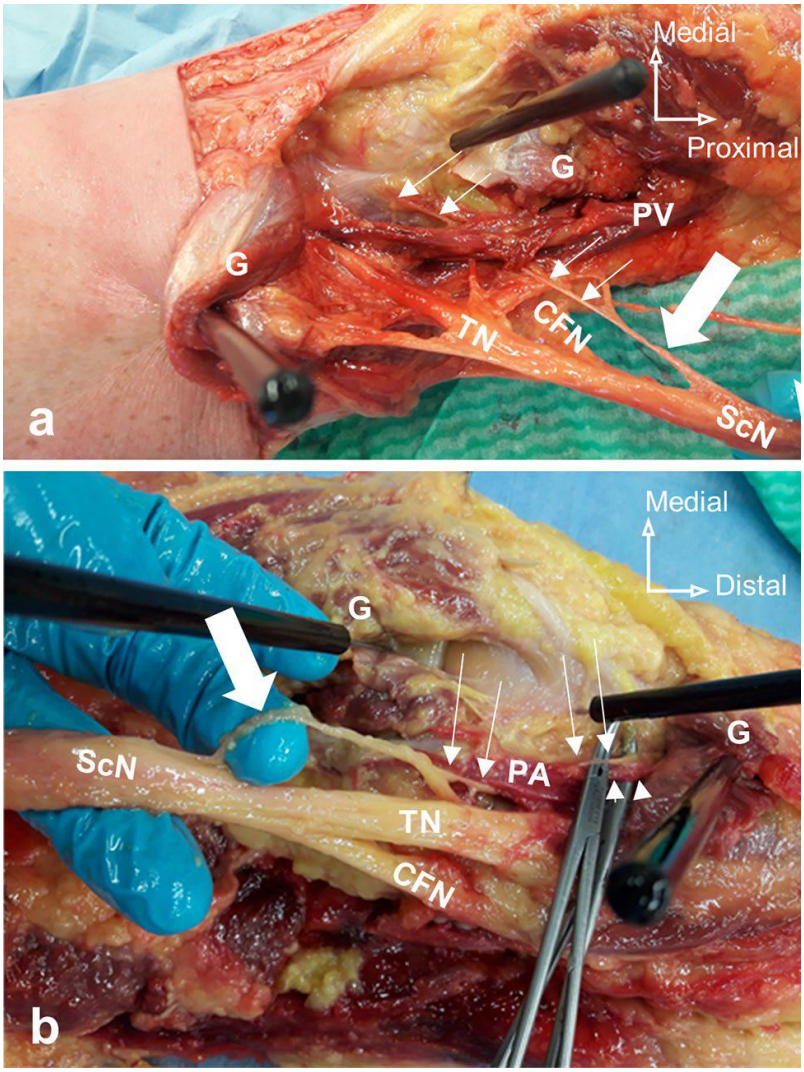


Fig. 7 Articular branch from sciatic nerve: posterior articular nerve (thick arrow). Posterior view of the knee joint, gastrocnemius muscle cut and reflected. a Trajectory of the infero-medial genicular nerve (IMGN, thin arrow) passing between the popliteal vessels (PV) and penetrating the knee capsule. b IMGN (thin arrows) running with the infero-medial genicular artery (arrowhead) at the posterior aspect of the knee, toward its antero-medial aspect . *Thick arrow*

posterior articular nerve, *Thin arrows* IMGN, *G* gastrocnemius muscle (cut and reflected), *ScN* sciatic nerve, *TN* tibial nerve, *CFN* common fibular nerve

Articular branches of the common fibular nerve (CFN)

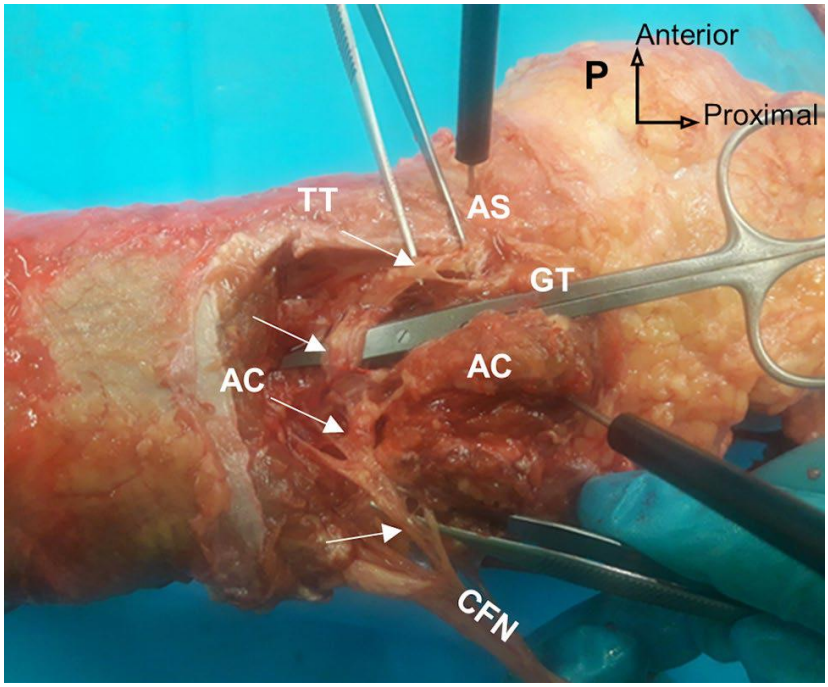


Fig. 8 Infero-lateral genicular nerve (ILGN) from the common fibular nerve (CFN). *Thin arrows* ILGN, *TT* tibial tuberosity, *GT* Gerdy's tubercle, *AC* anterior compartment muscles, *AS* Articular (femoro-tibial) space (black tip inserted into), *P* patella

We observed two constant articular branches detaching from the common fibular nerve, just before its bifurcation.

- The lateral recurrent genicular nerve was the first branch arising at the level of the fibula neck and destined to the proximal tibio-fibular joint.

- The infero-lateral genicular nerve (ILGN) was the second branch (figure 8). It detached at the level of the fibular neck and descended forward giving off many muscular collaterals. Then, the terminal branch emerged at the deep surface of the anterior tibial muscle and joined the lateral recurrent genicular vessels at the junction of the lateral condyle and the shaft of the tibia. They ascended together on the periosteum towards the infero-lateral aspect of the anterior knee capsule, passing between the tibial tuberosity and Gerdy's tubercle.

Constant genicular nerves and anatomical landmarks for Genicular nerve blockade and radiofrequency ablation

Based on this comprehensive cadaveric dissection, we have selected five constant articular branches that are potential targets during these emerging therapeutic procedures. The measurements from the anatomical landmarks are presented in Table 3.

1. **Supero-medial genicular nerve**: it was a branch from the NVM in all specimens. Under fluoroscopy, the target point was located in front of the adductor tubercle, at the superior edge of the medial femoral condyle on the antero-posterior (AP) view (figure 9a). On the lateral view, it was located at the posterior third of the condylar width (figure 9b), and not at the middle.

2. **Supero-lateral genicular nerve**: it was a direct branch from the sciatic nerve. Under fluoroscopy, the target point was located at the postero-

superior angle of the lateral condyle on the lateral view, corresponding to the upper edge of the lateral condyle height on AP view (figure 9).

3. **Infero-medial genicular nerve**: originating from the posterior articular nerve, which branches off from the sciatic nerve. It was found at the tibial metaphysis, beneath the deep surface of the tibial collateral ligament. Under fluoroscopy, the target point was located at the junction of the tibial shaft and medial condyle on the AP view, while on the lateral view, it was located at the middle of the tibial width (figure 9).

4. **Infero-lateral genicular nerve:** branched off from the CFN. The target point was located at the distal part of this nerve, just before entering the knee capsule, far away from the CFN, and after the muscular branches had been given off. This point was located at the intersection between the longitudinal line passing through Gerdy's tubercle and the transversal line passing through the top of tibial tuberosity.

5. **Infra-patellar branch of saphenous nerve**: The target of IPBSN was found to be a line, like recently described by Hu et al [91], with a slight modification. The landmark is the longitudinal line connecting the transversal lines passing through the apex patellae and tibial tuberosity, 4 cm medially to the apex patellae. In our study, this line crossed all the terminal branches of the IPBSN in 20 out of 21 specimens (95% of accuracy).

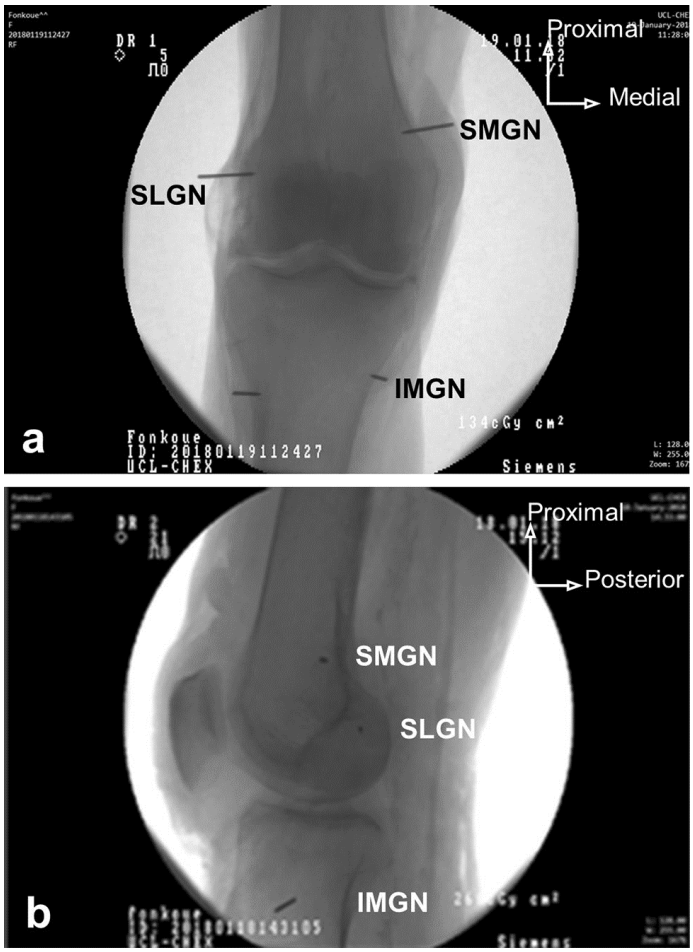


Fig. 9 Landmarks proposed for fluoroscopic-guided genicular nerve blockade of the SMGN, SLGN, and IMGN (during dissection, Kirshner wires have been inserted through the constant genicular nerves in the underlying bone at their target point, before radiographs have been done) a Antero-posterior incidence, b Lateral incidence. *SMGN* supero-medial genicular nerve, *SLGN* supero-lateral GN, *IMGN* infero-medial *GN*

Table 3. Measurements from the target point of each constant genicular nerve to the surrounding anatomical landmarks

NERVE	Origin	Quadrant of the knee capsule	From the targeted location of the nerve to:	Mean (±SD) Distance(mm)
SMGN	Nerve to vastus medialis	Supero-medial	Femoro-tibial interspace	48.4 ± 8.9
			Medial epicondyle	21.9 ± 3.2
SLGN	Sciatic nerve	Supero-lateral	Femoro-tibial interspace	40.1 ± 10.7
			Top of the fibula head	59.9 ± 9.6
			Lateral epicondyle	19.5 ± 5.15
IMGN	Posterior articular nerve (from sciatic nerve)	Inferior medial	Femoro-tibial interspace	38.0 ± 3.9
			Tibial tuberosity	43.9 ± 6.5
ILGN	Common fibular nerve	Inferior lateral	Gerdy tubercle	16,8 ± 3,3
			Tibial tuberosity	22.6 ± 5.6
IPBSN	Saphenous nerve	Inferior medial	Midpoint of the medial edge of the patella	58,2 ± 7,1
			Tip of the patella	51,3 ± 7,3

SD standard deviation, SMGN superior medial genicular nerve, ILGN inferior lateral genicular nerve, IMGN inferior medial genicular nerve, SLGN superior lateral genicular nerve, IPBSN infra-patellar branch of saphenous nerve

1.1.5 Discussion

The knee's sensory innervation has been described to be complex with a high degree of anatomical variability [17, 19, 21-23, 88]. However, a precise

knowledge of the distribution pattern of nerves supplying the knee makes some of them accessible to percutaneous denervation for the treatment of chronic knee pain. In this comprehensive cadaveric study, we dissected the three nerves of the lower limb from their origin, and we rigorously traced each of their branches to its termination to systematically check all of the articular nerves supplying the knee capsule. We have found that nerve supply to the medial aspect of the knee capsule originates from the saphenous nerve, the SMGN from the nerve to the VM, the IMGN from the sciatic nerve, and to some extent, the anterior branch of the obturator nerve. The lateral aspect of the knee is innervated by the nerve to the VL, the SLGN from the sciatic nerve, the lateral recurrent nerve and the ILGN from the common fibular nerve. The supra-patellar area is supplied by the median intermediate genicular nerve from the nerve to the vastus intermedius. The tibial nerve and the posterior branch of the obturator nerve supply the posterior aspect of the knee. Some of these nerves were accompanied by small vessels (SMGN, IMGN, ILGN, IPBSN), but it did not appear that the nerve course is scheduled to follow the genicular artery distribution.

Despite the anatomical variability of sensory nerves supplying the knee, we found more constant nerve branches with therapeutic significance than those used for genicular nerve blocks and radiofrequency ablation [10]. The success of genicular blocks or RF denervation depends on the target nerve being included within the volume of thermocoagulated tissue or immersed in anaesthetic [4, 10, 64]. Several research groups have focused on optimizing this technique, but we found that the anatomical description of the genicular nerves given by Choi and colleagues, on which these therapeutic procedures are based, is somewhat inaccurate concerning their origin and targets used. We selected

five genicular nerves whose distal course was found to be consistent, despite some variations in their proximal trajectory: the SMGN, IMGN, IPBSN, SLGN, and ILGN.

The NVM seems to play a much greater role as previously suggested by Burckett [17]. Almost all the authors since Gardner [21] described the trans-muscular branches of the NVM supplying the antero-medial aspect of the knee capsule following Hilton's law [92], but most of them failed to describe the only constant direct branch of the NVM to the medial joint capsule, which has the most important therapeutic interest. This might be because the trajectory of this thin nerve, hidden in a fascial tunnel, does not facilitate its dissection and identification. Additionally, if the fascia of the vastus medialis muscle is removed or damaged during dissection, it would no longer be possible to identify this nerve, which lies within it. We found that this intra-fascial direct branch, observed in all the specimens, running in front of the adductor tubercle and supplying the supero-medial quadrant of the knee capsule, corresponds to the SMGN. Recently, Burckett et al [17] described an extra-muscular branch of the NVM, found in only seven specimens out of 20, but three other very recent studies [16, 20, 88] described this branch (intra-fascial) in all their specimens, in accordance with our findings. We found like all these recent studies that the SMGN is not a branch of the tibial nerve like previously described since Gardner [21]. However, there remain some discrepancies concerning the origin of this nerve and the therapeutic target point. Unlike Tran et al [16] who suggested that this nerve originate directly from the femoral nerve, we clearly found (and illustrated) that it is a branch of NVM (figure 2 a-b), in accordance with Orduna-valls [20] and Bendsten [88]. Curiously, when looking carefully at the figure-4C provided by Tran, we observed that the

SMGN seems directly detached from the NVM. Another important difference we found is that, although most of the authors (including anatomical textbooks) state that the NVM lies within the adductor canal [17, 20], it was found outside the AC in our specimens. This finding is in accordance with Bendtsen et al [88] and Elabad [93] who found the NVM out of the AC in all of their specimens. This anatomic detail could be of relevant clinical interest, especially concerning adductor canal blockade.

This study shows that the combination of the SN and the NVM provides the substantial innervation to the antero-medial aspect of the knee joint (capsule and retinaculum). They should be the primordial therapeutic targets in medial knee pain. Contrary to Burckett [17] who found the contribution of the SN to knee joint innervation to be relatively modest with an inconsistent infrapatellar branch (11 specimens out of 25), we found this IPBSN in all specimens, in accordance with most of the studies [94-97]. We observed an anatomical variation of great clinical importance for pain physicians: in three of our specimens, because the IPBSN emerged proximally to the AC and coursed outside it, an AC blockade would have theoretically been less efficient for suppression of the afferent nerve influx from the IPBSN than a distal blockade at the level of the knee. In a recent study, Koch et al [97] did not observed this very proximal origin of the IPBSN. This might be due to the fact that, contrary to those authors who started the dissection of SN at its emergence from the AC, we dissected the entire thigh to trace the SN from its origin.

Although it is well admitted that the ON participates in the innervation of the knee capsule, there is no consensus on the patterns of distribution of the ON branches to the knee [18, 20, 21, 88]. Burckett [17] found no terminal branches of the ON that directly innervates the capsule of the knee joint. Horner and

Dellon [19] found ON contribution to knee innervation in only 11% of specimens. We found that the anterior branch of the obturator nerve enters the AC and contributes to the sensory innervation of the knee joint, through a plexus with the SN, and potentially through the branch penetrating the adductor hiatus with the femoral vessels (figure 5). The small branches that anastomose with branches of the SN in the AC were named subsartorial plexus in an old study by Druner [98]. A branch of the posterior ON perforates the adductor magnus muscle to penetrate the popliteal fossa and might contribute to the posterior innervation of the knee capsule via a popliteal plexus, as suggested in literature. However, no authors have illustrated this, and we could not identify a macroscopically customizable branch penetrating the posterior knee capsule or anastomosing with the tibial nerve branches. Moreover, unlike most descriptions since Gardner [21], we highlighted that the anterior branch of the ON, and not the posterior one, lies in the AC and penetrates the adductor hiatus. Nevertheless, the importance of the ON to the sensory innervation of the knee capsule is reinforced by clinical studies suggesting that ON blocks contribute to knee analgesia [99].

The contribution of the sciatic nerve to the knee innervation is well established, but the anatomical description of the specific nerves that enter the knee capsule is somewhat inappropriate. We found that the sciatic nerve gives two constants nerves for the knee capsule. The SLGN, constant in its origin and trajectory, found in 100% of our specimens, as recently described by Sutaria [100]. This nerve could be an important therapeutic target for postero-lateral knee pain. Surprisingly, most of the authors [12, 17, 23, 88] wrongly describe the SLGN as a branch of the NVL or the common fibular nerve. The second nerve, the posterior articular nerve, was first described by Gardner [21] as a branch of the

tibial nerve. However, it emerges from the tibial part of the sciatic nerve, before the bifurcation. We were able to demonstrate that in all the specimens, it gives a small branch that joins the infero-medial geniculate vessels and innervate the infero-medial aspect of the knee capsule. We did not find that specific trajectory description and illustration in literature.

The anatomic references supporting the genicular RF therapeutic procedure suggests that the tibial nerve gives off the SMGN and the IMGN [10]. We found this description inaccurate, in accordance with *Orduna et al* [20] in a recent cadaveric study, who were unable to determine a consistent pattern of the tibial nerve sensory branches. Contrary to the wide spread anatomical description, the SMGN and the IMGN are not direct branches of the tibial nerve. Many authors [17, 19, 22, 88] cited a popliteal plexus made of branches of obturator nerve and tibial nerve, which we did not specifically observe. We did not found a single illustration of this plexus in the literature.

The importance of the sensory branches from the common fibular nerve was described by Gardner [21] and subsequently confirmed by Horner [19]. The close proximity of the ILGN (recurrent fibular nerve for some authors [8, 26]) to the CFN has precluded radiofrequency as a therapeutic option [10, 20]. Then, to avoid accidental damage to the CFN trunk while targeting ILGN, all the authors strongly countermand the blockade of the ILGN. This is right if we consider the target point at the origin of the ILGN on the fibular neck, just after it detached from the CFN. However, we found that this nerve could safely be targeted in its distal trajectory, before it enters the knee capsule, far away from the CFN. More interesting, as the IPBSN, our proposed landmarks for targeting the ILGN does not require the absolute use of imaging devices, but

just the palpation of the superficial bony landmarks. To our knowledge, this is the first description of a potentially safe target point of the ILGN for RFA.

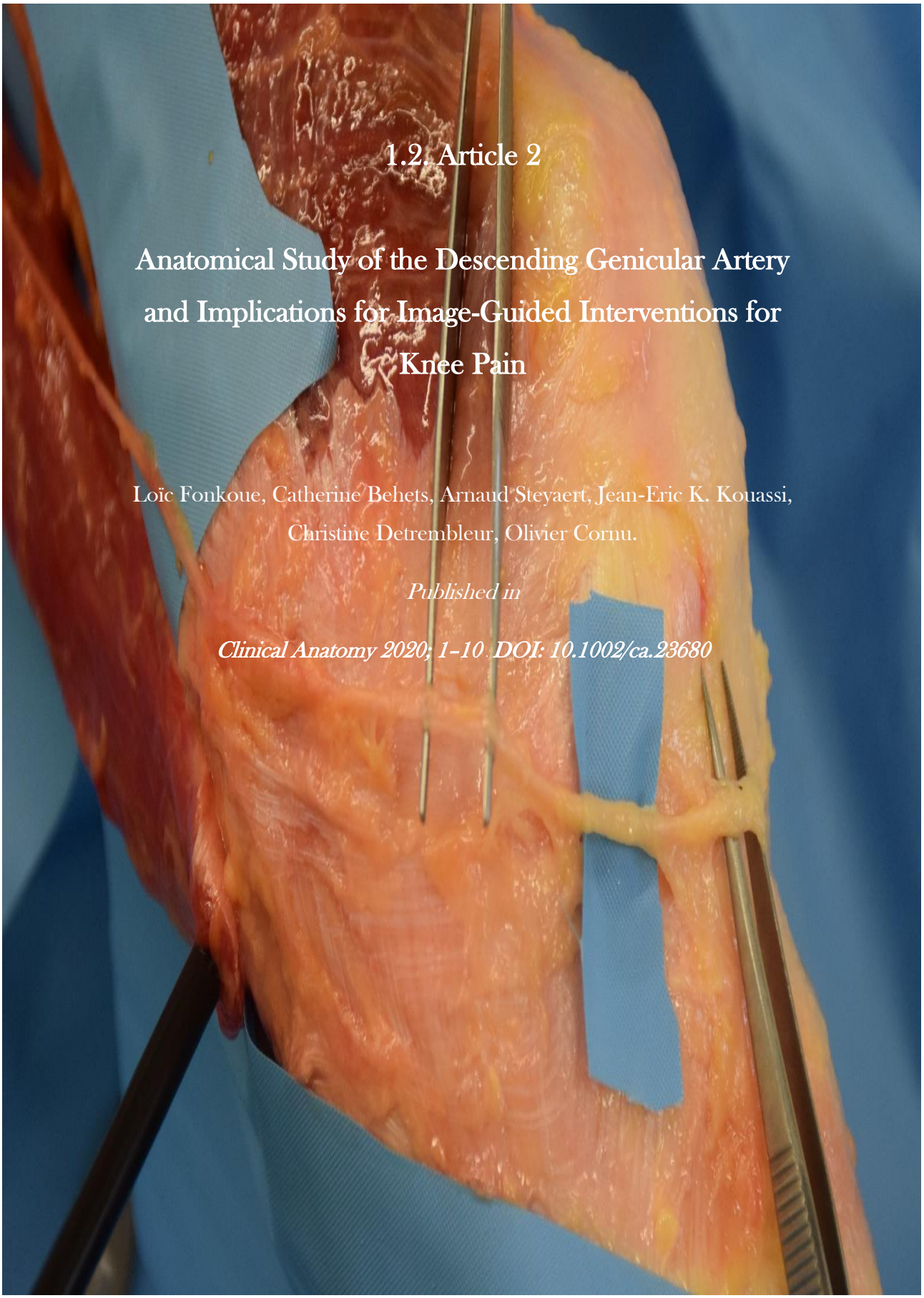
Radiographic landmarks improve the likelihood of successful inclusion of a segment of the relevant genicular nerve within the tissue volume thermocoagulated or immersed, providing better clinical response [23]. The originality of our method to determine the radiological landmark is that, after identifying the bony target point of a constant genicular nerve, a Kirshner wire was directly inserted through the nerve in the underlying bone, exactly at its target point, under direct visual observation. Then, true A-P and lateral radiographic images allowed us to determine the target point of each nerve under fluoroscopic guidance and to verify the consistency of their radiological landmarks in all specimens. The solid fixation of Kirshner wires in bone through the targeted nerve prevents any displacement during closure and handling for radiography, contrary to the method used by Franco [23] who just placed slender stainless-steel wires along the course of the genicular nerves. Our study showed some significant differences in radiological landmarks of the genicular nerve from those widely used for RFA since their description by Choi et al [10]. This advocates a clinical study to compare the therapeutic relevance of our proposed landmarks to that of the classical ones currently used for RFA.

Conclusion

This study was designed to revisit the sensory innervation of the human knee capsule and to re-examine the anatomical basis for the therapeutic selective denervation of the knee capsule widely used since the description of Choi et al. Our results shows that they failed to accurately determine the origin of some

of the genicular nerves on the one hand, and some of their recommended target points are not accurate on the other hand. The NVM, saphenous nerve, anterior branch of the ON and IMGN from sciatic nerve provide substantial innervation to the medial knee capsule and retinaculum. The sciatic nerve and the NVL supply sensory innervation to the supero-lateral quadrant of the knee joint, while the CFN supplies its infero-lateral side. Tibial nerve and posterior branch of the obturator nerve supply the posterior aspect of the knee capsule. According to our study, five constant genicular nerves with accurate landmarks could be targeted for therapeutic purpose. These findings warrant further clinical studies using these modified anatomical target points to compare their therapeutic efficacy with the current standard of art.

Acknowledgements The authors thank the donors of the cadavers used in this study and their families.



1.2. Article 2

Anatomical Study of the Descending Genicular Artery and Implications for Image-Guided Interventions for Knee Pain

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1.2.1 Abstract

Introduction. The descending genicular artery (DGA) has been recently mentioned as accompanying some nerves of the medial aspect of the knee joint. This could be clinically relevant as the arteries could serve as landmarks for accurate nerve capture during ultrasound-guided nerve blockade or ablation. The aim of this cadaveric study was to investigate the anatomical distribution of DGA, assess the nerves running alongside the branches of DGA and discuss the implications for regional anesthesia and knee pain interventions.

Methods. We dissected the femoral artery all along its course to identify the origin of the DGA, from which we carefully dissected all its branches, in twenty-seven fresh-frozen human specimens. Simultaneously, we systematically dissected, from proximally to distally, the nerves supplying the medial aspect of the knee and identified those running alongside branches of the DGA. The surrounding anatomical landmarks were identified and measurements were recorded.

Results. The DGA was found in all the specimens, arising from the femoral artery, at 130.5±17.5 mm (Mean ± SD) proximally to the knee joint line. Seven distribution patterns of the DGA were observed. We found three consistent branches from the DGA running alongside their corresponding nerves at the level of the medial aspect of the knee: the artery of the superior-medial genicular nerve, the artery of the infrapatellar branch of the saphenous nerve and the saphenous branch of the DGA.

Conclusion. The consistent arteries and surrounding landmarks found in this study could help improving the capture of the targeted nerves during ultrasound-guided interventions.

Keywords: Knee joint; arteries; innervation; ultrasonography, interventional.

1.2.2 Introduction

In the last decade, genicular nerve blockade (GNB) and radiofrequency ablation (RFA) have emerged as promising interventions for patients with chronic knee pain due to osteoarthritis or persistent after a total knee replacement [24]. These procedures are based on the selective inhibition of the consistent sensory nerves supplying the joint capsule, so called genicular nerves (GN). Given the small volume injected during nerve blockade and the very limited size of a radiofrequency lesion, the success of these techniques relies on the choice of accurate anatomical targets to capture the articular nerves supplying the knee. However, since the original description of these procedures [10], several research groups have concluded that their anatomical bases were inaccurate [14, 20, 101, 102], and studies currently focus on optimizing these techniques [16, 103, 104].

Due to the very small size of the genicular nerves, their accurate targeting in interventional pain medicine may be challenging. Under ultrasound guidance, direct visualisation of the genicular nerves is difficult, but the blood flow of genicular arteries traveling alongside the nerves can help to identify them more easily and increase injection success [68, 105]. This principle has been applied for ultrasound-guided elective neural ablation [105, 106]. Therefore, the genicular artery of interest should be the one running alongside the targeted nerve. Relying on wrong patterns of genicular arteries would lead to a poor outcome.

Recent studies have found that the contribution of the superior-medial genicular nerve (SMGN) and the infrapatellar branch of the saphenous nerve (IPBSN) to the sensitivity of the medial region of the knee joint makes them

primordial targets for relieving medial knee pain [17, 20, 101]. However, there are some discrepancies about the arteries accompanying these nerves and contrary to the original description, the descending genicular artery (DGA) has been recently mentioned as accompanying the SMGN [16, 101, 103].

Anatomical studies of the descending genicular artery have sparked great interest in the recent years due to the emergence and increasing indications of medial femoral condyle flap [107-114]. So far, anatomical studies on the DGA have dealt with plastic surgery. To our knowledge, no study has specifically investigated the anatomy of the DGA regarding its potential implications for regional anaesthesia and knee pain interventions. Therefore, the aims of this cadaveric study were (1) to describe the anatomical distribution of the descending genicular artery, (2) investigate the articular nerves running alongside the branches of the DGA and (3) discuss its potential implications for ultrasound-guided regional anesthesia and chronic pain interventions.

1.2.3. Materials and methods

Twenty-seven fresh frozen lower limbs (16 right, 11 left) from 21 adult cadavers (11 male, 10 female; average age at death 82.9 ± 9.4 years) without evidence of prior knee surgery or trauma, were observed macroscopically. All the bodies were donated to the institution for education and research purpose, in accordance with national laws and regulations. Approval was obtained from the University Research Ethics Committee. All the dissections were performed by an experienced anatomist, who had conducted the dissections of several previous studies addressing the knee joint innervation.

The dissection started with a skin incision and superficial cutaneous removal at the medial aspect of the thigh, from the groin to the middle of the leg. In supine position, we exposed the femoral artery and femoral nerve with its branches in the femoral triangle. We dissected the femoral artery all along its course to identify the origin of the descending genicular artery, from which we carefully dissected all the branches from proximally to distally. The DGA was studied with particular emphasis given to the knee nerves in close proximity. So, simultaneously with the arterial dissection, we performed a systematic dissection, from proximally to distally, of the nerves supplying the medial part of the knee joint. Then in each specimen, we identified the nerves supplying the medial aspect of the knee running alongside branches of the DGA. The surrounding anatomical structures that could serve as complementary landmarks were also identified.

We collected the following data:

- the pattern of origin and distribution of the DGA according to Dubois et al. [114] classification;
- the distance between the origin of the DGA and the medial femoro-tibial joint line;
- the length of the DGA from its origin up to its division;
- the distance from the origin of the DGA to the periosteum of the medial femoral condyle (MFC);
- the length of the branches of the DGA;

- the branches of the DGA running alongside the nerves supplying the knee joint;

- the longitudinal distance between the point where a branch of the DGA joins the corresponding nerve and the femoro-tibial joint line.

Dissections were performed under magnification with a 3.5 x surgical loupe. The measurements were taken in a full extension position with a sliding digital caliper. The findings were recorded with photographs. In two specimens, before dissection, the femoral artery was injected with red latex.

1.2.4. Results

Branching pattern of the descending genicular artery

The descending genicular artery was found in all the specimens. It branched off the medial side of the femoral artery (FA) just before the passage through the adductor hiatus. It was the last medial branch of the femoral artery. We identified seven branching patterns of the DGA from Dubois et al. classification (Table 1). The type I pattern (figure 1) was observed in 16 (59.3%) cases, type 2 (figure 2) in 9 (33.3%) cases and type III (figure 3) in 1 (3.7%) cases. In one case, the three branches emerged from a common trunk as in type I, but the osteo-articular branch occurs first, leaving behind a sapheno-muscular trunk (figure 1d). This subtype of the type I branching pattern is not included in the Dubois et al. classification.

The DGA originated on average 130.5 ± 17.5 mm (mean ± SD) proximally to the medial femoro-tibial joint line (Table 2). In most of the cases, after a short

descending course of 11.2 ± 8.0 mm, it divided into its terminal branches: the muscular, osteo-articular and saphenous branches (Fig. 4).

Table 1. Origin and distribution pattern of descending genicular artery in our series according to Dubois et al classification [21]

Branching pattern	Description	Frequency in our series
Type I.	The three branches emerge from a common trunk: the DGA	16/27 (59.3%)
Ia	The DGA divides into the three terminal branches	5/27 (18.5%)
Ib	The MB occurs first, leaving behind a sapheno-articular trunk	7/27 (26.0%)
Ic	The SB occurs first, and leaving behind a musculo-articular trunk	4/27 (14.8%)
Type II	One of the three branches arises directly from the femoral artery	9/27 (33.3%)
IIa	The AB arises directly from the FA	0/27 (0%)
IIb	The SB originates directly from the FA	4/27 (14.8%)
IIc	The MB originates directly from the FA	5/27 (18.5%)
Type III	The three branches (SB, AB and MB) arise separately from the femoral artery	1/27 (3.7%)
Non applicable	The three branches emerge from a common trunk, the AB occurring first, leaving behind a sapheno-muscular trunk	1/27 (3.7%)

Anatomical description of terminal branches and identification of knee nerves running along them

The muscular branch (MB) was the first to emerge in half of the specimens, from the short initial course of the DGA or directly from the FA. It was a strong branch with a short transverse course toward the vastus medialis muscle, where

it divided to supply the posterior-medial aspect of the muscle (Fig. 4). No nerve was found along this branch. The main trunk of the DGA then divided into 2 branches (Fig.4): a descending longitudinal branch (osteo-articular branch) and a posterior oblique blanch (saphenous branch).

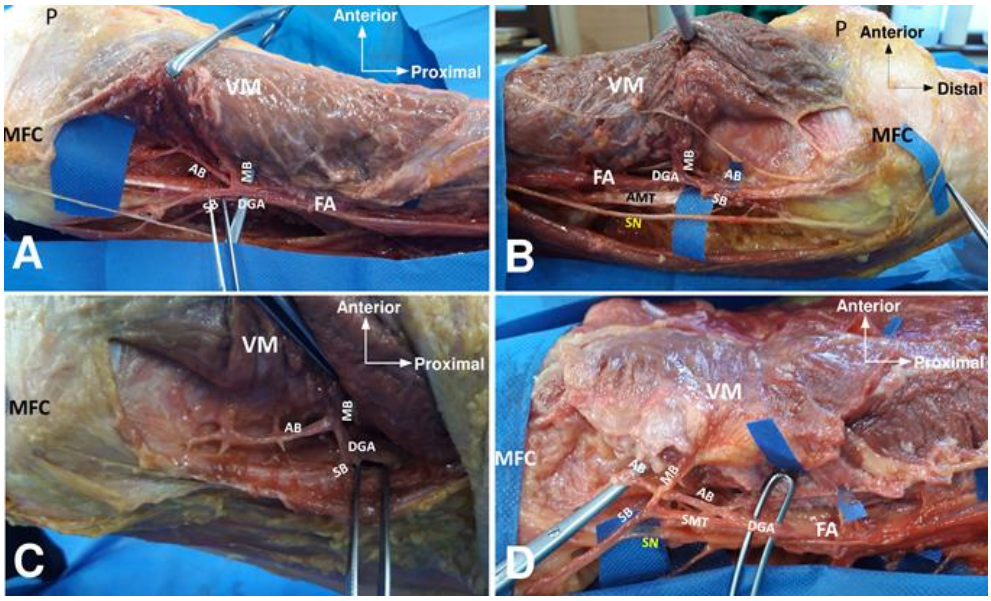

Fig. 1. Type I Branching patterns of descending genicular artery (DGA). A: Type Ia. The DGA divides at its origin into its three terminal branches: the muscular branch (MB), the saphenous branch (SB) and the osteo-articular branch (AB). B: Type Ib. The DGA originates from femoral artery (FA) and first gives the MB, leaving a sapheno-articular trunk, which divides into SB and AB. C: Type Ic. The DGA originates from FA and first gives the SB, leaving a musculo-articular trunk that divides into MB and AB. D: The DGA originates from FA and first gives the AB, leaving a sapheno-muscular trunk (SMT) that divides into MB and SB. SN, saphenous nerve; VM: vastus medialis muscle; MFC, medial femoral condyle; P, patella, AMT adductor magnus tendon.

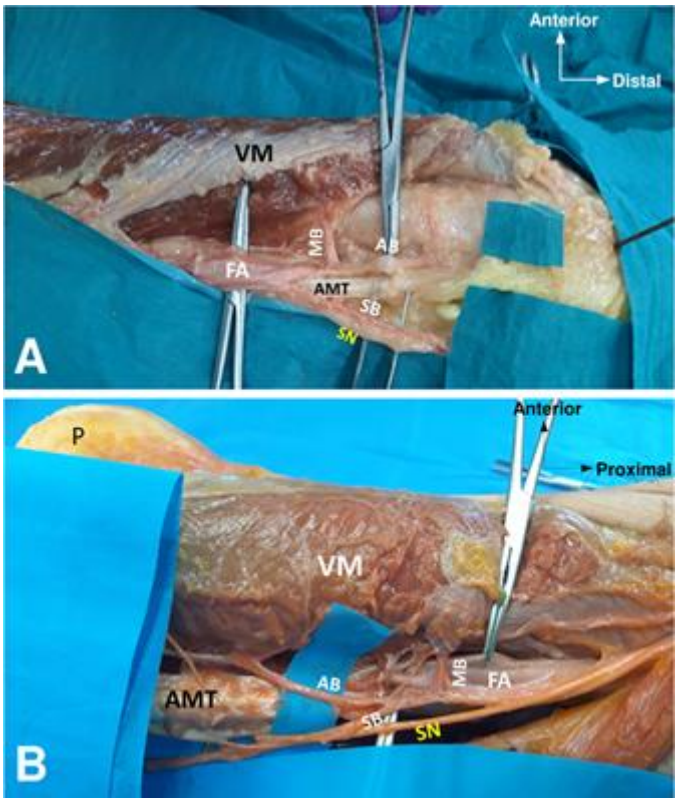

Fig. 2. Type II branching patterns of descending genicular artery (DGA). A: type IIb. The Saphenous branch (SB) originates directly from femoral artery (FA). B: type IIc. The muscular branch (MB) originates directly from FA. SN, saphenous nerve; VM, vastus medialis muscle; P, patella; AMT, adductor magnus tendon; AB, the osteo-articular branch.

The osteo-articular branch (AB) of the DGA was longitudinal, descending almost vertically toward the medial femoral condyle, with a course lateral to the adductor magnus tendon, close to the bone (Fig.4). Its average length was 79.6 ± 10.2 mm. The AB was observed in the sub-vastus region, between the posterior aspect of the vastus medialis muscle and the adductor magnus tendon, anterior to the medial intermuscular septum of the thigh. During its course, it detached 0 to 3 thin transverse muscular branches to the vastus medialis and one inconstant posterior branch which anastomosed with

popliteal artery (Fig. 4). The AB divided above the adductor tubercle into two terminal branches, almost perpendicular (Fig.4)

- A transverse branch, running forwards, on the periosteum at the junction of medial epicondyle and femoral diaphysis, 61.5 ± 5.8 mm from the joint line: the upper transverse artery of the medial condyle. This branch was not accompanied with a nerve.

- A longitudinal branch, running distally, to the medial femoral condyle (MFC): the central longitudinal artery of the MFC. It was an extension of the AB, passing beneath a transverse retinaculum stretched between the distal end of adductor magnus tendon and the periosteum of medial aspect of the femoral metaphysis, and supplying the medial femoral condyle (MFC).

Before its bifurcation, the AB gave rise to an artery that ran obliquely distally and medially to join the trunk of the superior medial genicular nerve (SMGN), which runs at the anterior surface of the adductor magnus tendon (AMT) above the adductor tubercle (Fig.5). In three cases, the artery of the SMGN arose from the distal muscular branch of the AB or the central longitudinal artery of the MFC, and in one case, it arose from the saphenous branch. We dissected and distinctly identified this consistent small artery, accompanying the SMGN, in 23 out of 27 (85%) specimens (Fig. 5 and 6). The SMGN and its artery joined on average 64.2 ± 9.7 mm above the knee joint line, traveled together in the same sheath on the adductor magnus tendon, passed just in front of the adductor tubercle and divided into three terminal branches to supply the superior medial aspect of the knee capsule (Fig.6). The point of bony contact of the SMGN before its division (corresponding to the target point for image-

guided genicular nerve blockade or radiofrequency ablation) was located at 44.3 ± 6.2 mm from the femoro-tibial joint line, versus 61.5 ± 5.8 mm for the upper transverse artery ($p<0.001$). The Superior medial genicular artery (SMGA) emerged from the popliteal artery, ran forwards passing between the end of the adductor magnus tendon (AMT) and metaphysis and joined the transverse terminal branch of the SMGN (running at the level of medial epicondyle), but not its trunk. Therefore, the SMGA and the artery of the SMGN were two different arteries.

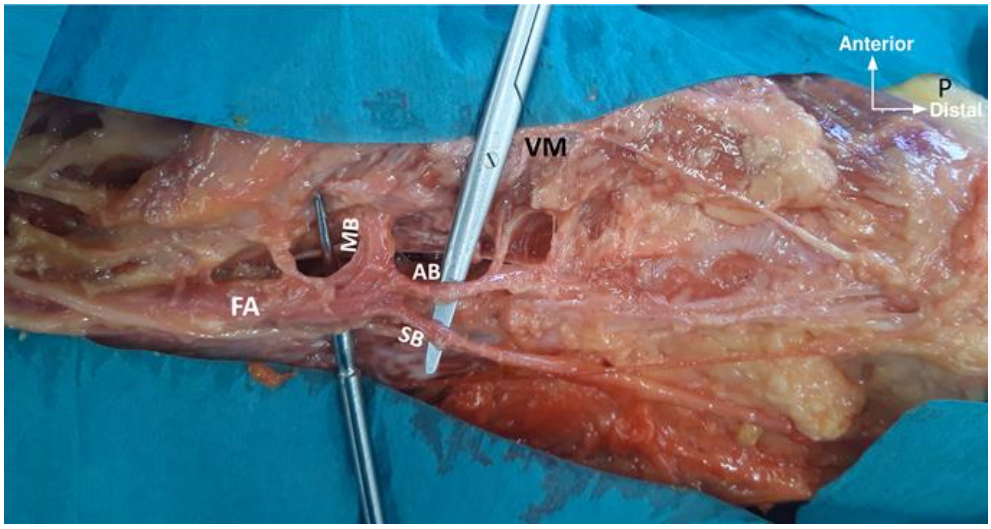

Fig. 3. Type III branching patterns of descending genicular artery (DGA). The muscular branch (MB), Saphenous branch (SB), and the osteo-articular branch (AB) originate separately from femoral artery (FA). VM, vastus medialis muscle; P, patella.

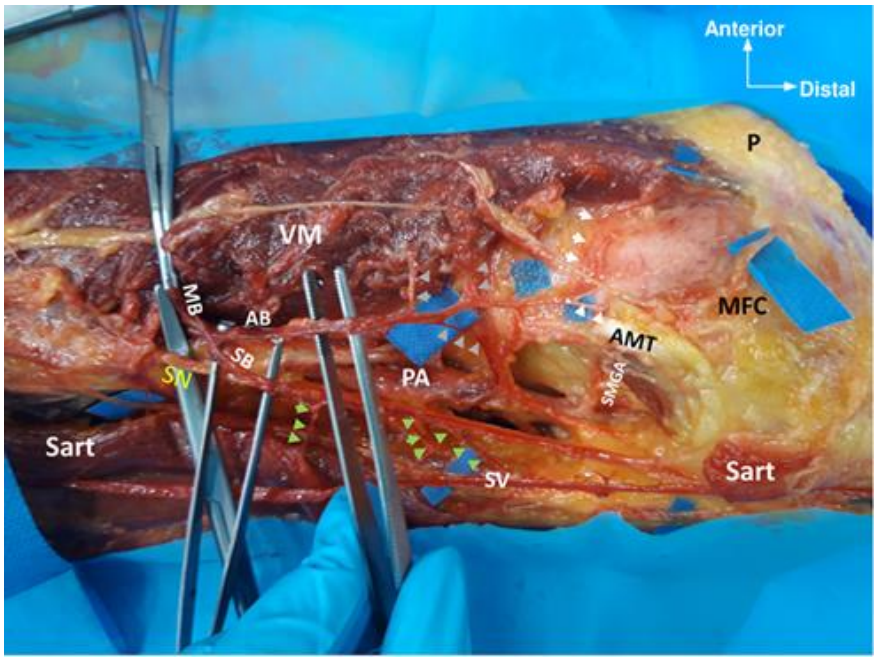

Fig. 4. Distribution of the DGA branches. The osteo-articular branch (AB) gives small anterior (muscular) and posterior (anastomosis with popliteal artery) collateral branches (gray arrowheads) and divides into its two terminal branches (white arrowheads). The saphenous branch (SB) joins the saphenous nerve (SN) and gives several (muscular and cutaneous) perforators (green arrowheads). The muscular branch (MB), strong and short, supplies the vastus medialis muscle (VM). SMGA, superior-medial genicular artery; PA, popliteal artery; Sart, Sartorius muscle; MFC, medial femoral condyle; P, patella; AMT, adductor magnus tendon; SV, great saphenous vein.

The saphenous branch (SB), just after its origin from the DGA, crossed the adductor magnus tendon and descended posteriorly and medially to join the saphenous nerve after its exit from the adductor canal (Fig.2, 4), at about 102.3 ± 13.7 mm from the knee joint line. Both travelled together in the subsartorial

space, from which they exited between the sartorius and the gracilis tendon below the femoral condyle and descended toward the medial aspect of the leg.

Table 2 Morphometric results

Distance measured (in mm)	Mean (SD)	Range
From the origin of DGA to the medial femoro-tibial joint line	130.5 (17.5)	85 - 154
From the origin of DGA to the periosteum of the MFC (maximum length of the pedicle)	96.7 (12.7)	62 - 120
From the origin of DGA to its division	11.2 (8.0)	0 - 40
DGA external diameter	3.7 (1.1)	1.7 – 5.0
From the origin of MB to the VM	14.5 (3.4)	10 - 21
From the origin of SB to medial femoro-tibial joint line	114.8 (13.8)	86 - 150
From the origin of AB to the periosteum of the MFC	79.6 (10.2)	59 - 103
From the origin of AB to its bifurcation	56.4 (11.6)	32 - 80
From the upper transverse artery to femoro-tibial joint line	61.5 (5.8)	53 - 71
Distance from the connexion of SMGN and its artery to the medial femoro-tibial joint line	64.2 (9.7)	44 - 79
Distance from the connexion of IPBSN and its artery to the medial femoro-tibial joint line	36.6 (29.6)	17 - 97
Distance from the connexion of SN and the SB branch of DGA to the medial femoro-tibial joint line	102.3 (13.7)	69 - 125

Data are presented as mean ± standard deviation and range. DGA: Descending genicular artery; MFC: Medial femoral condyle; SB: Saphenous branch; AB: Articular branch; SMGN: Superior-medial genicular nerve; SN: Saphenous nerve; IPBSN: infrapatellar branch of the saphenous nerve; VM: vastus medialis muscle.

During its course, the SB detached muscular perforators for vastus medialis and sartorius muscles, and cutaneous perforators (Fig.4). In addition, we observed that the SB detached a small artery that accompanies the infrapatellar branch of the saphenous nerve (IPBSN) at the inferior-medial quadrant of the knee (Fig.7). The artery of the IPBSN joined its nerve on average 36.6 ± 29.6 mm from the joint line.

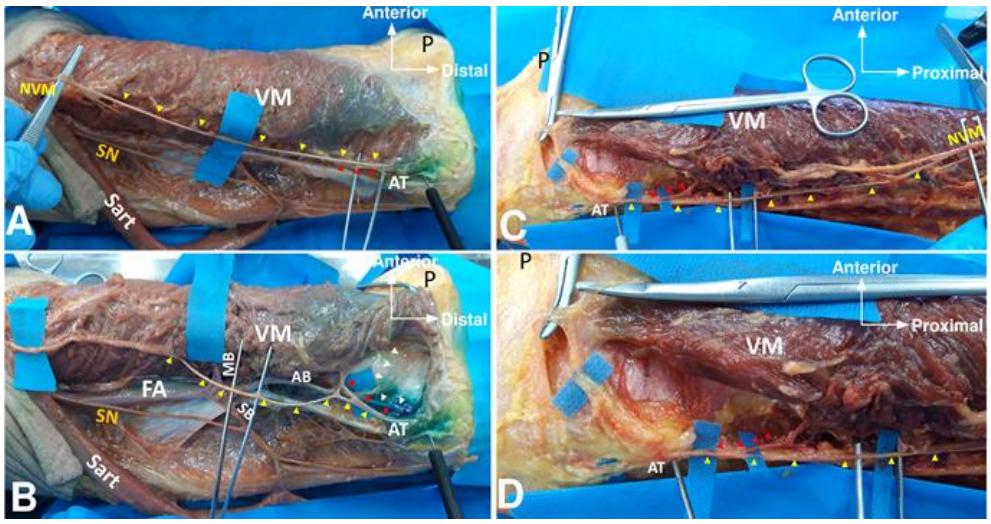

Fig. 5. Descending genicular artery (DGA) and superior medial genicular nerve (SMGN) A and B: The SMGN (yellow arrowheads), branched off the nerve to the vastus medialis (NVM), is joined on the adductor magnus tendon by its artery (red arrowheads) from osteo-articular branch (AB) of the DGA. Note the two terminal branches (white arrowheads) of the AB, which are not accompanied with nerve. C and D: The SMGN (yellow arrowheads) and its artery (red arrowheads) from AB of the DGA, running on the adductor magnus tendon and passing together in front of the adductor tubercle (AT). SB, saphenous branch; FA, femoral artery; SN, saphenous nerve; VM, vastus medialis muscle; Sa, Sartorius; P, patella; AT, adductor tubercle.

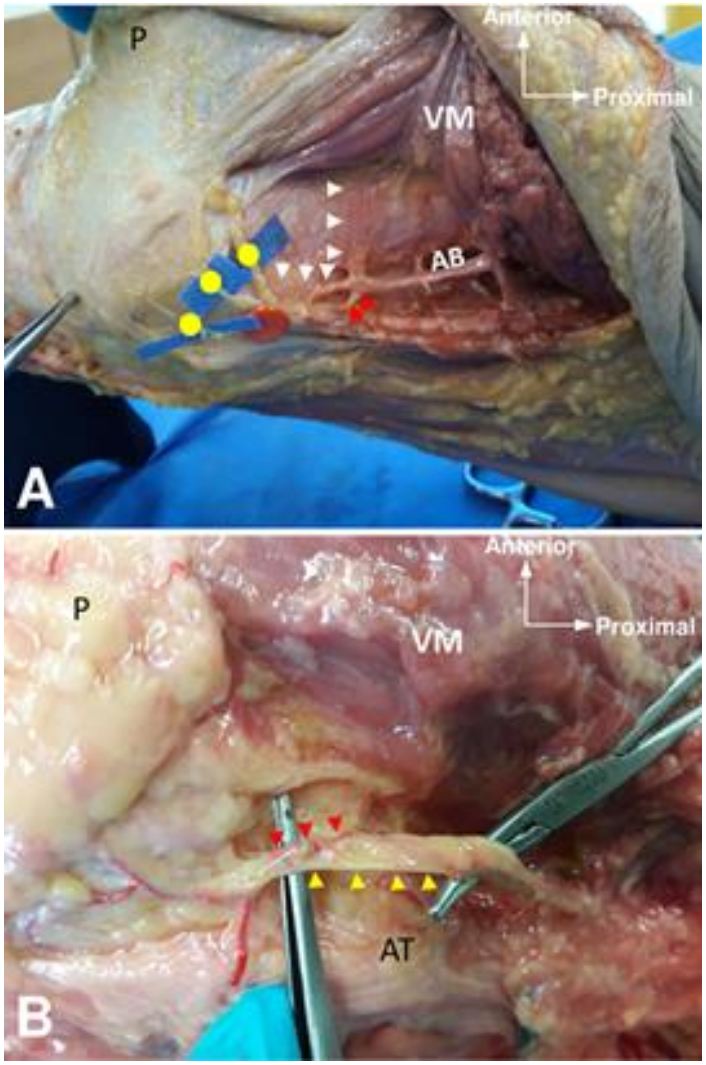

Fig. 6. Artery of the superior medial genicular nerve (SMGN). A: The artery of SMGN (red arrowheads) originates from osteo-articular branch (AB) of the DGA just before its bifurcation (white arrowheads), and pierces the fascia to join the superior-medial genicular nerve (SMGN) on the adductor magnus tendon. Only the distal branches (yellow points) of the SMGN are presented on this figure. B: The SMGN (yellow arrowheads) and its artery (red arrowheads) descending together in the same sheath in front of the adductor tubercle (AT). VM, vastus medialis muscle; P, patella; AT, adductor tubercle.

Potential branches from DGA that could serve as landmarks for the targeting and capture of nerves during ultrasound-guided interventions.

In total, we found DGA branches, accompanying the nerves at the medial aspect of the knee, which could serve as complementary landmarks for precise and specific targeting of those nerves during ultrasound-guided interventions. They include:

- The artery of the SMGN: on the adductor magnus tendon and the adductor tubercle (Fig. 5, 6)
- The saphenous branch of DGA: in the subsartorial space (Fig.1, 4)
- The artery of the IPBSN: at the inferior-medial aspect of the knee joint (Fig.4, 5).

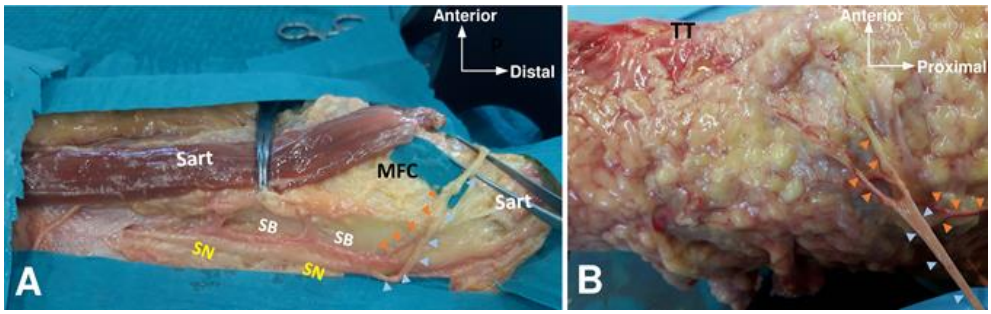

Fig. 7. Saphenous branch of the DGA and artery of the infrapatellar branch of the saphenous nerve (IPBSN). A (medial view of a left knee): The saphenous branch (SB) of the DGA detaches a small artery (orange arrowheads) that joins the IPBSN (blue arrowheads). B (anterior-medial view of a right knee): The IPBSN and its terminal branches (blue arrowheads) run together with the artery and its terminal branches (orange arrowheads) at the inferior-

medial aspect of the knee joint. SN, saphenous nerve; Sart, sartorius muscle; TT, Tibial buberosity; MFC, Medial femoral condyle.

1.2.5 Discussion

This study aimed to investigate the anatomy of the DGA and its branches. It highlights another potentially relevant clinical application of the anatomical study of DGA, serving as complementary landmarks to improve the capture of the targeted nerves during ultrasound-guided regional anesthesia and pain relief interventions. We found three constant arteries running at the medial side of the knee in close proximity to the nerves that are the primary targets for the above-mentioned clinical interventions: the artery of the SMGN, the saphenous branch of the DGA, and the artery of the IPBSN.

The distribution pattern of the DGA and the various distances were consistent with the literature, summarized in a recent exhaustive systematic review and meta-analysis [109], although we did not observe the type IIa pattern. We also observed an additional subtype of type I pattern where the osteo-articular branch occurs first from the common trunk, leaving behind a sapheno-muscular trunk. The classification of Dubois et al. [114] is the most frequently used because it provides a logical and clinically relevant tool to analyze the varieties of the DGA branching pattern, regarding their application in medial femoral condyle flaps. However, while the three main groups follow this logic, from the best branching pattern (type I allowing bone, muscle and skin flap with a long pedicle) to the most challenging (type III) and from the most to the least frequent (I to III), it is not the case in the subgroups (a, b, c). For instance, the subtype IIc appeared more frequent and has a clinically better branching pattern than subtype IIa. Logically, the subtype IIc should have been the most

challenging in the group II, which is not actually the case. Based on our study and literature review, we propose a slight modification of the scheduling of the subgroups to improve consistency and gradation in this sound classification, thus improving its clinical relevance (Table 3, Fig. 8).

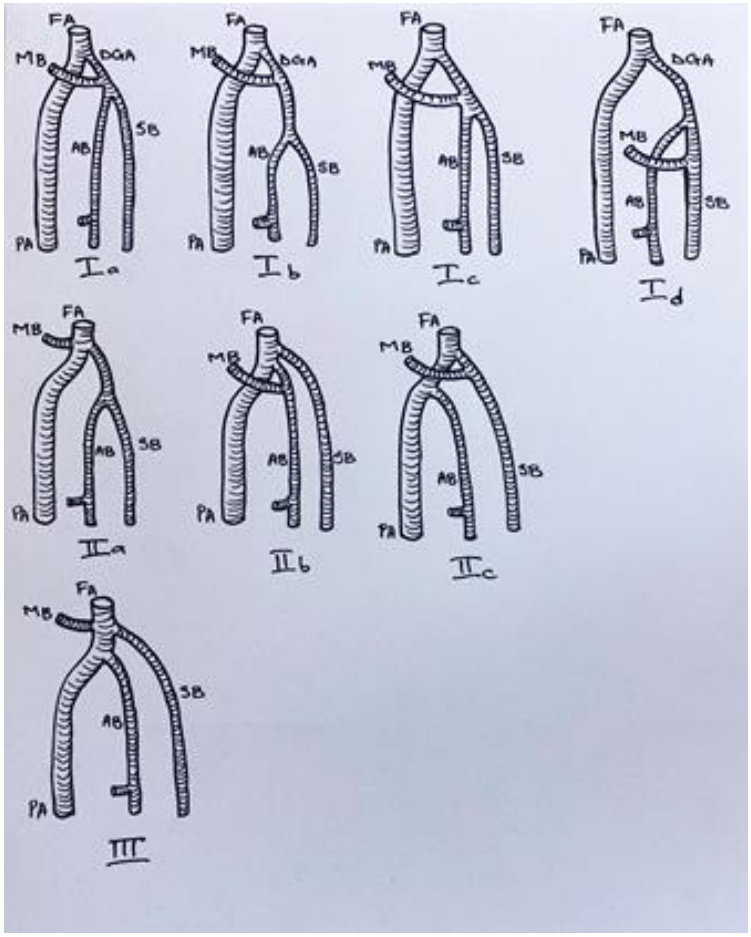

Fig. 8. Diagram of distribution of the DGA according to the proposed revision of the Dubois et al. classification. FA, femoral artery; DGA, descending genicular artery; MB, muscular branch; AB, osteo-articular branch; SB, saphenous branch; PA, popliteal artery.

For 10 years now, the SMGN has been one of the targeted nerves in genicular nerve blockade and radiofrequency ablation (RFA). However, controversies persist about the anatomical landmarks for accurate capture of this nerve, since the volume of a radiofrequency lesion is very limited. As an illustration, two recent anatomical studies on accuracy of ultrasound-guided RFA described two different landmarks for SMGN [12, 115], which keeps confusion among pain physicians.

Table 3. Proposal for a slight modification of the Dubois et al classification

Branching pattern	Description
Type I.	The three branches emerge from a common trunk: the DGA
Ia	The DGA divides into the three terminal branches
Ib	The MB occurs first, leaving behind a sapheno-articular trunk
Ic	The SB occurs first, and leaving behind a musculo-articular trunk
Id	The AB occurs first, leaving behind a sapheno-muscular trunk
Type II	One of the three branches arises directly from the femoral artery
IIa	The MB originates directly from the FA
IIb	The SB originates directly from the FA
IIc	The AB arises directly from the FA
Type III	The three branches (SB, AB and MB) arise separately from the femoral artery

DGA: Descending genicular artery; MB: Muscular branch; SB: Saphenous branch; AB: Articular branch; FA: Femoral artery

Earlier authors described the SMGN running alongside the superior-medial genicular artery (branch of the popliteal artery) at the junction between the medial femoral condyle and diaphysis [10, 21]. This anatomical basis for RFA

technique has been used until now. A few recent anatomical studies suggested that the SMGN runs rather with the DGA, without further precision [16, 101]. To our knowledge, this is the first anatomical description and illustration of this specific artery accompanying the SMGN. Moreover, this study demonstrates that the vessels running at "the medial junction between epiphysis and diaphysis" correspond to the upper transverse artery of the medial condyle (transverse branch of the osteo-articular branch from the DGA), instead of the superior-medial genicular artery. Neither the trunk nor a branch of the SMGN were found alongside that upper transverse artery. The superior-medial genicular artery emerged from the popliteal artery and was found distally, at the level of the femoral epicondyle, running alongside the transverse terminal branch of the SMGN (Fig. 9). Thus, during ultrasound-guided RFA, a lesion performed at "the midpoint of the medial junction between epiphysis and diaphysis" [115], therefore corresponding to the upper transverse arterial flow (and not the SMGA flow), would likely capture the upper transverse artery of the medial condyle but no nerve. A lesion performed distally at the level of the medial epicondyle, following the flow of the superior-medial genicular artery, would capture only the transverse branch of the SMGN. A lesion performed just in front or above the AT, targeting the flow of the artery of the SMGN which descends on the anterior side of the adductor magnus tendon, would capture the trunk of the SMGN, leading to inhibition of all its terminal branches. This seems to be the best target to capture the trunk of the SMGN, thus ablating all its terminal branches. Although Yasar et al. [12] anatomical description of the origin and course of the SMGN and its artery was not consistent with our findings, their proposed landmark for the SMGN during ultrasound-guided procedure appears relevant.

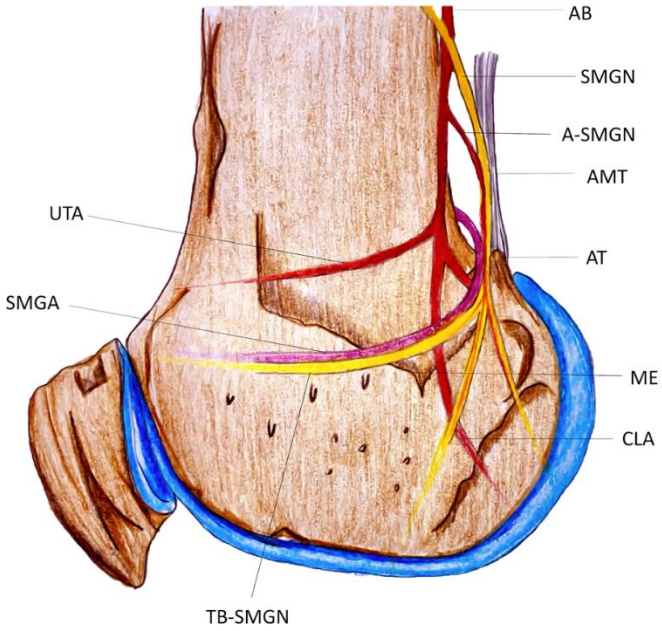

Fig. 9. Diagram of the anatomical relationships of SMGN and its terminal branches to the arteries at the superior medial aspect of the knee. The artery of the SMGN (A-SMGN) is detached from the trunk of the osteo-articular branch (AB) of the descending genicular artery, and descends with the SMGN on the adductor magnus tendon (AMT). The superior-medial genicular artery (from popliteal artery), runs alongside the transverse terminal branch of the SMGN (TB-SMGN) at the level of medial epicondyle. The upper transverse artery (UTA) runs at junction of medial femoral epiphysis and diaphysis, without a nerve branch. SMGN, superior-medial genicular nerve; AT, adductor tubercle; ME, medial femoral epicondyle; CLA, central longitudinal artery.

The IPBSN plays an important role in the innervation of inferior-medial aspect of the knee, including the joint capsule, skin and subcutaneous tissue [101, 103, 116]. It is a very thin branch whose elective ablation is challenging and requires special skills. Despite the thinness of the nerve, some studies have shown that experienced radiologists could identify the course of the nerve with high

resolution sonography and real-time imaging, in the subsartorial canal [20, 116]. However, since GNB and RFA techniques are assumed to be performed by pain physicians in real-life practice, complementary landmarks such as the artery that accompanies the IPBSN may be relevant to improve targeting of this nerve. In addition, the above-mentioned studies noted the difficulty to assess the nerve at the inferior medial aspect of the knee due to its small size and the hyperechoic subcutaneous fat [116]. However, in order to be safe, RFA of the IPBSN should not be performed in the subsartorial region but rather distally at the level of the knee. Tracing the blood flow that follows a trajectory similar to the subcutaneous arc-like theoretical course of the IPBSN at the inferior-medial aspect of the knee could improve its capture during ultrasound-guided RFA.

This study has some limitations. First, a larger sample size would have made it possible to identify more branching patterns and anatomical variations of the DGA. Secondly, since the small size of the arteries is an issue in clinical practice, our findings does not necessary imply that these arteries running alongside the genicular nerves would be clearly differentiated during US-guided interventions. However, this study shows that targeting the vessels running transversally at the junction of the epiphysis and the diaphysis, as it is commonly done in clinical practice, would not capture the SMGN. This is a sure and relevant clinical implication of these findings, as it reinforces the need to revise the current targets. Moreover, the arteries described in this study could be clinically useful in improving the target for genicular arteries embolization for medial knee pain [117]. A proof-of-concept study is required to evaluate the feasibility and the ablation success rate for SMGN and IPBSN based on the anatomical course of their respective arteries described in this study. Further

clinical studies are also expected to assess the effectiveness of these anatomical findings on the treatment of chronic knee pain.

CONCLUSION

The descending genicular artery supplies three distal branches that run alongside the nerves at the medial side of the knee: the artery of the SMGN, the artery of the IPBSN and the saphenous branch of the DGA. According to this anatomical description, these arteries may constitute complementary landmarks for accurate capture of the corresponding nerves during ultrasound-guided interventions for regional anesthesia and pain control.

ACKNOWLEDGEMENTS

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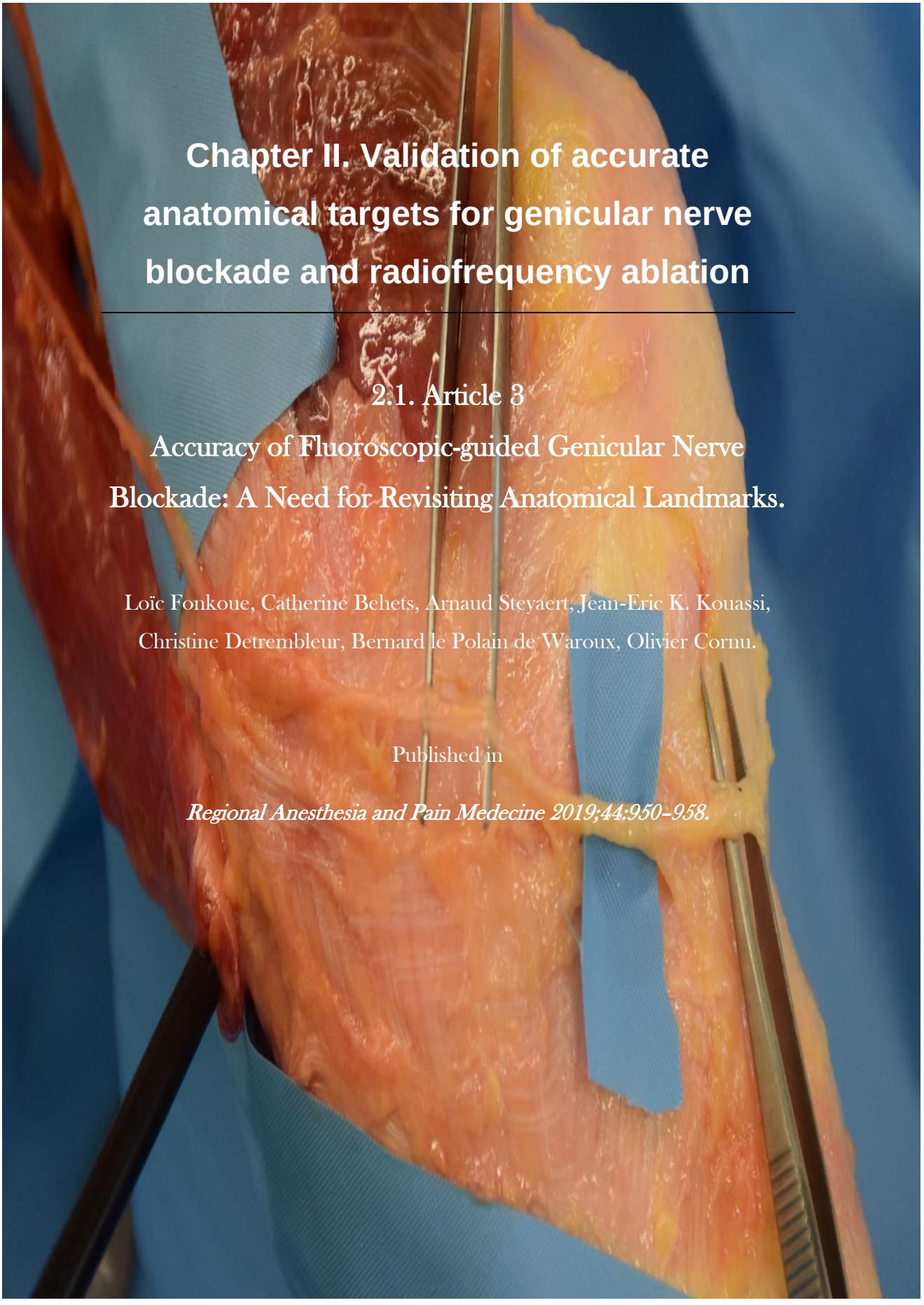

Chapter II. Validation of accurate anatomical targets for genicular nerve blockade and radiofrequency ablation

2.1. Article 3

Accuracy of Fluoroscopic-guided Genicular Nerve Blockade: A Need for Revisiting Anatomical Landmarks.

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2.1.1 Abstract

Background and Objectives: Genicular nerve blockade (GNB) and radiofrequency ablation (RFA) have recently emerged as treatment options for patients with chronic knee pain. However, an increasing number of anatomical studies and systematic reviews concluded that the anatomical basis for needle placement was unclear, incomplete and somewhat inaccurate. This study was designed to assess the accuracy of updated anatomical landmarks for fluoroscopy-guided blockade of the consistent genicular nerves in a cadaveric model.

Methods: Based on a comprehensive review of recent anatomical studies and prior dissection of 21 fresh cadaver knees, we defined bony landmarks with high likelihood of successful ablation of the five consistent genicular nerves (GN). We tested the accuracy of genicular nerve blocks using the above-stated anatomical landmarks in 10 intact fresh cadaveric knees. Needle placement was guided by fluoroscopy and 0.5 ml of 0.1% methylene blue was injected at the site of each nerve. The knees were subsequently dissected to assess the accuracy of the injections. If the nerve was dyed with blue ink, the placement was considered accurate.

Results: The accuracy of our injections was 100% for the superior medial genicular nerve, inferior medial GN, infrapatellar branch of saphenous nerve, and recurrent fibular nerve. The superior lateral GN was dyed in 90% of specimens.

Conclusion: This study provides physicians with precise anatomical landmarks for the five consistent GN for fluoroscopic-guided GNB. Our

revised technique, which targets more nerves with increased accuracy, could potentially lead to improved therapeutic benefits on chronic knee pain.

2.1.2 Introduction

Chronic knee pain conditions are very frequent in elderly, mainly due to osteoarthritis (OA). Their treatment remains a great challenge among medical practitioners. Conservative therapies have shown limited efficacy regarding long-term results [118]. While total knee arthroplasty (TKA) remains the gold standard treatment for advanced stages knee OA, up to 44% of patients report persistent pain after TKA, with 15% suffering from extremely severe pain [8, 119].

Genicular nerve block (GNB) and radiofrequency ablation (RFA) have recently emerged as novel alternatives in the treatment of chronic knee pain [10, 12, 120]. These methods are based on the principle that interrupting sensory nerve fibers to a painful structure may alleviate pain and restore function. Their targets are sensory nerves which lie on the periosteum before entering the knee joint capsule and can easily be located using bony landmarks under fluoroscopic guidance [10, 13, 23]. The success of GNB and RFA depends on the target nerve being included within the anaesthetized or thermocoagulated tissue volume [23]. It requires precise localization of the articular branches innervating the knee joint capsule, given the limited size of RFA lesions. The majority of the clinical studies involve fluoroscopic-guided RFA [4, 24, 57, 64, 75, 121] following Choi's et al [10] original landmarks, even though recent anatomical studies have shown that their anatomic foundations were somewhat inaccurate or incomplete [12, 16, 17, 20, 23, 88]. This may explain the variable results of these studies in terms of intensity and duration of the pain relief. Optimizing the effectiveness of the technique relies on lesioning more genicular nerves, in an accurate and safe manner [16].

To achieve this aim, a comprehensive review of recent anatomical studies [12, 16, 17, 20, 23, 88, 91, 100] and subsequent anatomical dissection of 21 fresh cadaveric knees allowed us to identify five consistent and easily targetable articular branches innervating the knee joint capsule: the superior medial, superior lateral, inferior medial genicular nerves, the recurrent fibular nerve and the infrapatellar branch of the saphenous nerve. Their precise clinical and radiological landmarks with high likelihood of ablation success were refined. This experimental study sought to assess the accuracy of these new anatomical landmarks for fluoroscopic-guided genicular nerve blockade in cadaveric models, and define a potentially more effective treatment approach targeting more genicular nerves than Choi et al [10]. To our knowledge, no previous cadaveric study assessing the accuracy of needle placement under fluoroscopic guidance for GNB/RFA is found in the literature.

2.1.3 Methods

This study was conducted at the laboratories of anatomy and experimental surgery of the Université catholique de Louvain. It followed the anatomical dissection of 21 cadaver knees by the same investigators, who intended to determine different patterns of sensory innervation of the knee, select consistently targetable genicular nerves and determine their anatomical landmarks for therapeutic purpose [122]. Here, we tested the accuracy of the revisited anatomical landmarks for genicular nerve blockade in 10 knees (5 left and 5 right) with physical integrity, from 10 fresh cadavers, by injecting 0.5 ml of methylene blue after fluoroscopy-assisted needle placement, as it would customarily be done in a pain clinic. The cadavers, five male and five female,

aged 89.6 ± 5.8 years, with no history of surgery or major procedure in their knees, were donated to the laboratory of anatomy in accordance with Belgium law and regulations. Ethics approval was received from the Research Ethic Board for health sciences of the Université Catholique de Louvain.

Injection procedure

The knees were injected by an experienced physician who specializes in local infiltrations techniques in our institution, following the procedures and the revisited anatomical landmarks described below. Each injection was performed after the correct needle placement targeting specific anatomical landmark under fluoroscopic guidance, as it would be done for genicular nerve blockade. We targeted five articular nerves supplying the knee joint capsule, whose anatomical landmarks around the knee were found to be consistent.

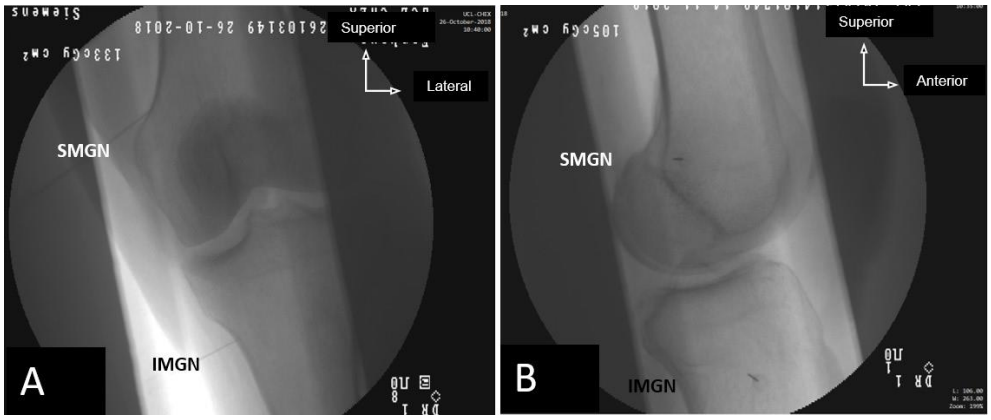

Figure 1 Fluoroscopic images of the final needle position for the injection of the SMGN and the IMGN: (A) anterior-posterior view and (B) lateral view. IMGN, inferior medial genicular nerve; SMGN, superior medial genicular nerve.

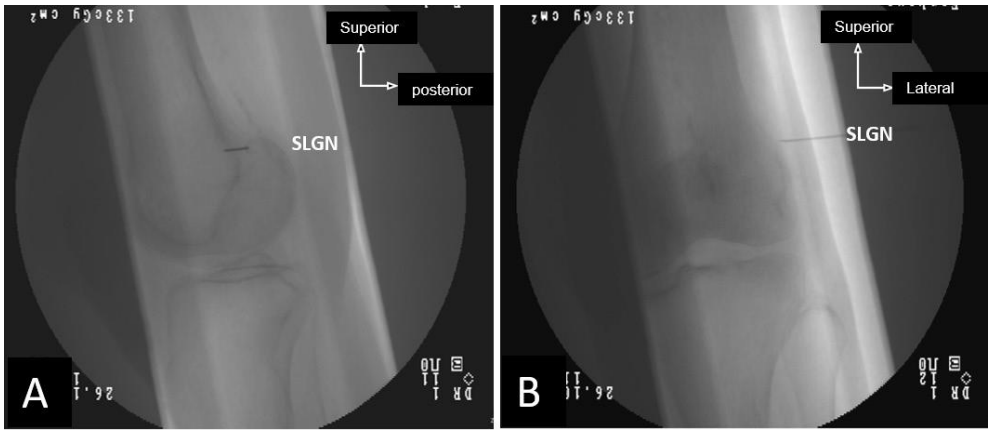

Figure 2 Fluoroscopic images of the final needle position for the injection of the SLGN. (A) Lateral view and (B) anterior-posterior view. SLGN, superior lateral genicular nerve.

The superior medial genicular nerve (SMGN) - Under fluoroscopic guidance, in supine position with the knee in extension, a 22-gauge needle was inserted toward the area just anterior to the adductor tubercle. On the anterior-posterior (A-P) view, the needle tip was advanced to the superior edge of the medial femoral condyle until it touched the bone (Fig. 1A). Then the C-arm was rotated to have a true lateral view of the knee with alignment of the two femoral condyles. The needle position was then readjusted to fit just anterior to the junction between medial condyle and posterior femoral cortex (Fig. 1B), but not at the middle of the femoral shaft like currently done in clinical practice [4, 10, 24, 64]. After verification of correct placement of the needle tip, 0.5 ml of 0.1% methylene blue was injected and the needle was removed.

The inferior medial genicular nerve (IMGN) – The needle placement location for the IMGN was like currently done in clinical practice [10].

The superior lateral genicular nerve (SLGN) - In supine position with the knee in extension, the C-arm was positioned to have a true lateral view. The

needle was inserted toward the target area located at the junction between superior edge of the lateral femoral condyle and the posterior femoral cortex, until the tip touched the bone (Fig. 2A). Then, the needle was withdrawn for about 2 mm. No readjustment was needed in A-P view; this point corresponds to the upper edge of the lateral condyle height (Fig 2B). Injection of 0.5 ml of 0.1% methylene blue was performed and the needle was removed.

The recurrent fibular nerve (RFN) - In the supine position with the leg in full extension, we first identified the Gerdy's tubercle and the tibial tuberosity by simple palpation. A longitudinal line was drawn below the Gerdy's tubercle and the target point was located on this line, 1 cm below the inferior edge of the tubercle (Fig. 3A). The needle was inserted at this point and advanced until the tip touched the bone. We performed the injection of 0.5 ml of 0.1% methylene blue with the needle tip still in contact with the bone, before removal of the needle.

The infra-patellar branch of saphenous nerve (IPBSN) - A target line was adapted from Hu's description [91], slightly modified according to our prior cadaveric dissections. We drew a transversal line passing by the apex patellae and another one passing by the top of the tibial tuberosity. Four centimeters medially to the apex patellae tip, we drew a longitudinal line connecting the two transversal lines (Fig. 3B). This longitudinal line corresponds to the targeted treatment line found to contain 95% of nerve branches in our prior cadaveric dissection of 21 specimens, rather than 85% for Hu's line [91]. We injected 1.0 ml of 0.1% methylene blue deeply under the subcutaneous tissue, throughout this target longitudinal line.

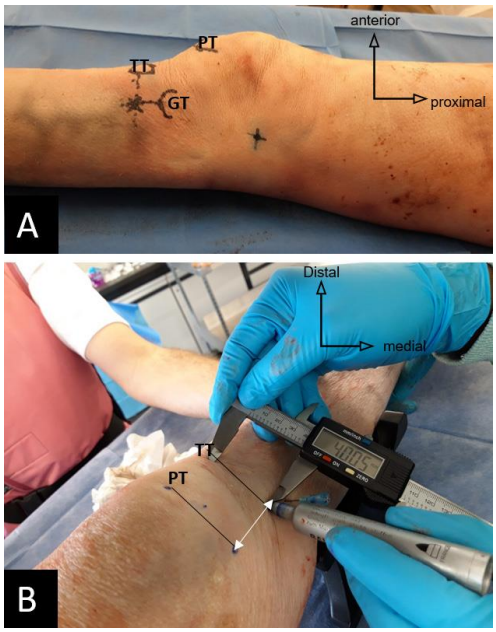

Figure 3 (A) Anatomical landmarks for the RFN. (B) Treatment line for the IPBSN (white double arrow). GT, Gerdy's tubercle; IPBSN, infrapatellar branch of saphenous nerve; P, patella; PT patellar tip (or apex patellae); TT, tibial tuberosity; RFN, recurrent fibular nerve

Assessment

After completion of all the injections in the 10 specimens, the limbs were dissected to evaluate the accuracy of the injections, based on location of the blue ink in the tissues. The dissections were performed by experienced anatomists and consultant orthopedic surgeon with more than eight years of experience in cadaveric dissection, who also conducted previous cadaveric study on the knee nerve supply. Each injection was considered accurate only if the nerve was dyed with the blue color during dissection. All other locations were considered inaccurate. We also looked for the safety of the injections. Injection was considered safe if no major nerve trunk (sciatic, tibial, common fibular or saphenous nerves) or major vessels were found dyed during dissection. The results were compiled for the analysis of the accuracy and the safety of the injections with these revised anatomical landmarks.

2.1.4 Results

The post-injection cadaveric dissections revealed that 100% of the needle placement for the SMGN, IMGN, RFN, IBPSN, and 90% for the SLGN were accurate. Concerning the safety, no major nerve trunk or major vessel was found dyed with blue ink during dissection.

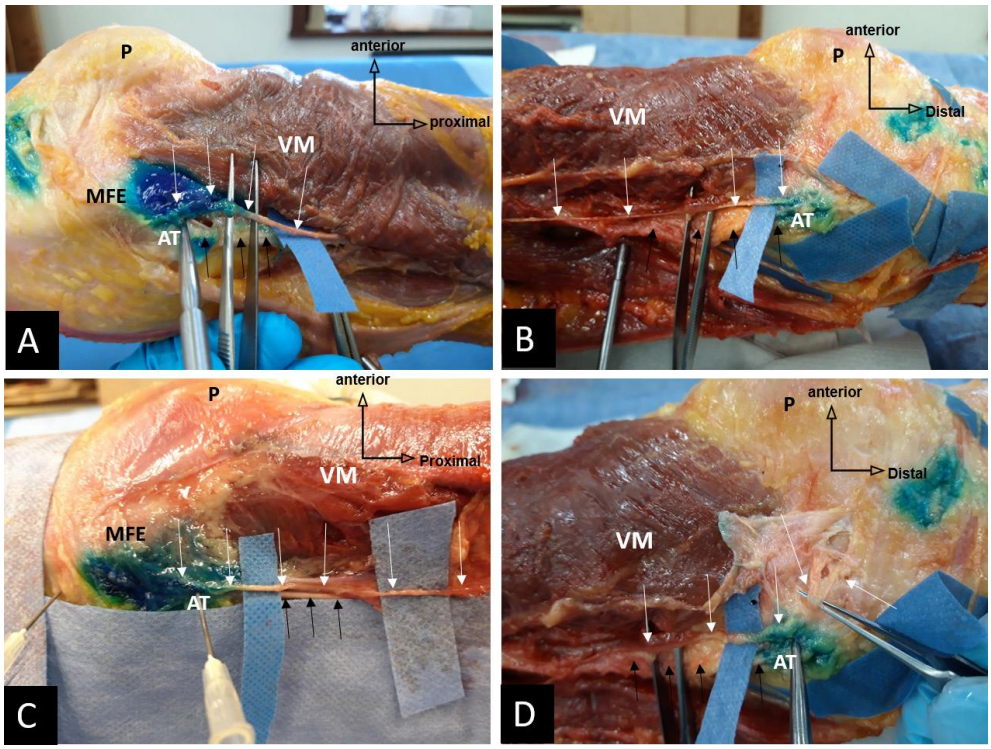

Figure 4 Postinjection anatomical dissection, showing the superior medial genicular nerve (white arrows) in various specimens, running on the adductor Magnus tendon (black arrows), dyed with blue around the AT. See the nerve passing just in front of the AT in all the specimens and accurately targeted. AT, adductor tubercle; MFE, medial femoral epicondyle; P, patella; VM, vastus medialis muscle.

In the 10 specimens, the SMGN was found, dyed with blue, in front of the adductor tubercle (AT) (Fig. 4). It was clearly a direct articular branch from the nerve to the vastus medialis in all the specimens, descending in a tunnel through the fascia of the vastus medialis muscle, then running on the adductor magnus tendon toward the AT. Blue coloring agent was spread 1 to 2 cm around the AT, and no nerve trunk (motor branches of the nerve to vastus medialis, saphenous nerve) was dyed.

The IMGN was found dyed with blue in all the specimens, beneath the deep surface of the medial collateral ligament (MCL) of the knee, running toward the inferior-medial quadrant of the anterior knee joint capsule, accompanied with inferior medial genicular vessels (Fig.5). The blue ink was spread under the MCL and no other structure was found dyed.

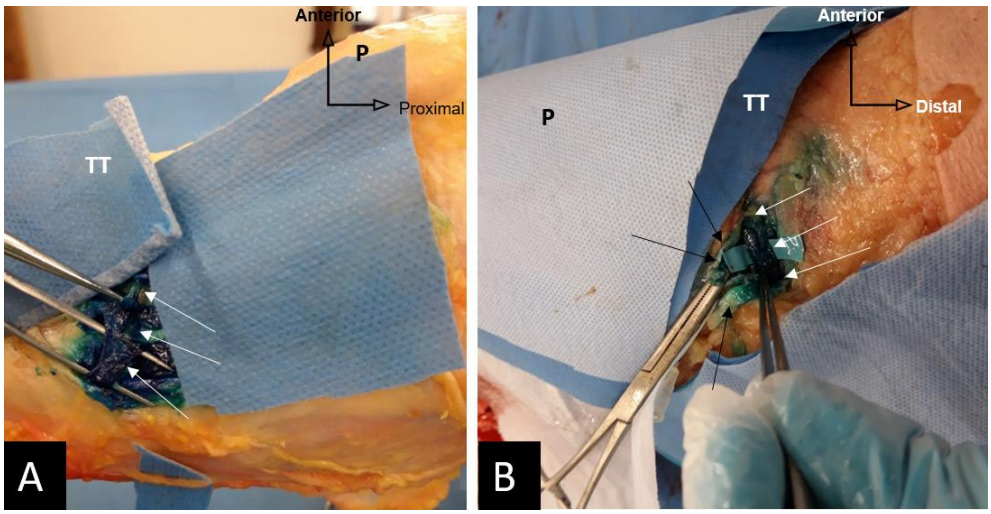

Figure 5 Postinjection anatomical dissection, inferior medial genicular nerve (white arrows) in the bundle with inferior medial genicular artery, dyed in blue, running beneath the medial collateral ligament of the knee (black arrows). (A) Anterior-medial view of a right knee. (B) Anterior-medial view of a left knee. P, patella; TT, tibial tuberosity.

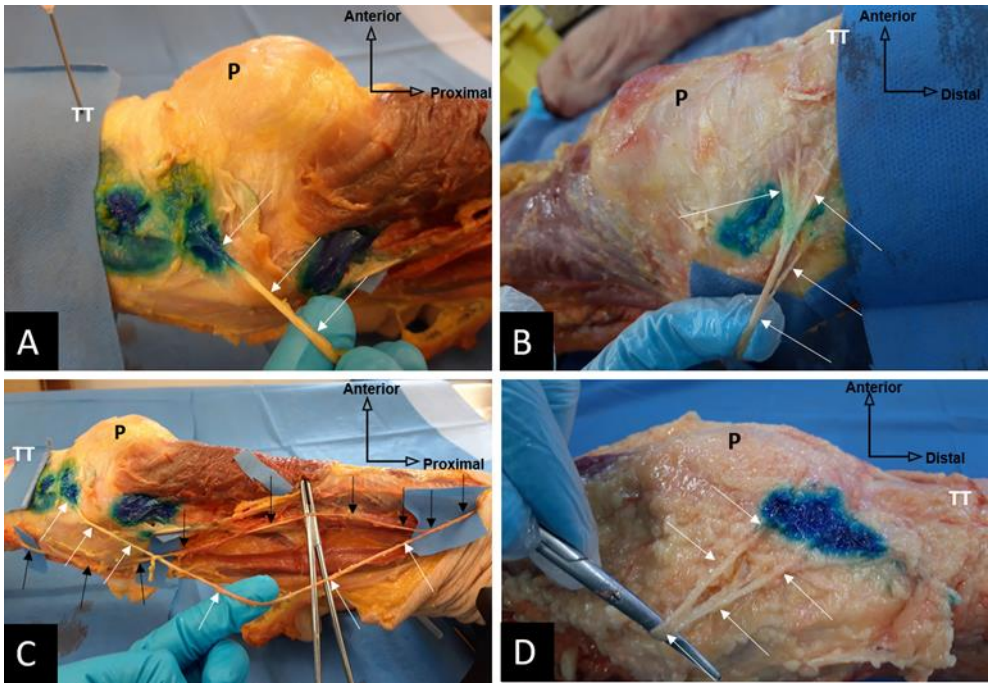

Figure 6 Postinjection anatomical dissection, IPBSN (white arrows) dyed in blue on the treatment line in all the specimens, supplying the inferior medial quadrant of the knee. (A) Anterior-medial view of a right knee, IPBSN crossing the treatment line. (B) Anterior-medial view of a left knee, terminal branches of the IPBSN penetrating the knee capsule, dyed with blue. (C) Anatomical variation of the origin of the IPBSN (white arrows) detached from saphenous nerve (black arrows) proximally above the adductor canal (vasto-adductor membrane removed), but the distal course at the level of the knee remains consistent and crosses the treatment line. (D) Bifurcation of IPBSN, all the branches are included in the tissue volume dyed with blue ink. IPBSN, infrapatellar branch of the saphenous nerve; P, patella; TT, tibial tuberosity.

The IPBSN crossed the treatment line in all the 10 specimens, regardless of the level where it detached from the saphenous nerve (Fig. 6). In three of the 10 cases, we found the IPBSN originating proximally, above the adductor canal

and then, running outside it (Fig.6-C). However, despite this anatomical variation in their proximal trajectory, their distal portion still crossed the treatment line, so was dyed with blue ink.

The distal portion of the RFN was dyed with blue in all the specimens, just before it reached the inferior lateral aspect of the anterior knee joint capsule (Fig. 7). This nerve originated from the common fibular nerve and joined the anterior tibial recurrent artery; they ascended together on the periosteum towards the knee joint, passing below the Gerdy's tubercle. Blue ink was localized at the deep surface of the initial fibers of anterior tibial muscle, just below the Gerdy's tubercle. The common fibular nerve was 4 to 5 cm far away from the colored tissue area, and none of the 10 CFN was dyed with blue ink (Fig. 7).

The SLGN was dyed with blue color in 9 of the 10 specimens (Fig. 8). It originated from the sciatic nerve in all the specimens, ran under the deep surface of the biceps femoris muscle toward area connecting the lateral femoral condyle and the posterior edge of the lateral side of femoral shaft, and then divided into two endings branches: a transversal branch running forward to the lateral retinaculum (lateral retinacular nerve) and a longitudinal branch descending towards the femoro-tibial (FT) space. The blue ink was localized to this area, dying the SLGN just before its bifurcation. No major nerve trunk (CFN, Tibial nerve) was found dyed during dissection. In one of the 10 specimens, the bifurcation of the SLGN was higher, and none of the 2 branches of the nerve was dyed.

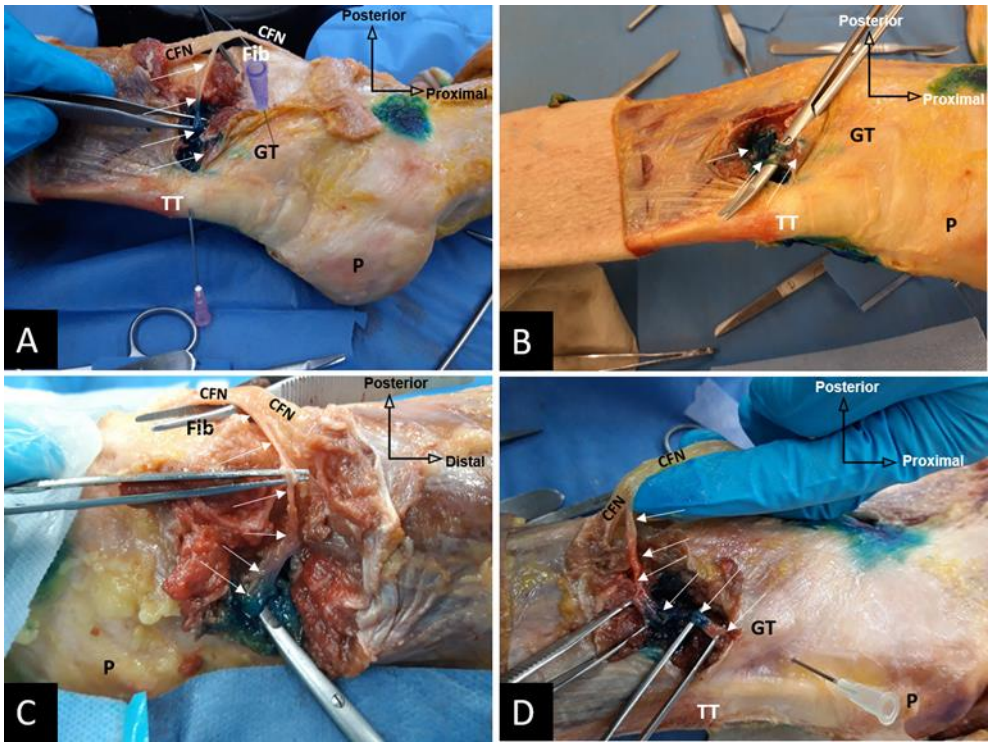

Figure 7 Postinjection anatomical dissection. RFN (white arrows) originating from CFN, joining the anterior tibial recurrent artery at the deep surface of the muscles, and ascending together on the periosteum to supply the inferior lateral quadrant of the knee. (A–D) RFN dyed in blue by deep injection below the GT in various specimens; note the integrity of CFN, which is far away from the colored tissue volume. CFN, common fibular nerve; Fib, fibula head; GT, Gerdy's tubercle; P, patella; RFN, recurrent fibular nerve.

2.1.5 Discussion

To the best of our knowledge, this is the first study specifically designed to assess the accuracy of anatomical landmarks for fluoroscopic-guided genicular nerve block in a cadaveric model. It is based on the anatomical updated data

regarding the innervation of the knee joint, which warrants revisiting the widely used technique for fluoroscopic-guided genicular denervation of Choi et al [10]. A recent review concluded that the anatomical basis for radiofrequency cannula placement was unclear [14] and most of the studies describe lesioning of only three nerves (SMGN, SLGN and IMGN). This cadaveric study found that our updated anatomical landmarks for the five consistent articular nerves supplying the knee capsule (SMGN, IMGN, SLGN, RFN, and IPBSN) are accurate, safe and reproducible. To optimize the therapeutic effect of the GNB, we suggest the five-sites denervation technique provided in this study.

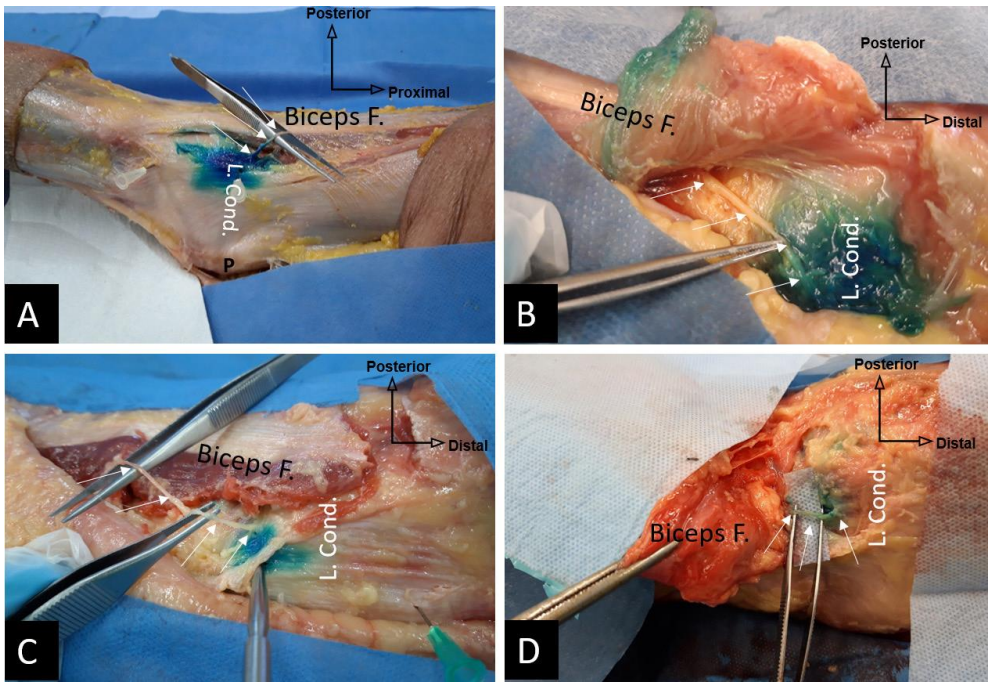

Figure 8 Postinjection anatomical dissection. SLGN (white arrows) from sciatic nerve, descending in an oblique trajectory at the deep surface of the biceps femoris muscle (Biceps F.), toward the area connecting the posterior cortex of the lateral side of the femur shaft and

the lateral condyle, before distributing to the superior lateral quadrant of the knee capsule. (A) Posterior-superior-lateral view of a right knee, biceps femoris just retracted. (B–D) Posterior-superior-lateral views of various left knees, biceps femoris sectioned and reflected to highlight the SLGN (white arrows). L. Cond. Lateral condyle; Biceps F., biceps femoris; P, patella; SLGN, superior lateral genicular nerve.

There is a lack of consensus concerning the origin and the landmarks of the SMGN. In all our specimens, it was a branch from the nerve to vastus medialis and not from tibial nerve like previously suggested by Choi et al [10]. Tran et al [16] suggested that it is a branch of femoral nerve, but when looking carefully at the Fig 4C they provided to illustrate this statement, the SMGN is detached from NVM. In the classic fluoroscopic-guided RFA procedure, the SMGN site is located at the confluence of the medial femoral shaft and the medial femoral condyle in the A-P view; and at the midpoint of the femoral shaft width in the lateral view [4, 10, 64]. We found this landmark inaccurate. Surprisingly, there is a huge discrepancy between anatomical descriptions of the SMGN located by almost all the authors at the adductor tubercle [12, 16, 17, 88], and the targeted point during fluoroscopic-guided RFA. In fact, in the lateral plane radiographic image, the AT is projected at the posterior edge of the area connecting the shaft of the femur and medial condyle. The SMGN should thus be targeted just few millimeters anterior to the AT, and not at the midpoint of the femur shaft width (Fig. 9). In our study, the injection performed just anterior to the adductor tubercle provided 100 % accuracy on the SMGN.

The classical landmark for the SLGN during RFA procedure is located at the confluence of the femoral shaft and the lateral femoral condyle in the A-P view; and the midpoint of the femur A-P width in the lateral view [4, 10, 23]. We

found this landmark somewhat inappropriate (Fig. 9). In this study, on the true lateral view, the injection performed in the area connecting the posterior cortex of the femur shaft and the superior edge of the lateral condyle provided a 90 % success rate on the SLGN. At this level, the needle should not be advanced too far, behind the femur, to avoid spreading to the CFN. We found that the classical landmark corresponds to the trajectory of superior lateral genicular artery (SLGA), which was inconsistently joined by the transversal division from the SLGN (the lateral retinacular nerve) contrary to Sutaria et al [100] who found the LRN and SLGA running together in all their specimens. Our landmarks allows us to capture the SLGN before or just at the level of its bifurcation so that all the endings branches were treated in 90% of specimens. Some authors suggested to target the articular branch from the NVL [23], but we found that the higher variability of the distal distribution of the NVL does not allow its precise localization for RFA.

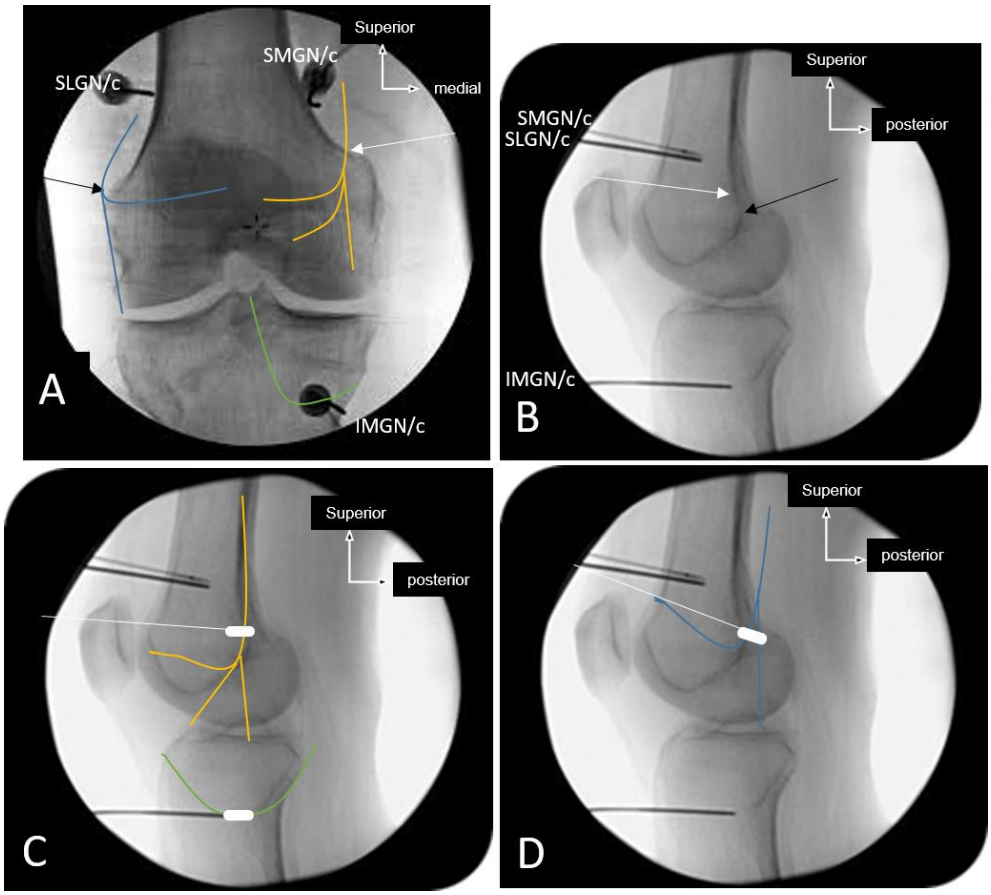

Figure 9 Differences between classical landmarks (SLGN/c, SMGN/c, and IMGN/c) and our proposed landmarks for fluoroscopic-guided GNB and RFA; the trajectory of the SLGN (blue) from sciatic nerve, SMGN (yellow) from nerve to vastus medialis and IMGN (green) from posterior articular nerve (branch of the sciatic nerve) have been drawn on classical fluoroscopic images. (A) A-P view and (B) lateral view. Classical fluoroscopic image of the final needle position during GNB/RFA. Note the important differences with our proposed treatment targets areas for the SMGN (white arrow) and SLGN (black arrow) on the A-P and lateral views. (C) Trajectory of the SMGN (yellow) and IMGN (green) intercepted by the active tip of the electrodes with our new positioning (white). Note that the classical electrode position (upper black electrode) could clearly not intercept the trajectory of SMGN. (D) SLGN trajectory (blue) intercepted by the active tip of the electrode with our new positioning (white). Note that the

classical electrode position (upper black electrode) could clearly not intercept the trajectory of SLGN. A-P, anterior-posterior; GNB, genicular nerve block; IMGN, inferiormedial genicular nerve; IPBSN, infrapatellar branch of saphenous nerve; RFA, radiofrequency ablation; RFN, recurrent fibular nerve; SLGN, superior lateral genicular nerve; SMGN, superiormedial genicular nerve.

This study is the first to describe a new approach for safe targeting of the RFN without lesioning of the CFN. The RFN plays an important role in sensory innervation of the inferior-lateral quadrant of the knee [16, 20, 23]. However, all the authors have excluded it as a potential target for ablation therapy, due to its close proximity to the CFN. This is because they all assumed a target area located on the fibular neck where the RFN originate, which could indeed be dangerous for the CFN trunk. We considered a different approach: targeting the nerve at its distal end, far away from the CFN, just before it reaches the articular capsule. We found that this nerve dives under the deep surface of the muscles to join the anterior tibial recurrent artery at the anterior aspect of the lateral tibial condyle. They ascend together in the same bundle, lying on the periosteum, passing about 1 cm below the Gerdy's tubercle, and end in the anterolateral knee capsule. The injection performed 1 cm below the Gerdy' tubercle, deeply on the periosteum, provided 100% accuracy without any diffusion to the CFN.

The inferior-medial quadrant of the knee joint is innervated by the IPBSN and IMGN. We found that the classical landmarks used for needle placement to treat the IMGN were 100 % accurate, although this nerve was found to be mostly a branch of posterior articular nerve (from sciatic nerve) rather than tibial nerve like previously described [10, 12, 16]. Concerning the IPBSN, its

contribution to the sensory innervation of the inferior-medial region of the knee joint makes it an important therapeutic target [17, 20]. Contrary to Tran et al who reported that the IPBSN was mainly cutaneous and only innervated the inferior-medial quadrant of the anterior knee joint capsule in 3/15 (20%) specimens, we and other authors [18, 19] found that the IPBSN supplied the inferior medial aspect of the anterior knee capsule and the overlying skin and subcutaneous tissue, in all the specimens. Its importance is reinforced by recent clinical studies where ablative treatment of IPBSN alone resulted in a significant decrease of knee pain in patients with knee osteoarthritis [72, 90, 123], with results comparable to those observed in studies performing classical ablative therapy of three genicular nerve [4, 10, 14, 64]. Hu et al [91] demonstrated that a vertical treatment line originating at 50 mm medial to the apex patellae and connecting to a point just inferior to the level of tibial tuberosity, would encompass 80 % of the nerve innervating the anteromedial region of the inferior knee. Our landmark, adapted from Hu et al with a slight modification for more precision, was accurate in 100% of our specimens. Ablative therapy combining all these nerves, with more accurate treatment targets, would likely potentiate their analgesic effects. RFA therapy on the IPBSN should be applied deep enough to prevent cutaneous lesions [20].

The teaching images in a recent article by Cushman et al [124] suggested that, using Choi's et al [10] targets, the SLGN and IMGN would likely be anesthetized and lesioned, whereas the SMGN would likely be anesthetized by 1.0 ml of local anesthetic, but may not be lesioned. In contrast, the current study (Fig. 9) found that the SMGN and SLGN would not be anesthetized or lesioned, while the IMGN would be using Choi's et al targets. The fundamental difference between the 2 studies is that we dissected all the limbs to visually

check for accuracy i.e. is the nerve dyed or not, while in their study, accuracy was hypothetically assessed using estimated courses of the nerves based on Tran et al [16] study. Since Cushman et al demonstrated that local injection of 0.5 ml of anesthetic spread beyond the boundaries of typical RFA lesions, the volume of anesthetic to be injected for accuracy studies should not be more than 0.5 ml. Of course, a larger volume of anesthetic would spread on a greater surface (just 1 ml covers the entire A-P surface of the femur [124]), and then, would capture all the nerves without any specificity, even if the needle placement is inaccurate. This may explain the higher rate of false positive diagnostic blocks. When analyzing the Fig. 3 provided by Cushman et al [124], the SMGN would likely not be anesthetized by 0.5 ml of local anesthetic, nor be lesioned, just as we stated. Concerning the SLGN, the estimated course of the nerve depicted by Cushman et al [124] is not the same as we found from our dissections, nor the same as in Fig. 2b provided by Tran et al [16] or Fig. 1 provided by Sutaria et al [100]. The main trunk of the SLGN remains posterior (running with the biceps femoris) until it reaches the area connecting the posterior edge of the lateral surface of the femur to the lateral femoral condyle (Fig. 9) where it divides in its terminal branches. The Choi's et al targets could inconsistently capture the LRN [100] or the NVL [23], but not the SLGN.

To date, the fluoroscopic-guided method is the most frequently used for GNB and RFA in the studies around the world [12, 105]. Since the targeted genicular nerves establish periosteal contact at the same anatomical areas before distributing to the knee joint, accurate needle placement can reliably be obtained by targeting bony landmarks under fluoroscopic guidance [10, 23]. This is a simple, accurate, and easily reproducible method. Its most important disadvantage is patient and physician exposure to radiation during the process.

The correct superposition of both femoral condyles on the true lateral fluoroscopic image is a key of the success for accurate needle placement for SLGN and SMGN. Although the ultrasound-guided technique can provide similar results without radiation, it relies much more on equipment quality and operator-dependent skills [105, 121]. In addition, the very small size of genicular nerves may not allow their direct visualization during ultrasonography [12, 105]; the described procedure tends to visualize neurovascular bundle based on artery beat [70, 105].

The limitations of our study include the relatively small sample size. However, due to the consistent anatomical location of the distal trajectory of targeted genicular nerve despite some variation in their proximal trajectory, we postulate that these landmarks would follow the same patterns in most individuals. The proposed GNB/RFA technique only targets five nerves, not all the articular branches innervating the knee joint. Our study warrants further clinical trials to investigate the therapeutic benefit and safety of this revised technique compared to Choi's technique for fluoroscopic guided GNB and RFA.

Conclusion

This study confirms that the anatomical landmarks currently used for fluoroscopy-guided GNB need to be revised for more accuracy. The findings of this study suggest that our updated anatomical landmarks for the five consistent articular nerves of the knee joint capsule (SMGN, IMGN, SLGN, RFN, and IPBSN) are accurate, safe and reproducible. Our study facilitates proper identification and needle placement during GNB procedures with fluoroscopic guidance. These findings provide physicians with a better technique to accurately target a larger panel of consistent genicular nerves for

selective denervation, which could potentially lead to improved treatment for patients suffering from chronic knee pain.

ACKNOWLEDGEMENTS

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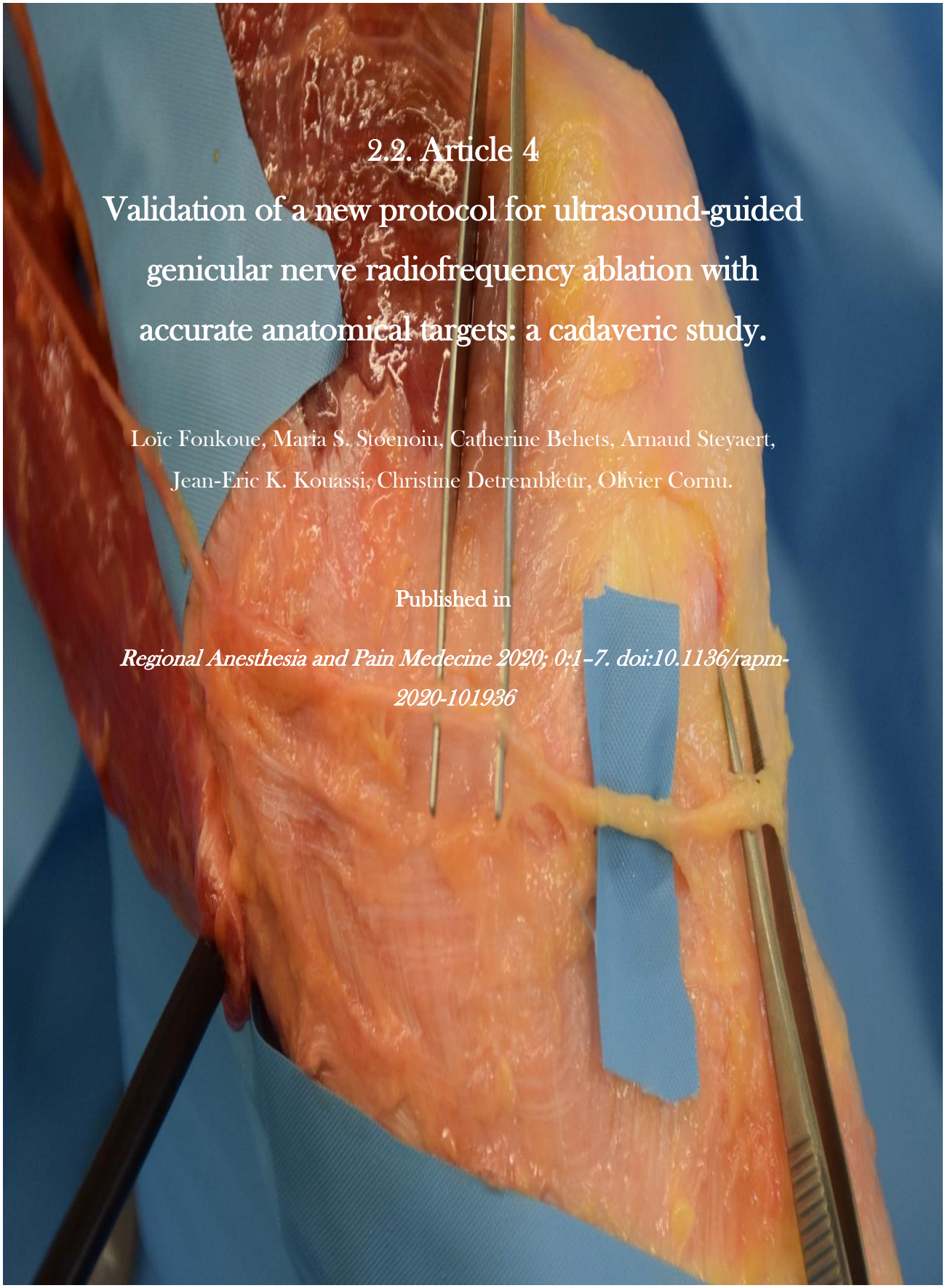

2.2. Article 4

Validation of a new protocol for ultrasound-guided genicular nerve radiofrequency ablation with accurate anatomical targets: a cadaveric study.

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2.2.1 Abstract

Introduction Ultrasound guided radiofrequency ablation (RFA) of genicular nerves (GN) is increasingly performed to manage chronic knee pain. The anatomical foundations supporting the choice of original targets for ultrasound-guided GN-RFA have been thoroughly improved by recent anatomical studies. Therefore, this study aimed to provide a new protocol with revised anatomical targets for ultrasound-guided GN-RFA and to assess their accuracy in a cadaveric model.

Materials and methods Fourteen fresh-frozen cadaveric knees were used. After a pilot study with 4 knees, five consistent nerves were targeted in the other 10 knees with revised anatomical landmarks: superior-medial GN (SMGN), superior-lateral GN (SLGN), inferior-medial GN (IMGN), recurrent fibular nerve (RFN) and the infrapatellar branch of saphenous nerve (IPBSN). For each nerve, the lumen of radiofrequency cannula was prefilled with non-diffusible black paint, and then the cannula was inserted at the target site under ultrasound guidance. After ultrasound verification of correct placement, the stylet was introduced in the cannula to create a limited black mark on the tissues at the top of the active tip. Anatomical dissection was performed to assess for accuracy.

Results The proportion of nerves directly found in contact with the black mark was 7/10, 8/10, 10/10 and 9/10 for the SMGN, SLGN, IMGN and RFN respectively. The proportions of nerve captured by the theoretical largest monopolar RF lesions were 100% for the SMGN, IMGN and RFN, IPBSN, and 95% for SLGN. The mean distances from the center of the black mark to

the targeted nerve were 2.1 ± 2.2 mm, 1.0 ± 1.4 mm, 0.75 ± mm and 2.4 ± 4.5 mm for the SMGN, SLGN, IMGN and RFN respectively

Conclusion. Ultrasound-guided GN-RFA with revised anatomical targets resulted in accurate capture of the five targeted nerves. This protocol provides precise sensory denervation of a larger panel of nerves, targeting those whose constancy regarding anatomical location has been clearly demonstrated. It is expected to improve the clinical outcomes.

Key words: genicular nerve – radiofrequency ablation – ultrasound-guided – anatomical targets

2.2.2 Introduction

Radiofrequency ablation (RFA) of genicular nerves (GN) has demonstrated some efficacy in the management of chronic knee pain [10, 14, 24, 60, 64, 65, 69, 121]. While the original procedure involved fluoroscopy-guided needle placement, ultrasound-guided technique is gaining interest [67-70, 86, 105, 106]. In addition to bony landmarks used in fluoroscopy-guided procedures, ultrasound (US) allows the visualization of surrounding soft tissues, i.e. tendons, muscles, ligaments, and fasciae as well as arteries running alongside the genicular nerves[12, 20, 86, 115], which could improve the precision of the cannula placement during RFA[14, 16, 20]. Moreover, ultrasound is free of radiation, more easily accessible, reliable and cheaper [12, 86].

The anatomical bases supporting the original targets for image-guided (fluoroscopy or ultrasound) GN-RFA have been thoroughly improved thanks to recent anatomical studies providing sound targets [16, 20, 101-103]. To date,

the large majority of the studies assessing US-guided GN-RFA have used targets which are based on the original description of genicular nerves [67-71, 86, 105, 106, 120, 125], but there is evidence that these classical targets fail to accurately capture the trunk of two out of three commonly treated genicular nerves [126]. Since direct visualization of the GN is challenging, most described US-guided techniques are based on the identification of genicular arteries running alongside the targeted nerves [68, 71, 86, 105, 120]. However, it has been shown that some of the genicular nerves do not run alongside nor in the same direction with the currently targeted genicular arteries [16, 126]. This highlights the need for new ultrasound-guided GN-RFA protocols, based on updated and more precise anatomical landmarks.

Therefore, this study aimed to provide revised anatomical targets for ultrasound-guided GN-RFA and assess their accuracy in a cadaveric model.

2.2.3 Methods

Fourteen knees from 10 fresh frozen adult cadavers (6 females, mean age 81.9 ± 5.7 years), without evidence of surgery or major knee trauma, were used in this study conducted at UCLouvain Laboratory of Human Anatomy. Donation procedures and the use of the human cadavers were in accordance with national laws and regulations. Approval was granted by the institutional ethics committee. Four knees were used for the pilot trials and 10 for the main study.

Pilot trial

The pilot study was conducted for sonographic exploration of the anatomical landmarks and confirmation of feasibility of our technical protocol to assess the

position of the RF cannulas. US examination of the cadaveric knees was performed by a sonographer (MSS) with more than 10 years' experience in musculoskeletal US using a high-resolution ultrasound (General Electrics Logic E9; GE Medical systems, USA), equipped with two multifrequency linear array transducers, a 18-MHz transducer for superficial areas (8-18 MHz hockey stick probe) and a 6- to 15-MHz transducer (ML6-15) for medium and deep areas. According to the revised anatomical targets from recent studies [16, 20, 101-103], RF cannula were inserted to fit the target of each of the 5 consistent genicular nerves. Bones, tendons, vessels, enthesis and superficial landmarks were used to increase ultrasound accuracy and needle positioning. The localization of the tip of the cannula was demonstrated on two perpendiculars planes. Needle was redirected under ultrasound guidance in order to reach the target, if needed.

For the simulation of RF lesions, since the injection of even a very small volume (0.1ml) of dyed solution is likely to diffuse beyond the limits of RF lesions, we marked the tissue at the top of the active tip with non-aqueous black paint. The stylet of the 18-gauge 10 mm active tip, 10 cm long RF cannula (Cosman Medical, Inc., Burlington, MA, USA) was removed and the cannula was pre-filled with a syringe containing the black paint. Then, the cannula was detached from the syringe and its tip was cleaned. Under direct ultrasound guidance, the anatomical landmarks for each nerve were identified and the cannula was advanced to the target. After verification of the correct cannula placement, the stylet was reintroduced into its cannula while ensuring that it did not move from its final position. The stylet, and then the cannula were removed from the knee. After completion of the procedure and subsequent meticulous anatomical dissection, we found a clear limited black mark (mean 5.36 mm (SD 2.61) ×

3.69 mm (SD 1.49) at all the targeted points. We concluded that the method was reliable for accessing the accuracy of lesions produced by ultrasound-guided RFA.

During dissection, we securely fixed a thick echoic stainless-steel wire on each targeted nerve. The distal end of the steel wire was bent over itself and fixed on the nerve at its target point, by strong sutures to avoid secondary displacement during handling. Then, the anatomical structures were carefully repositioned and sutured layer by layer before skin closure. A second ultrasound exploration was performed the day after the anatomical dissection. The reverberation US artefact generated by metals was used to identify the position of the steel wire in order to refine ultrasound landmarks.

Main Study

In the other ten lower limbs, US-guided RF lesions were simulated as described above, targeting five nerves, in accordance with previous anatomical studies and the current pilot trial. All the procedures were performed in supine position with the knee extended.

Superior-medial genicular nerve (SMGN) (figure 1 A-D)

The US transducer was aligned in a coronal plane over the medial femoro-tibial joint line and move cephalad and posteriorly to identify the adductor tubercle (AT) and the insertion of the adductor magnus tendon. The skin was marked transversally at the level of the AT. Then, the transducer was turned into the axial orientation at that level, and translated posteriorly to identify the posterior cortex of the femoral metaphysis. With the probe in that position, a

RF cannula was inserted about 2-3 cm medially from the superior-medial angle of the patella, and advanced in an in-plane position from front to back (90° from the coronal plane) until the posterior cortex, on or above the AT, about 1 mm from the periosteum.

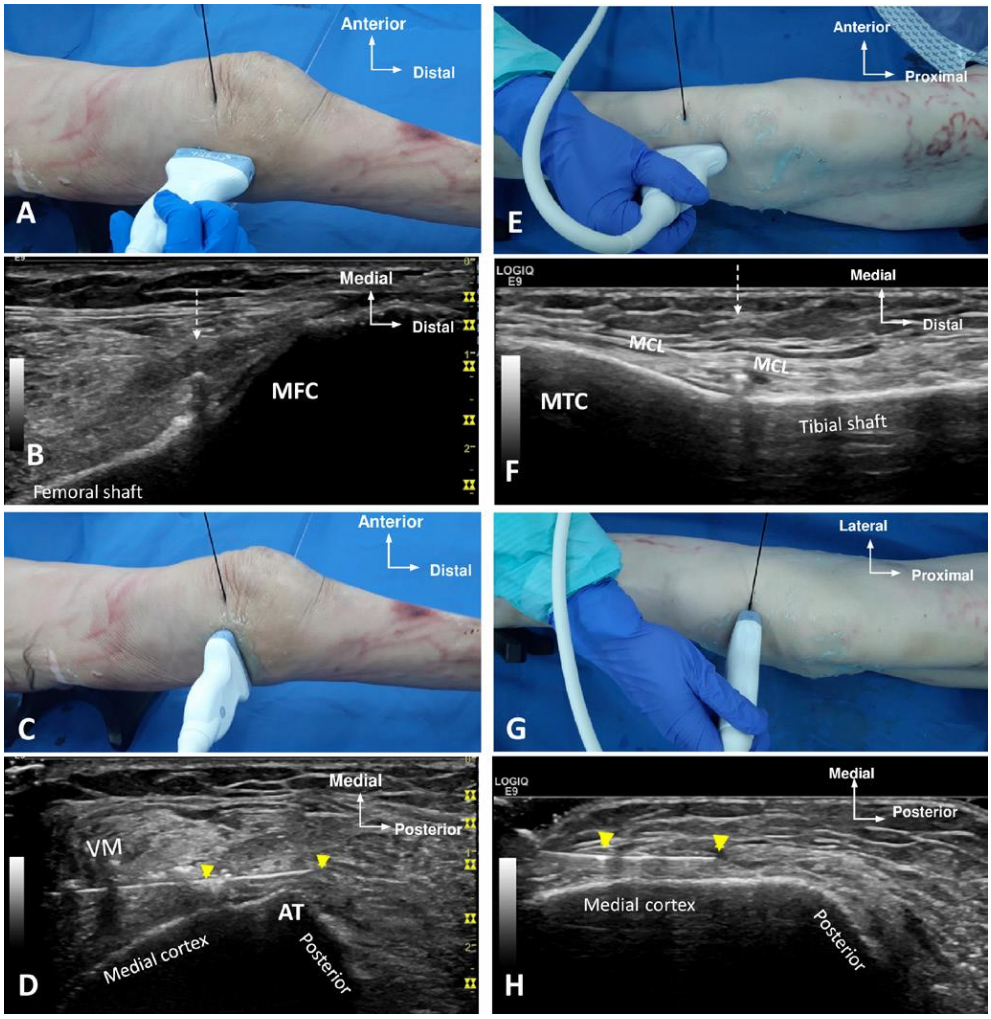

Figure 1 Cannula placement and ultrasound landmarks for SMGN and IMGN in cadaveric knee. (A,B) Coronal plane: target point for SMGN. (C,D) Axial plane: final position of the RF cannula for SMGN (with the active tip highlighted with two yellow arrowheads). (E,F) Coronal plane: target point for IMGN. (G,H) Axial plane: target point for IMGN. Vertical dashed arrows indicate target level on coronal view; yellow arrowheads indicate limits of the active tip.

AT, adductor tubercle; IMGN, inferior medial genicular nerve; MCL, medial collateral ligament; MFC, medial femoral condyle; MTC, medial tibial condyle; SMGN, superior medial genicular nerve; VM, vastus medialis.

Superior lateral genicular nerve (SLGN) (figure 2)

The transducer was aligned in a coronal plane (figure 2A) over the lateral femoro-tibial joint line and move cephalad to identify the junction between lateral femoral condyle and the shaft. This corresponded to a transitional area and we marked the junction between the convexity and concavity (figure 2B). The skin was marked transversally at that level. Then the transducer was positioned into axial plane according to this transversal skin mark (figure 2C) and translated posteriorly to identify the posterior edge of the lateral femoral cortex which is easily identifiable as a crest separating the lateral and posterior sides (figure 2D). The skin was marked at the point corresponding to the junction between the posterior edge of the lateral femoral cortex and the superior edge of the lateral condyle, which was the target (figure 2E). As we observed in the pilot study that the correct approach for cannula placement was at about 45° from coronal plane, the skin entry point was placed about 3 cm anterior and 3 cm proximal to that skin marking point (figure 2F). Under direct US guidance, a RF cannula was inserted obliquely, about 45° from coronal plane, and advanced obliquely from anterior to posterior toward the target (figure 2G-H). Then, the transducer was repositioned in the axial plane (figure 2K), centered on the skin mark of the target point, and the active tip position was adjusted to fit the target (figure 2L), about 2-3 mm from the periosteum.

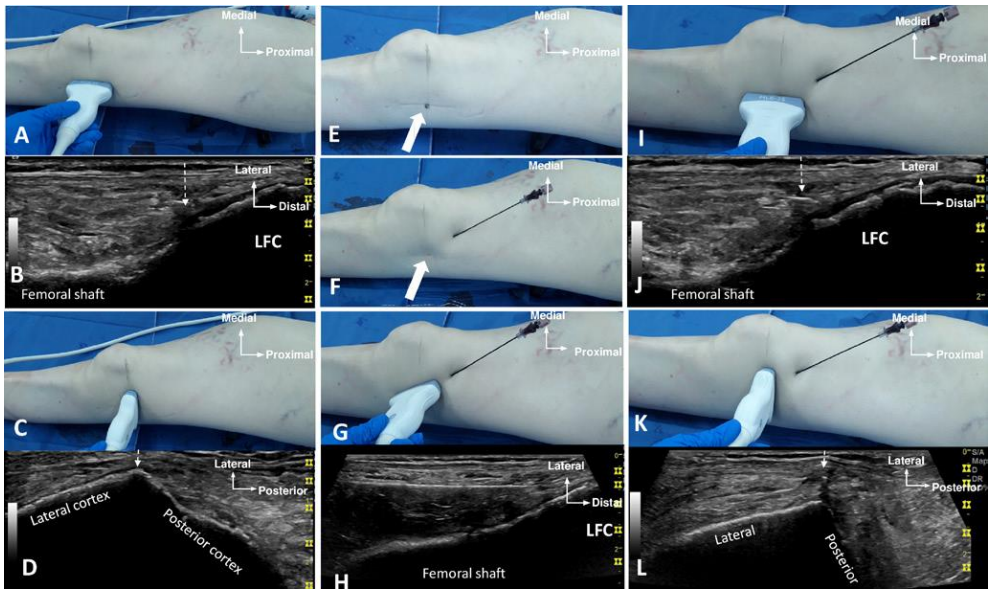

Figure 2 Cannula placement and ultrasound landmarks for SLGN in cadaveric knee. (A, B) coronal plane: target point for SLGN and transversal skin mark. (C, D) Axial plane: target point for SLGN. (E) Target Skin point. (F): 45° cannula introduction. (G, H) oblique in-plane insertion of cannula. (I, J) Coronal plane: final position of the cannula tip. (K, L) Axial plane: final position of the cannula tip. Vertical dashed arrows indicates the US target point. SLGN, superior lateral genicular nerve; LFC, lateral femoral condyle; US, ultrasound.

Inferior medial genicular nerve (IMGN) (figure 1 I-L)

The US transducer was aligned in a coronal plane over the medial femoro-tibial joint line and translated distally to identify the metaphyseal-diaphyseal junction of the tibia and the distal insertion of the medial collateral ligament (MCL). We tried to visualize the short axis view of the nerve, running on the periosteum with the inferior-medial vessels. The skin was marked transversally at that level. The US transducer was turned into an axial orientation, at the level of the transversal skin mark. A RF cannula was inserted (with the entry point on the skin mark, 1cm medially to the tibial tuberosity) in an in-plane approach

and advanced from anterior to posterior to fit at the midpoint of the tibial width, close to the periosteum. A supplementary coronal view allowed to check the position of the active tip beneath the MCL, close to the vessels and the nerve.

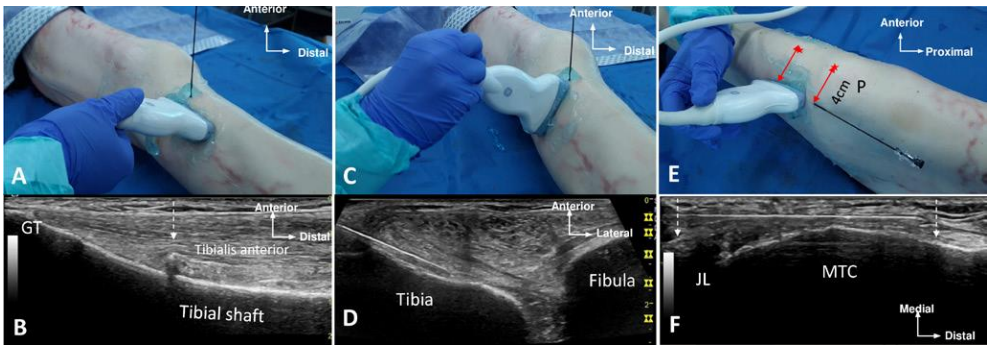

Figure 3 Cannula placement and US landmarks for RFN and IPBSN in the cadaveric knee. (A, B) Coronal plane: target point for RFN. (C, D) Axial plane: final position of the RF cannula for the RFN. (E, F) Coronal plane: RF cannula placement on the treatment line for the IPBSN. Red stars indicate the patella apex and tibial tuberosity; vertical dashed arrows indicate the target levels on US view. GT, Gerdy's tubercle; IPBSN, infrapatellar branch of the saphenous nerve; JL, medial femorotibial joint line; MTC, medial tibial condyle; RF, radiofrequency; RFN, recurrent fibular nerve; US, ultrasound.

Recurrent fibular nerve (RFN) (figure 3A-D)

The US transducer was aligned in a coronal plane over the lateral femoro-tibial joint line and translated distally to identify the Gerdy's tubercle (GT) and the insertion of the iliotibialis tract. The transducer was translated about 2 cm distally to visualize the short axis view of pedicle containing the RFN and the anterior tibial recurrent artery, located just below the GT, beneath the tibialis anterior muscle. The skin was marked transversally at that level. The US transducer was turned 90° into an axial orientation at the level of the transversal skin mark. A RF cannula was inserted (with the entry point on the skin mark,

just lateral to the tibial tuberosity) in an in-plane approach and advanced close to the bone, from the anterior to posterior to fit at midpoint of the tibial width, far from the common fibular nerve.

Infrapatellar Branch of the saphenous nerve (IPBSN) (figure 3 E-F)

We drew the IPBSN treatment line, i.e. a longitudinal line, 4 cm medially to the patella apex, connecting both transversal lines passing by the patella apex and the top of the tibial tuberosity. We investigated direct US visualization and indirect targeting of the IPBSN.

- Direct visualization of the IPBSN at the level of the knee: The probe was aligned in the coronal plane throughout the treatment line to try to visualize the short axis view of the nerve as hypoechogenic ovoid structure in the subcutaneous tissue, lying on the MCL, running with its small artery. If the nerve was not identified there, the probe was translated posterior-medially, and cephalad to search for it (retrograde ultrasound exploration). In the case where the IPBSN was not identified at the inferior medial aspect of the knee, the saphenous nerve was identified at a mid-femoral level, and we tried to identify the emergence of the IPBSN, and to follow its course until the knee (anterograde ultrasound exploration).

- Indirect targeting of the IPBSN: If the nerve was not directly identified, the transducer was placed in coronal view on the treatment line, and the RF cannula was inserted through a skin point located at the superior edge of the treatment line, advanced from proximal to distal along the line, deep in subcutaneous tissue, just superficial to the MCL (figure 2 E-F).

For each nerve, after verification of correct cannula placement, one RF lesion was simulated as described above. For the SLGN, three consecutive contiguous lesions were performed: at the level of the target area described above, then the cannula was advanced (1 cm distally) and the second lesion was performed, and the cannula was withdrawn (1 cm proximally) for the third lesion. For the IPBSN, if the nerve was directly identified, the lesion was performed directly on the nerve. If not, a black mark was made at both extremities of the treatment line.

After the completion of all the simulated RF lesions, the limbs were dissected by an experienced anatomist to assess the nerve capture rate, which was our primary outcome. The midpoint of the black mark was considered the final location of the top of the active tip. Therefore, according to this black mark and considering the direction of the cannula and its final position, we traced the location of the 10 mm active tip and the theoretical limits of the largest RF lesion volume (transversal distance 7.4 mm, longitudinal distance 12.9 mm, and distance beyond the tip 2.4 mm)[73]. The anatomical targets for cannula placement were considered accurate either if the nerve was in contact with black mark, or if it was included within the limits of the presumed RF lesion. Using a sliding digital caliper, we measured the shortest distance from center of the black mark to the nerve, and the distance from limits of the presumed RF lesion to the nerve. We also measured the distance from the edge of the RF lesions for RFN to the common fibular nerve (CFN).

Statistical analysis was performed using SPSS 25.0 (Chicago, Illinois, USA). For each nerve, the accuracy rate of the cannula placement was described as proportions. The various distances were described as mean (SD). Analysis of variance test was used to compare the mean distances from the black mark

between the different nerves. We considered a P value < 0.05 statistically significant.

2.2.4 Results

The mean distances from the center of the black mark to the targeted nerve were 2.1 ± 2.2 mm, 1.0 ± 1.4 mm, 0.75 ± 1.1 mm and 2.4 ± 4.5 mm for the SMGN, SLGN, IMGN and RFN respectively (table 1). We did not find a statistical difference in these distances between the nerves (p = 0.31).

The mean distances from the edge of the simulated RF lesion to the targeted nerve were zero mm for the SMGN, IMGN, and RFN, and 0.5 ± 1.2 mm for the SLGN (Table 1).

Table 1. Distances from the nerves to the marks

Distance measured (in mm)	Mean (SD)	Median	Range
SMGN distance 1	2.1 (2.2)	2.0	0.0 - 8
SMGN distance 2	0 (0.0)	0	0
IMGN distance 1	1.0 (1.4)	0	0 - 4
IMGN distance 2	0 (0.0)	0	0
RFN distance 1	0.75 (1.1)	0	0 - 3
RFN distance 2	0 (0.0)	0	0
SLGN distance 1	2.4 (4.5)	0	0 - 14
SLGN distance 2	0.5 (1.2)	0	0 - 4

Distance 1 : distance from the center of the black mark to the nerve
Distance 2: distance from the edge of the theoretical RF lesion to the nerve
SMGN, superior-medial genicular nerve; SLGN, superior-lateral genicular nerve; IMGN, inferior -medial genicular nerve; RFN, recurrent fibular nerve.

The mean distance from the edge of the RF lesions to the CFN was 37.33 [range 30 – 42] mm

The proportion of nerves directly in contact with the black mark was 7/10, 8/10, 10/10 and 9/10 for the SMGN (figure 3), SLGN (figure 4), RFN (figure 5A-B) and IMGN (figure 5C-D) respectively (table 2).

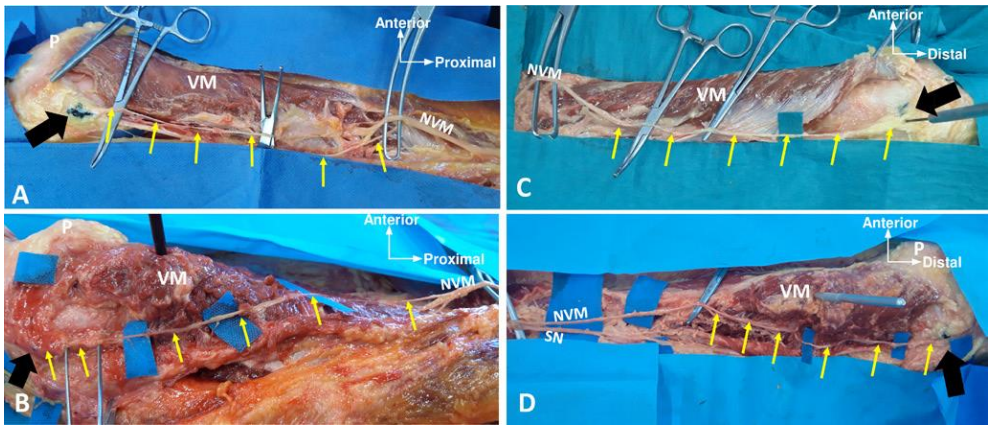

Figure 4 Postprocedural anatomical dissections, medial view: superior medial genicular nerve (yellow arrows). (A, B) Right knees and (C, D) left knees. Tick black arrows show the black mark. NVM, nerve to the vastus medialis; P, patella; SN, saphenous nerve; VM, vastus medialis muscle.

The proportions of nerve capture (accuracy rate) with the theoretical largest monopolar RF lesions were 100% for the SMGN, IMGN and RFN (table 2). For the SLGN, the trunk of the nerve was captured before its bifurcation in 9/10 cases; in 1/10 case, only the transversal branch was captured, resulting in an overall accuracy rate of 95%.

The IPBSN was directly visualized in 2/10 cases, with a successful direct capture (figure 5E). In the eight remaining cases, the IPBSN was found within

the black marks at both extremities of the treatment line (figure 5F), giving an accuracy rate of 100% with this indirect technique.

Table 2. Staining and accuracy rates for different targeted nerves

Targeted nerves	Contact of the black mark with the nerve n (%)	Nerve within the limits of the RF lesion n (%)
SMGN	7 (70%)	10 (100%)
SLGN	8 (80%)	9 + ½ (95%)
IMGN	10 (100%)	10 (100%)
RFN	9 (90%)	10 (100%)
IPBSN	Non applicable	10 (100 %)

SMGN, superior-medial genicular nerve; SLGN, superior-lateral genicular nerve; IMGN, inferior -medial genicular nerve; RFN, recurrent fibular nerve; IPBSN, infrapatellar branch of saphenous nerve

2.2.5 Discussion

This cadaveric study was designed to provide updated anatomical targets for ultrasound-guided GN blockade and RFA, and assess for accuracy of a new protocol. According to our results, US-guided GN-RFA using revised anatomical targets is feasible and accurately captures the five most consistent sensory nerves of the knee joint capsule: SMGN, SLGN, IMGN, RFN and IPBSN.

The increasing number of publications on the use of US-guided GN blockade and RFA to alleviate chronic knee pain reflects the growing interest of pain physicians for this technique [67-72, 86, 120]. However, very few anatomical

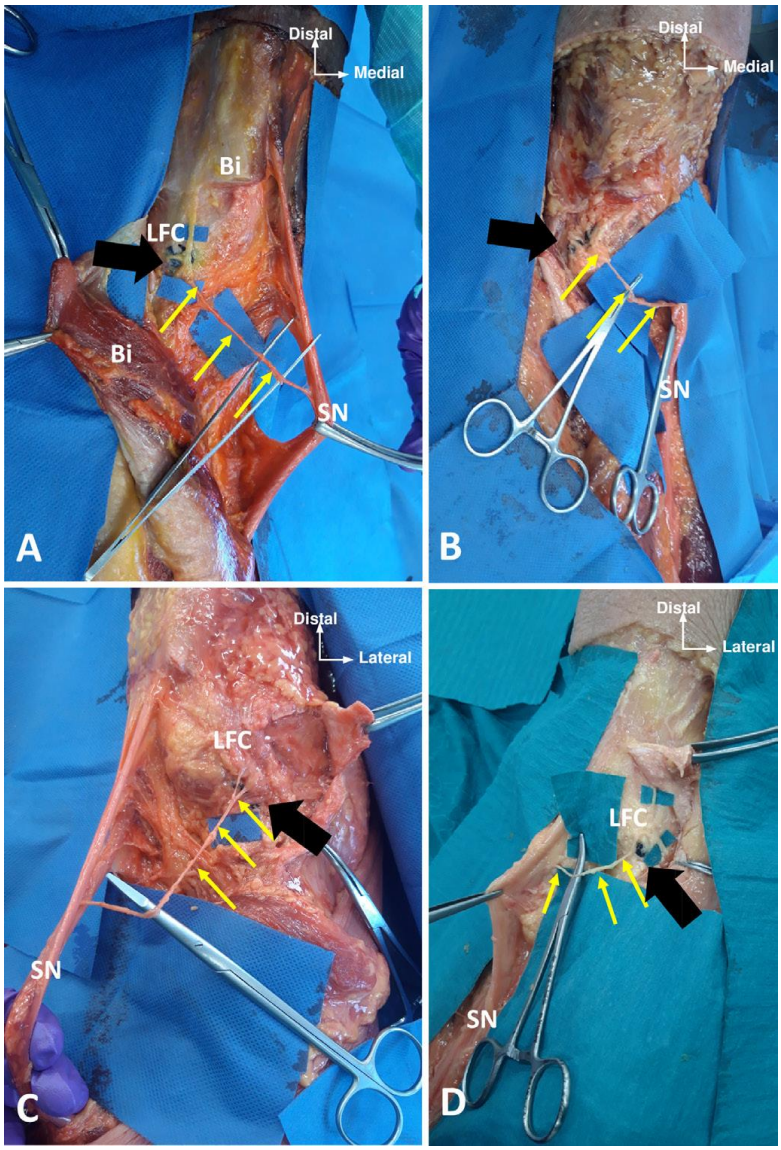

Figure 5 Postprocedural anatomical dissections, posterior lateral view: superior lateral genicular nerve (yellow arrows). (A,B) Right knees and (C,D) left knees. Tick black arrows show the black marks. Bi, biceps femoris muscle (cut and reflected); LFC, lateral femoral condyle; SN, sciatic nerve.

studies have assessed the accuracy of targets used for ultrasound-guided intervention [12, 115]. Moreover, the anatomical targets commonly used are based on the original anatomical descriptions, which have since then been improved. Therefore, revised targets, based on updated and accurate anatomical data, are paramount to expect improving outcomes. While using anatomical landmarks based on original description of genicular nerves, a recent cadaveric study [115] found that the commonly used targets for US-guided RFA on SMGN, SLGN, and IMGN were accurate. Two major methodological differences may explain the discrepancies between both studies. First, they injected a dyed solution – even 0.1 ml of soluble dyed solution diffuse beyond the limits of RF lesions [126] - to visualize the final position of cannula. In the current study, to assess the precision of cannula placement, we simulated the RF lesion by creating a limited black mark on the tissues at the top of RF cannula using a non-diffusible paint. Secondly, we performed a systematic anterograde dissection of genicular nerves from origin to ending, to ensure that we really visualized nerves. Indeed, small genicular nerves can be confused with small vessels on a cadaver (especially an embalmed specimen) if the nerve is not dissected since its origin (which is big and easily identifiable), or the vessels are not injected before dissection [126]. Therefore, in cadaveric validation studies, post interventional dissections and illustrations of the nerves should allow the researcher and the reader to discriminate between the very thin genicular nerves and vessels. Dissection of the GN trough a distal "window" could be misleading.

Our target for SMGN is different from that of the commonly described technique [86, 115, 120, 127], which relies on the course of the vessels running transversally forward at the junction between epiphysis and diaphysis. This

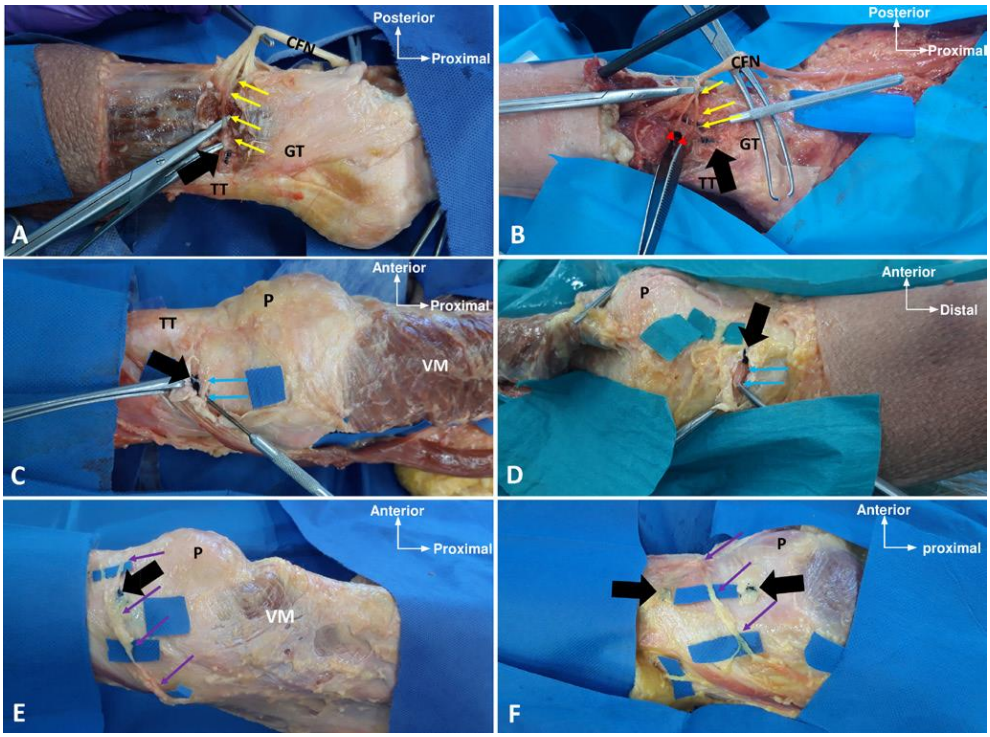

Figure 6 Postprocedural anatomical dissections. (A, B) Recurrent fibular nerve (yellow arrows) accompanied by anterior tibial recurrent vessels (red arrowheads). (C, D) Inferior medial genicular nerve (blue arrows) with accompanying vessels. (E) IPBSN (purple arrows) captured under direct ultrasound visualization. (F) IPBSN passing within the two extremities of the treatment line. Tick black arrows show the black marks; CFN, common fibular nerve; GT, Gerdy's tubercle; IPBSN, infrapatellar branch of the saphenous nerve; P, patella; TT, tibial tuberosity; VM, vastus medialis muscle.

does in fact not correspond to the superior-medial genicular artery (SMGA), but to the upper transverse artery from the articular branch of the descending genicular artery (DGA), which does not run with SMGN [126, 128]. Recent studies have found that the SMGN has a descending course, along with its artery from the DGA [16, 101, 103, 128]. Its transversal terminal branch runs forward with SMGA at the level of medial epicondyle, and not at junction between medial femoral condyle and diaphysis [128], as targeted in classical

technique. In our proposed protocol, the active tip of the RF cannula should be advanced totally posteriorly on the medial femoral axial view (figure 1D), to cross the course of the nerve. To capture the trunk of the nerve, the cannula should not be distal to the adductor tubercle. We observed that in all our specimens, the base (superior pole) of the patella corresponded to the correct level of cannula insertion. Identification of the distal end of the adductor magnus tendon and the artery running on its surface with the SMGN could be complementary landmarks to improve capture of the SMGN in patients.

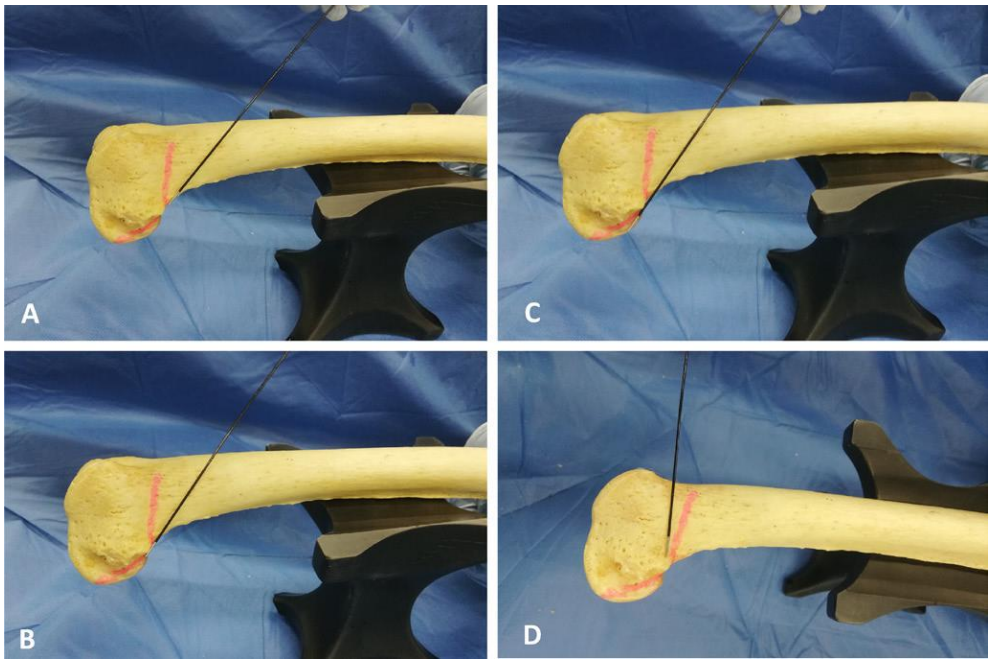

Figure 7 Targeting approach for the SLGN, illustration on a real human femur skeleton, lateral view. (A) Oblique approach with the three contiguous lesions proposed to capture the terminal branches of SLGN: proximal lesion (see the position of the active tip). (B) Central lesion: the active tip fit exactly at the junction between the posterior edge of the lateral cortex and the lateral condyle. (C) Distal lesion: the RF cannula is advanced 1 cm from central position. (D) Anterior–posterior vertical approach: the proximal expansion of the lateral epicondyle prevents the tip to fit properly the target area; in addition, the three contiguous lesions are not feasible. Red lines represent transverse and longitudinal terminal branches of SLGN. RF, radiofrequency; SLGN, superior lateral genicular nerve

Due to the anatomical conformation on the lateral femoral condyle and epicondyle, we observed that it is difficult to reach the target area of the SLGN when the cannula is at 90° from the coronal plane, because the proximal part of lateral epicondyle prevents the tip from reaching the target (figure 7). We found that a 45° approach provided a better trajectory to the target area (figure 7). Due to the variability of the SLGN position, we propose a palisade of three contiguous lesions (Figure 7 A, B, C). Our results show that this technique improved the capture rate of that nerve from 65% in a previous study with single lesion [126] to 95% in the current study. While this would prolong the procedural time for about 5 minutes, we believe it is worth it. The needle should not be too close from the bone, but at 2-3 mm from the periosteum. In our proposed technique, while the needle insertion technique was extremely simple and basic for the other targeted nerves, the needle proper positioning for the SLGN was the less easy to achieve. That is why we provided a more detailed description of the procedure, which could be reproduced by any pain physician (figure 2). Fluoroscopy could be used to confirm the needle position, especially during the learning phase of this technique. Some physicians use both devices (fluoroscopy and ultrasound) to confirm the needle positioning during genicular nerves RFA. For those who are very experienced sonographers, an alternative technique to identify the target area could be as follow: coronal view to determine the junction between lateral femoral condyle and shaft and note the depth; then turn the probe 90° to see the junction between the posterior and lateral cortex with the same depth, while paying attention to make sure that the probe is in the true lateral plane.

The proposed technique for capture of RFN is safe and accurate. With this anterior approach under direct US guidance, the lesion is deep enough from

the skin (beneath the deep surface of the tibialis anterior muscle), and far enough from the CFN which can be visualized during the procedure. The vessels running with the nerve in a recurrent course are easily identifiable, just below the Gerdy's tubercle. One may choose not to use US-guidance to target this nerve as we previously described [103, 126], but the US technique has an advantage in obese patients where the Gerdy's tubercle is not easy to palpate.

Some authors described direct identification of the IPBSN [20, 116, 129] with US but in our specimens, we found it difficult to identify systematically. In a recent study, Gong et al [129] found that the IPBSN could be visualized distinctly in four out of five subjects. Their landmarks was 5 cm superior to the medial femoral condyle and the nerve was visualized superficial to the junction between vastus medialis and sartorius. We did not made the same observations. Moreover, we believe that even if this landmark could be used for IPBSN blockade, it seems too proximal for RFA. We found a variability in the proximal trajectory of IPBSN, but its distal course at the level of the knee is remarkably constant, crossing the proposed treatment line in 100% of cases. Therefore, for RFA of IPBSN, we propose a two-step protocol. First, try direct visualization of the nerve alongside its artery [128] at the level of the treatment line, which we succeeded in only 2 specimens (in patients, the arterial flow could be helpful). If direct identification fails, just perform indirect targeting as we previously described [103, 126]. Introduce the cannula deep at the proximal end of the treatment line, and advance it longitudinally, deeply and progressively along the treatment line while performing sensory stimulation. A sensation in the territory of the IPBSN would confirm a close proximity between the active tip and the nerve. After ensuring that there is at least 8-10 mm between the active tip and the surface of the skin, a lesion could be

performed. Due to the risk of cutaneous lesions, pulsed radiofrequency is indicated for IPBSN.

In fluoroscopy-guided intervention, only the bony landmarks are used to localize the probable position of the targeted nerves, since their trajectory is consistent. Some authors suggest that US is better than fluoroscopy for guiding needle placement during this treatment [86, 105, 106], while others describe the use of both tools [86]. The proposed ultrasonographic landmarks allow the visualization of several anatomical structures such as bony landmarks, muscles, tendons, ligaments, for each targeted nerve. In addition, since the pattern of vessels accompanying each genicular nerve has been well established, the arterial blood flow could help to better localize them, as long as we follow the correct artery. Another possible advantage of technique is the fact that the cannulas do not need to be inserted directly on periosteum and advanced on it, because this could make the procedure more painful. Moreover, it has been shown that an active tip directly placed on the bone significantly limits the volume of RF lesion [73]. Therefore, we suggest keeping a 1-2 mm distance between the tip and bone. Finally, after technical optimizing i.e. better and accurate anatomical targets, larger lesion volume, optimal use of ultrasound and/or fluoroscopy, we believe that GN-RFA appears to become very effective and widely indicated for more patients across the world.

This study has some limitations. First, the most valuable method for assessing the accuracy of needle placement for RFA is to create a true RF lesion under clinical-like conditions, before performing anatomical dissection. Since studies have failed to create visually identifiable RF lesions on cadavers [115, 126], we did not use this method. However, the use of a black mark as surrogate for identifying needle position, rather than the injection of dyed solution, seems

more reliable, given the limited size of RF lesions. Second, due to the absence of blood flow through the arteries of cadavers, we were unable to use the Doppler-US to assess the blood flow of arteries running alongside the genicular nerves. In a living patient, in addition to the anatomical landmarks used in this study, arterial blood flow could help increase the success rate of cannula placement, but identifying the correct artery is the key. Thirdly, we only explored monopolar RF lesions. However, we believe that since the size of cooled RF lesions is bigger, the technique would also be accurate when using cooled radiofrequency devices. Finally, only a clinical validation study of the proposed technique will allow to assess its efficacy and safety.

Conclusion

This study shows that the protocol for ultrasound-guided GNB and RFA with revised anatomical targets resulted in accurate capture of the five targeted nerves. This protocol provides more complete sensory denervation, targeting only the nerves whose constancy regarding anatomical location is clearly established. It is expected to improve the clinical outcomes. It could be directly useful for physicians who perform ultrasound guided radiofrequency ablation of genicular nerves for chronic knee pain. Clinical studies will be needed to assess the safety and efficacy of the proposed technique and compare it to the commonly used one.

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2.3. Article *5*

Anatomical evidence supporting the revision of classical landmarks for genicular nerve ablation

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We would like to thank Tran et al [130] for their interest in our paper [103]. They expressed their concerns about two of the five anatomical landmarks we proposed to target with increased accuracy for genicular nerve ablation: the superior medial (SMGN) and the superior lateral (SLGN) genicular nerves. We would like to respond to the issues raised and to clarify some anatomical and methodological disagreements.

Concerning our landmark for SMGN, located just anterior to the adductor tubercle (AT), Tran et al [130] stated that it would capture "only the distal branches of SMGN which supply the knee joint capsule in the region of medial epicondyle (figure 1B, blue lesion)". When looking carefully at their figure 1B [130], there seems to be a confusion between the AT and the medial epicondyle (ME): the blue lesion (their representation of our landmark) is incorrectly placed above the ME rather than just anterior to the AT. If that blue lesion is raised a little bit to fit the real point we described (figure 9) [103], it would capture the trunk of the SMGN, like what we observed in our validation study [103]. It is important to note that in their figure 1B [130], the classical lesion (orange) has been moved posteriorly, whereas it should be normally centered at the midpoint of the femoral shaft, represented by the longitudinal dash line. Moreover, the distal distribution they draw in their figure map do not correspond to our findings [101, 103]. In a very recent review of the knee joint innervation published at the same time as our current study, Roberts et al [102] stated that "the adductor tubercle is a more precise anatomic target for the SMGN than the current target". In our study [103], the injection performed just anterior to the AT captured the trunk of the nerve, before its distribution, leading to ablation of all its terminal branches. The classical landmark, at the midpoint of the femoral shaft, would not capture the SMGN (Figure 1).

The Tran et al's [16] description of the distribution of the SLGN is somewhat short. They just stated that the SLGN "joins the superior lateral genicular vessels just before entering the knee capsule". Similar to Sutaria et al [100], who performed the only published study specifically dedicated to the terminal branches of the SLGN, we found that the SLGN runs under the deep surface of the biceps femoris muscle toward the area connecting the lateral femoral condyle and the posterior edge of the lateral side of femoral shaft, and then divides into two terminal branches: a transversal branch (lateral retinacular nerve) and a longitudinal (descending) branch [103]. These can be observed on Tran et al's figure 2B [16]. Based on that figure, an injection performed at the point of bifurcation of the SLGN would capture both terminal branches. Surprisingly, on their figure 1A [130] (dissection), Tran et al represented the classical landmark for the SLGN (orange lesion) almost behind the midline. If the orange lesion was centered on the midpoint of the femoral shaft (longitudinal dash line), corresponding then to the true classical target, the SLGN would not be captured. Moreover, if our proposed landmark was properly placed on the superior edge of the femoral condyle (horizontal dash line), it would capture the nerve before its bifurcation, ablating all its terminal branches. Although with a slightly different terminology, the Roberts et al's [102] proposed target for this nerve is similar to ours. The classical landmark would only targets its transversal terminal branch.

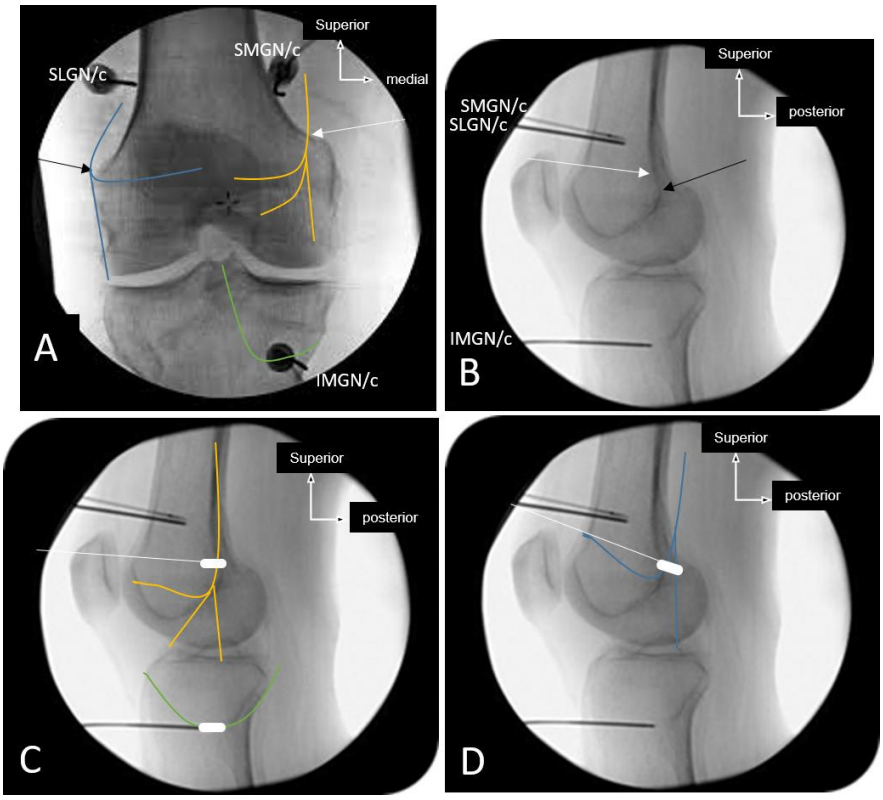
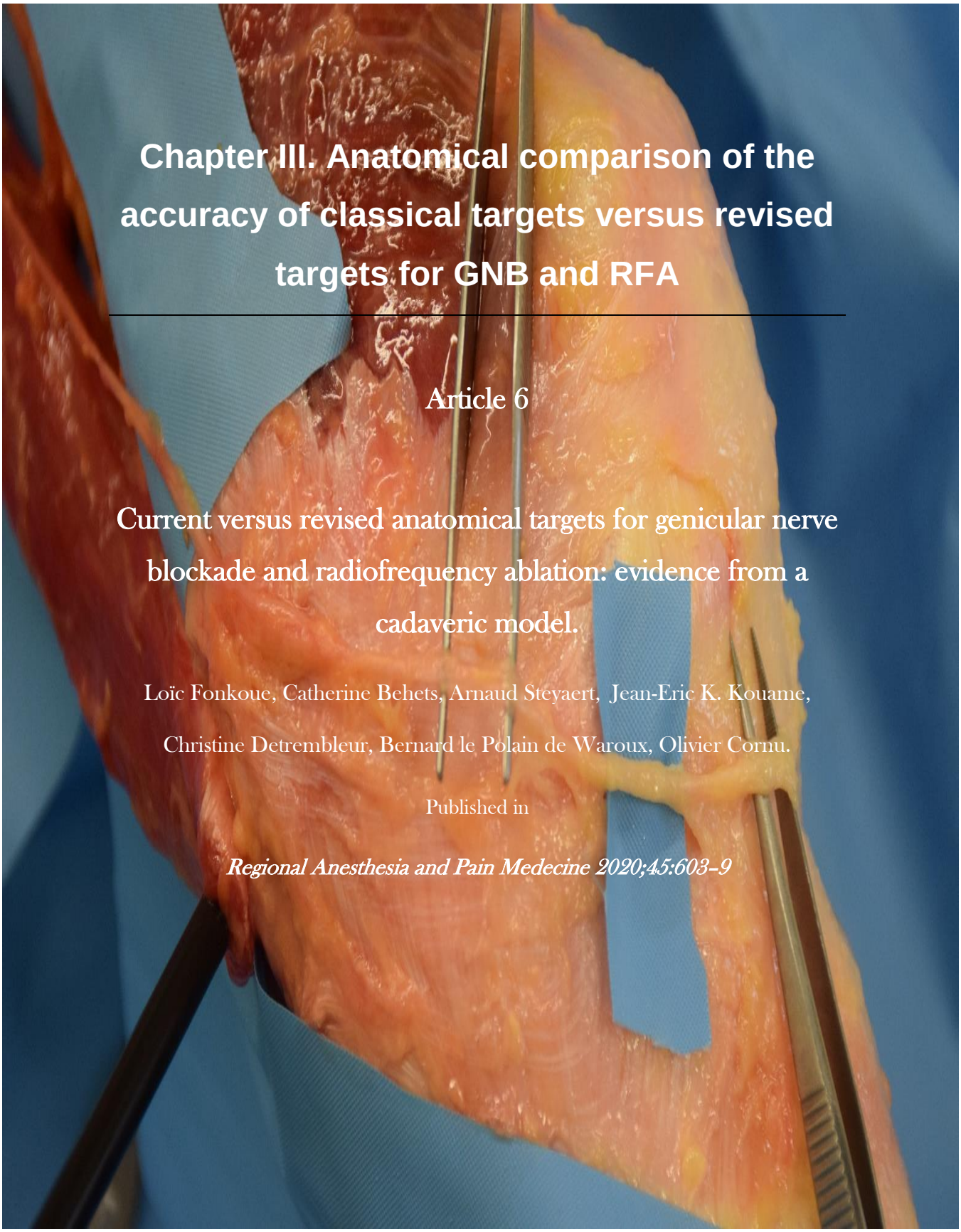


Figure 1 Comparison of classical (SLGN/c, SMGN/c, and IMGN/c) and our proposed landmarks for fluoroscopic-guided GNB and RFA. The trajectory of the SLGN (blue) from sciatic or common fibular nerve, SMGN (yellow) from nerve to vastus medialis and IMGN (green) have been drawn on fluoroscopic images. ((A) (A-P view) and (B) (lateral view)) Differences between classical and our proposed treatment targets areas for the SMGN (white arrow), and SLGN (black arrow) on the A-P and lateral views. (C) Trunk of the SMGN (yellow) captured before its distribution, by the active tip of an RF cannula with our new positioning (white). Note that the classical electrode position (upper black electrode) could not intercept the trunk of SMGN. (D) SLGN trajectory (blue) captured by the active tip of an RF cannula with our new positioning (white). If the classical electrode (upper black electrode) is lowered a bit, it would target only the transversal terminal branch of the SLGN. GNB genicular nerve blockade; IMGN, inferior medial genicular nerve; RFA, radiofrequency ablation; SLGN, superior lateral genicular nerve; SMGN, superior medial genicular nerve.

In conclusion, the need for revisiting anatomical landmarks for GNB/RFA is emphasized by a number of recently published studies based on anatomical

updates (including Tran et al's [16] study), proposing modified targets [102, 104, 124]. Also, recent reviews [14, 24] of the effectiveness of RFA to relieve chronic knee pain concluded that the anatomical basis is unclear and more research is needed to identify better targets. This shows that there is a real need of precise, validated anatomical landmarks for GNB/RFA to optimize clinical outcomes [131]. In their conclusion, Tran et al[1] stated that "the accuracy of their proposed landmarks should not be concluded as the need to revise classical landmarks". This is paradoxical since the need to revise the classical landmarks is also corroborated by the appropriate analysis of the results of their cadaveric dissections.



Chapter III. Anatomical comparison of the accuracy of classical targets versus revised targets for GNB and RFA

Article 6

Current versus revised anatomical targets for genicular nerve blockade and radiofrequency ablation: evidence from a cadaveric model.

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3.1 Abstract

Introduction Recent studies have proposed revised anatomical targets to improve accuracy of genicular nerve (GN) radiofrequency ablation (RFA). This study aimed to compare the accuracy of classical and revised techniques for fluoroscopic-guided GN-RFA in cadaveric models.

Materials and methods Fourteen knees from seven fresh frozen human cadavers were included in this study. For each cadaver, RF cannulas were placed to capture the GN according to the current targets in one knee, and the revised targets in the other knee, randomly. The stylet was removed from the cannula, plunged into non-diffusible black paint, and reintroduced entirely in the cannula, to create a limited black spot on the tissues at the top of the active tip. Anatomical dissection was performed, and the accuracy of both techniques was compared.

Results The mean distance from the top of the active tip to the nerve was significantly lower with revised than current targets for the superior-medial GN (0.7 mm vs 17.8 mm, p = 0.01) and the descending branch of the superior-lateral GN (3.7 mm vs 24.4 mm, p = 0.02). In both superior medial GN and superior lateral GN, the accuracy rate was higher with revised than current targets: 100% vs 0% and 64% vs 35%, respectively. In addition, the accuracy of revised targets for the recurrent fibular nerve (RFN) and the infrapatellar branch of saphenous nerve (IPBSN) was 100%.

Conclusion. This study demonstrates that the revised targets are much more accurate than current targets for GN-RFA.

3.2 Introduction

First described by Choi et al [10] in 2011, genicular nerve (GN) radiofrequency ablation (RFA) is a promising technique for the treatment of chronic knee pain. It disrupts articular sensory afferent pathways from the knee joint to the central nervous system, decreasing the nociceptive input [66]. Because of the limited size of radiofrequency lesions, its success relies on the precise placement of the cannulas, as close as possible to the nerves supplying the knee joint capsule. However, the complexity of the knee innervation has resulted in a disparity in procedural techniques among the available controlled and observational studies [24]. Two recent reviews have concluded that there is a lack of clarity about anatomical targets of this procedure and that more research is needed to better identify neural targets [14, 24]. Newer, more robust cadaveric dissection studies [16, 20, 101] have called into question the anatomical foundations of the targets originally proposed by Choi et al [10]. These have resulted in several papers proposing new protocols with revised anatomical targets to capture GN with more accuracy [102-104, 124]. Two very recent studies combined a comprehensive literature review with anatomical dissections of 21 cadavers to identify reliable targets [101], and validated their accuracy in a cadaveric model for GN blockade [103].

Since the current anatomical targets for GN-RFA used clinically for a decade have allowed chronic knee pain reduction to a certain degree, it is necessary to compare, with a robust methodology, first the accuracy of the revised targets to the current targets in a cadaveric model, and secondly their effectiveness in patients suffering

from chronic knee pain. The current study aims to compare the accuracy of the revised anatomical targets [103] to that of the current targets for fluoroscopic-guided GN-RFA in cadaveric knees. Moreover, as the course, the precise location and the target point of the superior medial genicular nerve (SMGN) and superior lateral genicular nerve (SLGN) as well as their relation to the genicular arteries are still debated [130, 132], we hoped to clarify these controversies with new anatomical material.

3.3 Methods

This study was conducted at the Laboratories of Anatomy and Experimental Surgery, UCLouvain. All the bodies were donated to the institution in accordance with Belgium law and regulations. Approval from the University's Research Ethics Committee was obtained. The study was conducted in 2 parts. In the first part, we used 4 cadaveric knees (2 fresh frozen and 2 embalmed with zinc chloride solution) for pilot trials in order to design the best way to assess the accuracy of anatomical landmarks for fluoroscopic guided GN-RFA. In the second part (main study), we compared the accuracy of current versus revised targets in 14 fresh frozen knees.

Pilot study

In the knees of one fresh frozen cadaver, we tried to reproduce the clinical conditions allowing to create radiofrequency lesions on the genicular nerves that could be appreciated. After thawing at room temperature for 24 hours prior to the experimentation, both knees were protected in a waterproof bag and heated by

immersion in a water bath at 56°C for 30 minutes, to reach a nearly normal body temperature. A 18-gauge 10 mm active tip, 145 mm long monopolar RF introducer cannula was placed at each anatomic site under fluoroscopic guidance, according to current targets [10, 64, 66, 75, 102] for one knee and revised targets[103] for the contralateral knee. The initial temperature of the limbs was 34°C, as measured by the thermocouple built in each electrode. Each site was lesioned with a RF generator (Baylis Pain Management Generator V3.0®) at tissue temperature of 80°C for 90 seconds. Both limbs were dissected by an anatomist with 9 years of experience, who had performed the dissections of several previous studies addressing the innervation of the knee joint. Unfortunately, even with the use of 3.5x magnification lens, no lesion could be identified in the tissues of both limbs. The limbs were closed and we performed several successive radiofrequency tests at different sites and different tissues in order to highlight the lesioned tissue so that it could be visually appreciated. We raised the temperature to 90°C for 120 s, we injected 2 ml of 0.9% saline or 1% lidocaine prior to lesioning [133] and we also tested the injection 1ml of egg white prior to lesioning [134]. Lesions were clearly visualized when RF was applied on muscle and skin, but not on the nerves, tendons, knee capsule, fat or deep tissues.

In one knee of the second cadaver, 22-gauge, 10 mm active tip, 100 mm long RF cannulas were placed under fluoroscopic guidance at each site, according to current targets for one knee and revised for the other one. Through each cannula, we injected a volume of 0.1 ml of colored lidocaine (1 mg of methylene blue powder per ml of 1% lidocaine solution). After completion of all the injections, the limbs were dissected to check for accuracy. Since our study aimed to assess the

accuracy of anatomical landmarks with regards to RF lesion size, we first measured the diffusion surface of blue lidocaine with a sliding digital caliper. We found 14.6 mm (SD 4.9) × 21.1 mm (SD 6.1). We observed that the blue solution spread beyond the limits of all types of RF lesion, and therefore, would not reliably assess the accuracy for RFA.

In the next knee, the same RF cannulas were placed, but instead of inserting a RF electrode or injecting a very small volume, the stylet was removed from the cannula and plunged into black paint, then reintroduced entirely into the cannula. The procedure was repeated 2 times to ensure that the black paint stained the tissue at the top of the active tip like a fountain pen stains the paper. After dissection, a limited black spot was consistently observed, without diffusion to surrounding tissues. We concluded that this would be a more reliable method to assess the accuracy of RF lesions regarding the anatomical targets.

Main study

Fourteen knees from 7 fresh frozen cadavers, 4 men and 3 women, aged 78.4 ± 10.0 years, without evidence of prior knee surgery or trauma, were used. For each cadaver, one knee was randomly assigned to the RF simulation procedure with current targets [64, 66, 75, 102], while the other one underwent the same procedure with revised targets (figure 1) as described below.

For the SMGN, we started with an anterior-posterior (A-P) X-ray view. The RF cannula was inserted 1 – 2 cm medial to the femur, at the junction of the medial femoral cortex and the medial condyle and advanced to the superior edge of the

medial condyle until the tip touched the bone. The C-arm then was rotated to have a true lateral view in which both femoral condyles are superimposed. The tip of the cannula was then adjusted to fit above or just in front the adductor tubercle (AT), (figure 1A, B).

The inferior medial genicular nerve (IMGN) was targeted like currently done in clinical practice [10, 66] (figure 1A, B).

For the superior lateral genicular nerve (SLGN), on the A-P view, the RF cannula was inserted 1 – 2 cm lateral to the femur and advanced obliquely toward the superior edge of the lateral femoral condyle until the tip touched the bone. Then, in a true lateral view, the needle tip was adjusted to fit the target area located at the junction between the superior edge of the lateral condyle and the posterior femoral cortex (figure 1A, B).

For the infra-patellar branch of saphenous nerve (IPBSN), we drew a transversal line passing by the apex patellae and another one passing by the top of the tibial tuberosity. Four centimeters medially to the apex patellae, we drew a longitudinal line connecting both transversal lines (figure 1C), which corresponds to the targeted treatment line. The RF cannula was inserted perpendicularly through the skin wheal placed at the 2 extremities of this line to mark the limits of the treatment zone.

For the recurrent fibular nerve (RFN), a longitudinal line was drawn below the Gerdy's tubercle and the target point was located on this line, 1 cm below the inferior edge of the tubercle (figure 1D). The RF cannula was inserted just below

the Gerdy's tubercle and advanced longitudinally under the muscles until the tip touched the bone. The length of the cannula inserted above the 10 mm active tip was marked so as not to exceed 1 cm.

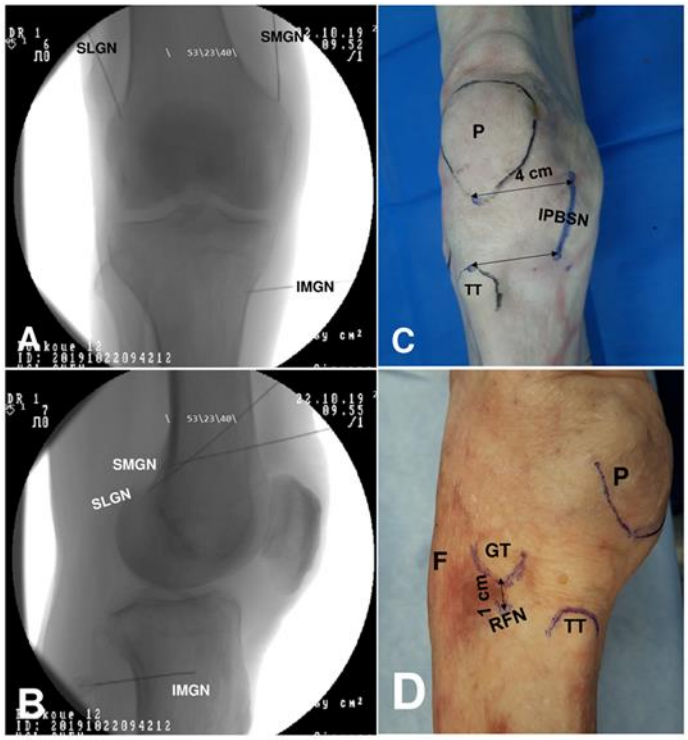

FIGURE 1 Revised anatomical targets for fluoroscopic guided RF ablation of genicular nerves. (A) A-P X-ray view. (B) Lateral X-ray view. (C) Landmarks for IPBSN targeting. (D) Landmarks for RFN targeting. SLGN, superior lateral genicular nerve; SMGN, superior medial genicular nerve; IMGN, inferior medial genicular nerve; IPBSN, infrapatellar branch of saphenous nerve; RFN, recurrent fibular nerve; P, patella; TT, tibial tuberosity; GT Gerdy's tubercle; F, fibula head.

All procedures were performed under fluoroscopic guidance with 22G, 10 mm active tip, 100 mm long RF cannulas (Cosman Medical, Inc., Burlington, MA, USA). For all the targeted sites, after verification of adequate cannula placement, the stylet was removed, soaked entirely in black paint and reintroduced entirely in the cannula until the distal opening of the active tip. This operation was repeated two times for each site to ensure that the tissue at the top of the active tip was dyed. Fluoroscopic images were obtained before and after the marking to verify the needle position. The stylet was then removed, after which the cannula was removed too.

After the completion of all RF simulation procedures, the limbs were dissected by the same experienced anatomist to assess for accuracy, based on location of the black mark relative to the targeted genicular nerve. The shortest distance from the midpoint of the black mark to the targeted nerve was measured with a sliding digital caliper. Then, considering the midpoint of the black mark as the top of the active tip, and considering the direction of cannula placement and its final position during the procedure, we traced the theoretical location of the 10 mm active tip. We measured the shortest distance from the 10 mm active tip to the targeted nerve. To assess the accuracy of each cannula placement, we traced the hypothetical largest RF lesion volume (transversal distance 7.4 mm, longitudinal distance 12.9 mm, distance beyond the tip 2.4 mm) [73, 74] around the 10 mm active tip to investigate if the targeted nerve would have been captured if a RF lesion had been applied. For the IPBSN, we considered the target accurate if the nerve was found within the limits of the treatment line.

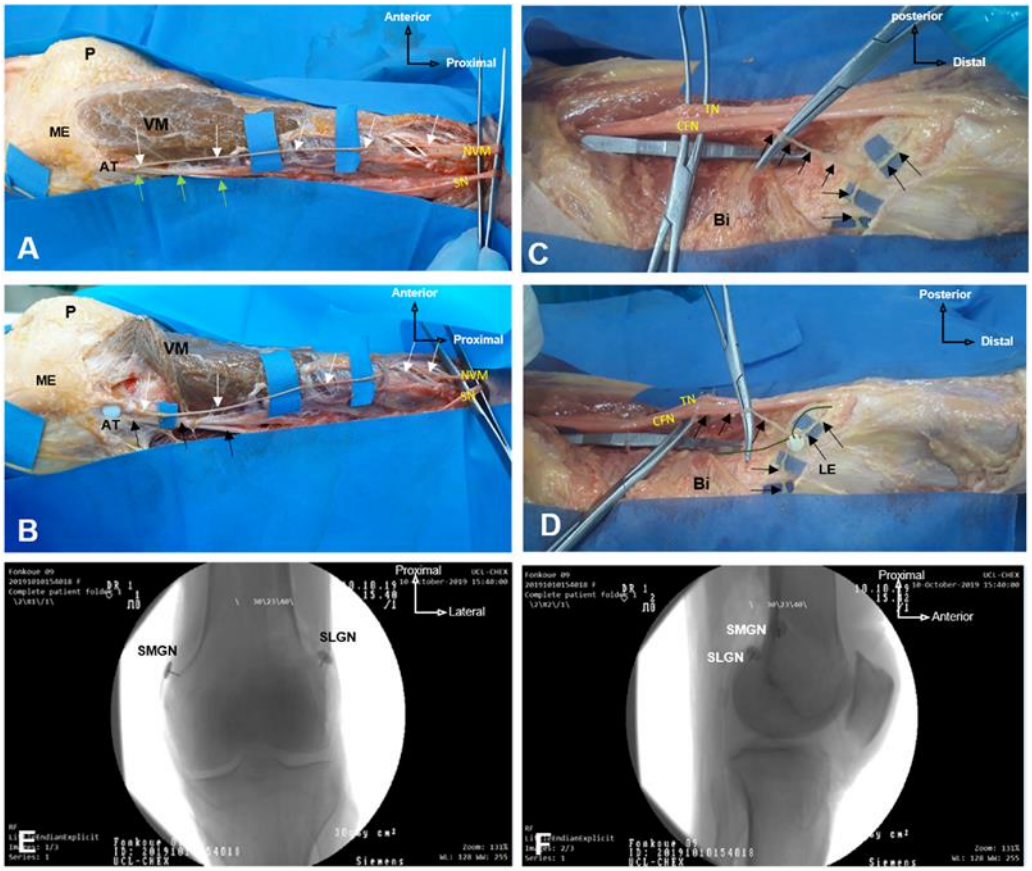

FIGURE 2 Identification process of the exact points to accurately target the trunk of the SMGN and SLGN in each specimen for fluoroscopic guided RF ablation. (A) Medial aspect of the thigh and the knee, adductor canal opened: SMGN (white arrows) originating from the NVM, running distally along the adductor magnus tendon (green arrows) towards the adductor tubercle (AT). (B) A white radio-opaque thumbtack is fixed through the nerve at its bony contact before its distribution to the knee joint. (C) and (D) Posterior-lateral aspect of the distal thigh and the knee, biceps femoris muscle (Bi) cut and retracted: SLGN (black arrows) establishing a bony contact in the area connecting the posterior cortical of the lateral shaft of the femur (green line) to the posterior-lateral edge of the lateral condyle (green curve), and then dividing in its 2 terminal branches. A white radio-

opaque thumbtack is fixed through the nerve before its bifurcation to capture both terminal branches. (E) Antero-posterior and (F) lateral radiographs of the knee after dissection, showing the location of the thumbtacks. P, patella; ME, medial epicondyle; VM, vastus medialis muscle; SN, saphenous nerve; NVM, nerve to the vastus medialis; CFN, common fibular nerve; TN, tibial nerve; Bi, biceps femoris muscle; LE, lateral epicondyle, SMGN, superior medial genicular nerve; SLGN, superior lateral genicular nerve.

Additionally, during the dissection of the 14 specimens, we checked for the origin of the SMGN and the SLGN, and also investigated if these nerves (or their branches) were running with the SM or SL genicular vessels. Finally, at the end of the dissection of each knee, we fixed a thumbtack through the trunk of SMGN and SLGN into the underlying bone, before their distribution to the knee capsule, and performed true AP and lateral radiographs (figure 2). These locations, for the 14 specimens, were consolidated on unique A-P and lateral radiographs to generate a frequency map of the most accurate targets for fluoroscopic guided GN-RFA in our sample.

Statistical analysis was performed using SPSS 25.0 (Chicago, Illinois, USA). The various distances are described as median [range]. The accuracy of the cannula placement for each nerve with both techniques was described as proportions and compared using the Fischer's exact test. We used the Mann Whitney-U test to compare the distances from the nerve to the black mark in both techniques. A P value < 0.05 was taken to indicate a significant difference.

3.4 Results

Table 1. Median distance and range from genicular nerve to the active tip of RF cannula: Comparison of classical targets versus revised targets with Mann Whitney test

Genicular nerve	Anatomical target	Median distance 1* [range], in mm	P value	Median distance 2** [range], in mm	P value
SMGN	Classical	19.0 [14.0 – 20.0]	0.01	18.0 [14 – 23]	0.02
	Revised	0.0 [0.0 – 2.0]		0.0 [0.0 – 2.0]	
SLGN-L	Classical	1.0 [0.0 – 18.4]	0.65	1.0 [0.0 – 18.4]	0.32
	Revised	2.0 [0.0 – 11.0]		0.0 [0.0 – 10.0]	
SLGN-D	Classical	24.0 [19.0 – 30.6]	0.02	24.0 [19.0 – 30.6]	0.02
	Revised	2.0 [0.0 – 10.0]		2.0 [0.0 – 10.0]	
IMGN	Classical	0.0 [0 – 2.0]	0.83	0.0 [0 – 2.0]	0.83
	Revised	0.0 [0 – 2.0]		0.0 [0 – 2.0]	

*Distance 1: from the top of the active tip to the nerve
**Distance 2: shortest distance from the entire length of the active tip to the nerve
SMGN indicates superior medial genicular nerve; SLGN-L, superior lateral genicular nerve – transversal branch; SLGN-D, superior lateral genicular nerve – descending branch; IMGN, inferior medial genicular nerve.

The median distance from the top of the active tip to the targeted nerve was significantly lower using revised targets than classical targets for the SMGN (0.0 mm vs 19.0 mm, p = 0.01) and the descending branch of the SLGN (2.0 mm vs 24.0 mm, p = 0.02) (Table 1).

Moreover, for the SMGN, the median shortest distance from the 10 mm active tip to the targeted nerve was significantly lower using revised targets than classical targets (0.0 mm vs 18.0 mm, p = 0.02). It was also the case of the descending branch of the SLGN (2.0 mm vs 24.0 mm, p = 0.02) (Table 1).

In our specimens, the accuracy rate of the simulated RF monopolar lesions was higher with revised targets than classical targets for the SMGN (100% vs 0%) and the SLGN (64% vs 35%) (Table 2).

Table 2. Comparison of the accuracy rate of a monopolar RF lesion with classical Vs revised targets

Nerve	Accuracy		*p*
	Classical targets	Revised targets	
SMGN	0/7 (0%)	7/7 (100%)	< 0.001
SLGN	2.5/7 (36%)	4.5/7 (64%)	0.257
IMGN	7/7 (100%)	7/7 (100%)	N/A
IPBSN	No treated	7/7 (100%)	N/A
RFN	No treated	7/7 (100%)	N/A

SMGN indicates superior medial genicular nerve; SLGN, superior lateral genicular nerve; IMGN, inferior medial genicular nerve; IPBSN, infrapatellar branch of saphenous nerve; RFN, recurrent fibular nerve; N/A, non-applicable.

The accuracy rate for the IMGN was 100% in both techniques. There was no difference between the mean distances from the IMGN to the top of the active tip in both techniques.

The IPBSN was found in all the specimens and the revised targets was 100% accurate.

With revised targets, the RFN was captured in 100 % of specimens, without any lesion to the common fibular nerve.

In the 14 specimens, the SMGN originated from the nerve to the vastus medialis (NVM) (figures 2-3), and detached no direct articular branch above the adductor tubercle (figure 4). In 8 cases, a small branch was detached from the nerve above the AT, and ran to the distal part of the vastus medialis muscle. We found that the current targets capture the transversal vessels detached from the descending genicular artery (at the periosteal areas connecting the shaft to the medial condyle), which were not accompanied with a terminal branch of the SMGN (figure 4).

The SLGN originated from the sciatic nerve in 6/14 cases and common fibular nerve in 8/14cases, and divided into 2 terminal branches around the area connecting the posterior edge of the femoral shaft and the lateral femoral condyle (figures 2-3). Its ascending (transversal) branch joined the superior lateral genicular vessels (SLGV) in 10/14 cases, but its descending branch was not accompanied with vessels. In 4 cases, the transversal branch of the nerve was found about 1cm below the SLGV.

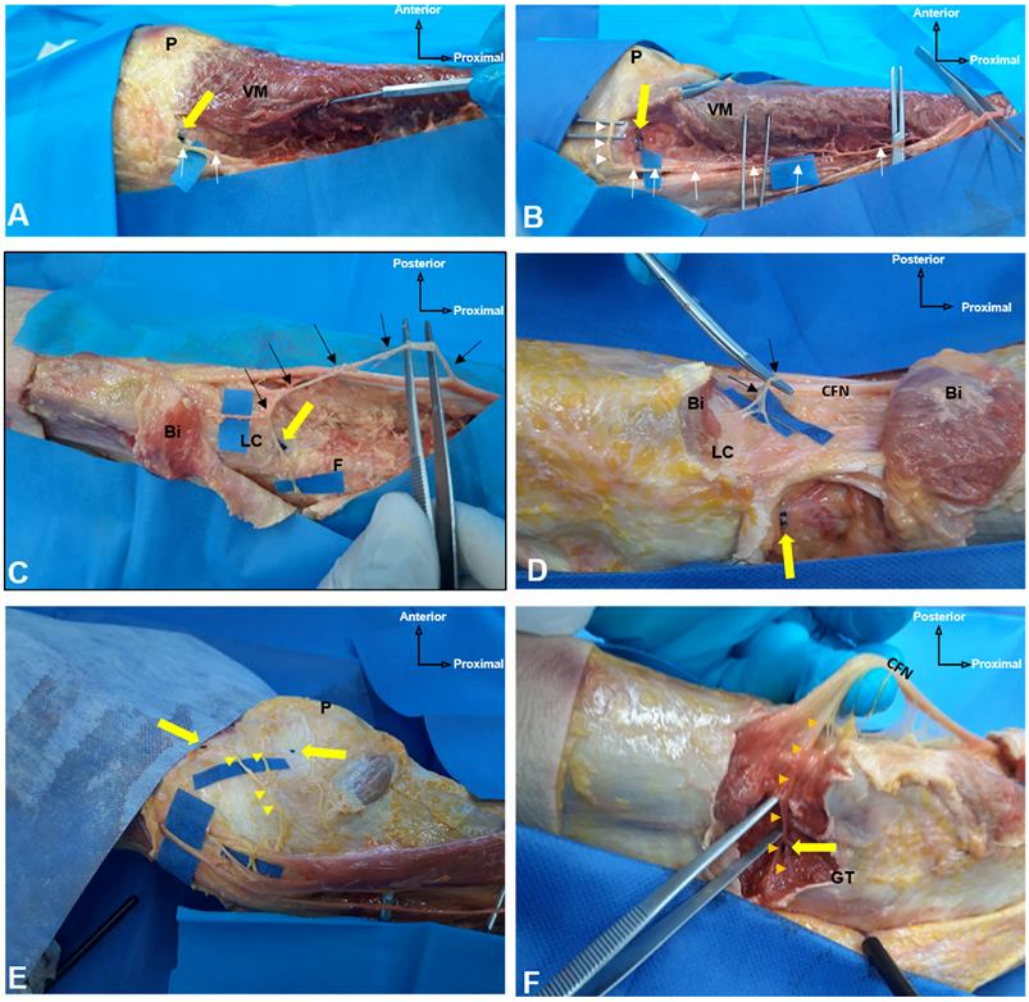

Figure 3 Post-procedural anatomical dissections. (A) Medial aspect of the distal thigh and the knee, vastus medialis muscle is partially lifted. Lesioning of the SMGN (white arrows) using revised target: the nerve is in contact with black mark (yellow thick arrow). (B) Medial aspect of the distal thigh and the knee, vastus medialis muscle is partially lifted. Lesioning of the SMGN (white arrows) using current target: the SMGN is too far from the black mark. Even its transversal terminal branch (white

arrowheads) cannot be lesioned. (C) Posterior-lateral view of the knee, biceps femoris (Bi) cut and retracted. Lesioning of the SLGN using revised target: in this specimen, the bony contact of the SLGN is lower, on the posterior edge of lateral condyle (LC). Only the ascending terminal branch is captured. (D) Posterior-lateral view of the knee, biceps femoris (Bi) cut and retracted. With current targets, only the distal part of the ascending terminal branch could be captured. (E) anterior-medial view of the knee: IPBSN with 2 terminal branches (yellow arrowheads) running within both extremities of the treatment line. (F) Lateral view of the knee and proximal leg, the proximal part of the muscles has been removed. RFN (orange arrowheads) captured by the black mark at its distal extremity, far away from the CFN. P, patella; LC, lateral condyle; VM, vastus medialis muscle; Bi, biceps femoris muscle; F, posterior cortex of the lateral femoral shaft; CFN, common fibular nerve; GT, Gerdy's tubercle.

The frequency map of the most accurate targets for the SLGN and the SMGN during fluoroscopic guided procedures is presented in figure 5. The location of the SMGN was constant in all the specimens; revised targets would have captured the nerve in 14/14 knees. There was a little variability in the most accurate target for the SLGN; the revised landmarks would have captured the trunk of the nerve in 10/14 knees (whereas the classical targets wouldn't have captured it). In fact, there are 2 specimens in which the target should have been more proximal and 2 others more distal. To get close to a 100% accuracy with revised targets for the SLGN, a proximal and a distal lesion should be added to take this variability in account.

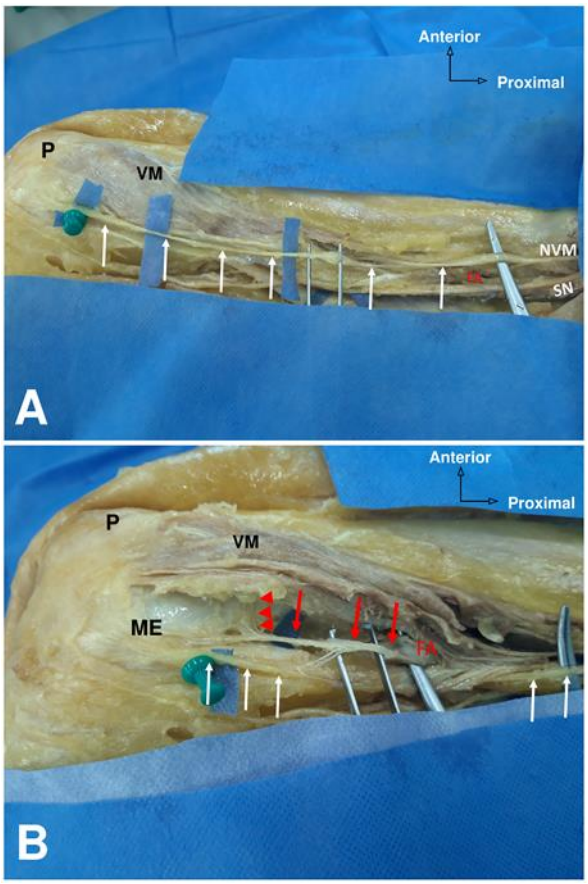

FIGURE 4 (A) Medial aspect of the thigh and the knee of an embalmed specimen, adductor canal opened: SMGN (white arrows) dissected all along its course. (B) Same view in the same specimen, with the distal part of the vastus medialis muscle (VM) partially retracted anteriorly: evidence that the transversal branches (red arrowheads) at the junction of femoral shaft and medial condyle are vessels from the descending genicular artery (red arrows) with no contribution of the SMGN (white arrows). P, patella; ME, medial epicondyle; VM, vastus medialis muscle; NVM, nerve to the vastus medialis; SN, saphenous nerve; FA, femoral artery.

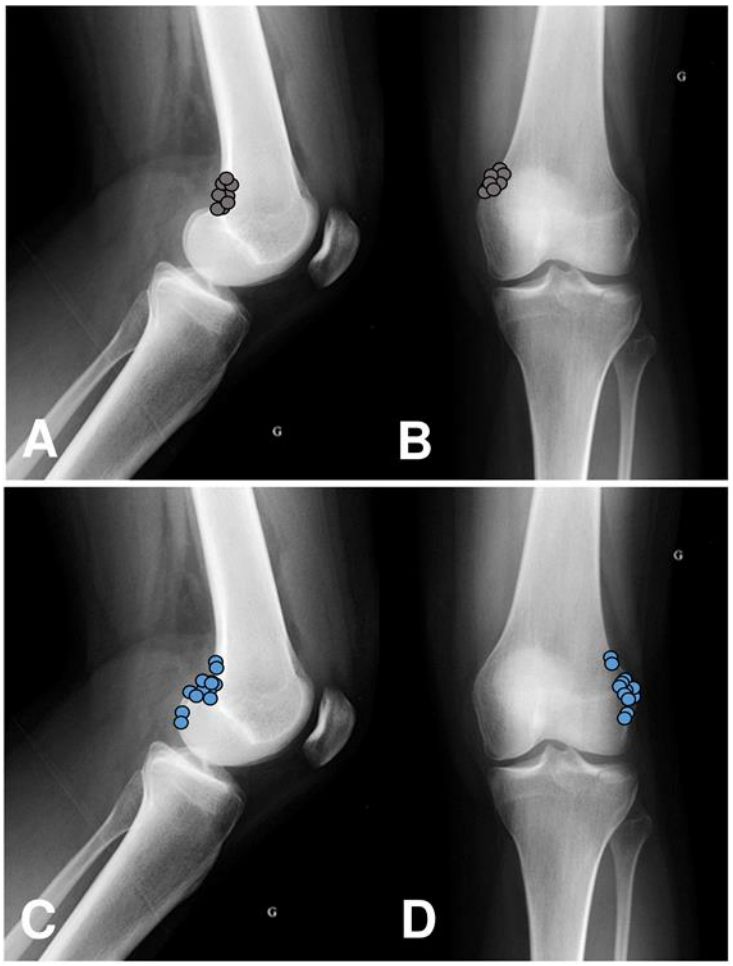

FIGURE *5* Scatter plot representing, on single lateral and A-P X-ray views, the aggregation of all the exact target points of the 14 specimens for accurate capture of the trunk of the SMGN (A and B) and SLGN (C and D). Each dot represents the most accurate target point to capture the specific genicular nerve in one specimen, on the corresponding X-ray view.

3.5 Discussion

This study demonstrates that the revised targets for RFA of the SMGN and SLGN are more accurate than the classical targets. Moreover, the revised targets are 100% accurate on the RFN and the IPBSN, which play an important role in the sensory innervation of inferior lateral and inferior medial quadrants of the knee joint, but are not targeted by the current procedure. It shows once more that there is a real need to move forward toward a better technique, with accurate and validated anatomical targets [131]. The frequency map (figure 5) of the accurate targets points to capture the trunk of the SMGN and SLGN before their distribution to the knee joint capsule is a unique tool that gives precise and reliable locations of the nerves. We believe that it should guide physicians during RF procedures under fluoroscopic guidance.

The anatomical bases for the classical targets for RF ablation of genicular nerves are somewhat weak. Choi et al [10] who first described the procedure dissected only 2 specimens. They chose to target only 3 nerves and acknowledged that denervation of other articular branches would probably give different results. Concerning the SMGN, the current target was based on an early description of its origin and course [21], describing the SMGN as a branch of the tibial nerve, running transversally from posterior to anterior in the same trajectory as the superior medial genicular vessels. Despite the fact that the subsequent anatomical dissection studies [19, 22] did not find such results, and the few studies [12, 18] that repeated it did not show a single illustration, that description has been widely admitted. Choi et al chose the current cannula placement "*to be parallel to the*

target nerve", but this was based on incorrect anatomical information. Almost all the recent anatomical studies [12, 16, 17, 20, 101-103] found that the SMGN descends vertically along the adductor magnus tendon toward the adductor tubercle, which is the best target for the SMGN [12, 102]. The SMGN divides distally to the adductor tubercle into its terminal branches. Thus, a lesion made above or just in front of the adductor tubercle would capture the trunk of the nerve (Figure 6A), but a lesion performed distally to the AT may not capture all terminal branches. In the current study, most of the thumbtacks fixed on the SMGN were above the AT. Since the course of the SMGN has been clarified by recent studies and it has been demonstrated that it descends completely posteriorly, the classical target is no more relevant. Given the limited size of the radiofrequency lesion and the average A-P depth of the distal part of the femoral shaft, an active tip which is at midpoint or at 60% from the anterior cortex of the femoral shaft would not capture the SMGN (Figure 6A). To cross the trajectory of the SMGN and ensure its capture, the active tip should be advanced totally posteriorly, above or just in front of the AT (figure 6A). Moreover, the present study shows that the current target does not even capture the transversal terminal branch of the SMGN (figure 4B), which runs at the level of medial epicondyle, and is accompanied by vessels.

The accuracy of cannula placement for the SLGN using revised target was 64% (vs 35% for current target). This can be due to 2 reasons. First, in 2 cases, the nerve established its bony contact at the posterior edge of the lateral condyle (figures 3C and 5C) and then, only one of its terminal branches was captured (figure 3C). Secondly, in 2 cases, the nerve bifurcated proximally, before its bony contact, and then, only the transversal branch was captured. To improve the capture of both

terminal branches of the SLGN, we propose not only one lesion, but a palisade of lesions (2-3 contiguous lesions), starting from the area connecting the posterior cortex of femoral shaft to the lateral femoral condyle and moving backwards and distally to the posterior edge of the lateral condyle (Figure 6B). In addition to better accuracy, the revised target avoids lesioning the superior lateral genicular vessels, contrary to current targets. In addition to the SLGN, Tran et al [16] reported in all their specimens, a "*long articular branch that originated just inferior to the bifurcation of the sciatic nerve to the superior border of the lateral condyle*". Thus, they reported two constant articular nerves, both found in all the specimens, originating from common fibular nerve/sciatic nerve, and innervating the superior-lateral aspect of the knee joint. We did not find those two simultaneous nerves, although we performed systematical dissections. To our knowledge, no other author who performed cadaveric dissection described such findings.

The frequency map provided in this study only concerns the SLGN and SMGN, which are controversial among authors. The anatomical target for the IMGN is not debated as all the authors have found that the current landmark is accurate. Concerning the IPBSN and RFN, we previously defined accurate clinical targets, easily identifiable and reproducible. Building a fluoroscopic-based frequency map for the IPBSN and RFN as we have done for the SMGN and SLGN would not be relevant. Ultrasound could be helpful, but the use of fluoroscopy is not clinically justified for the IPBSN. It should be noted that, since the IPBSN is subcutaneous, the cannula should be inserted deep enough to avoid skin lesion when using conventional RF and that pulsed RF could be preferable. The physician should be

careful when lesioning the inferior-medial quadrant of the knee (IMGN and IPBSN), which requires multiple lesioning compared to other quadrants.

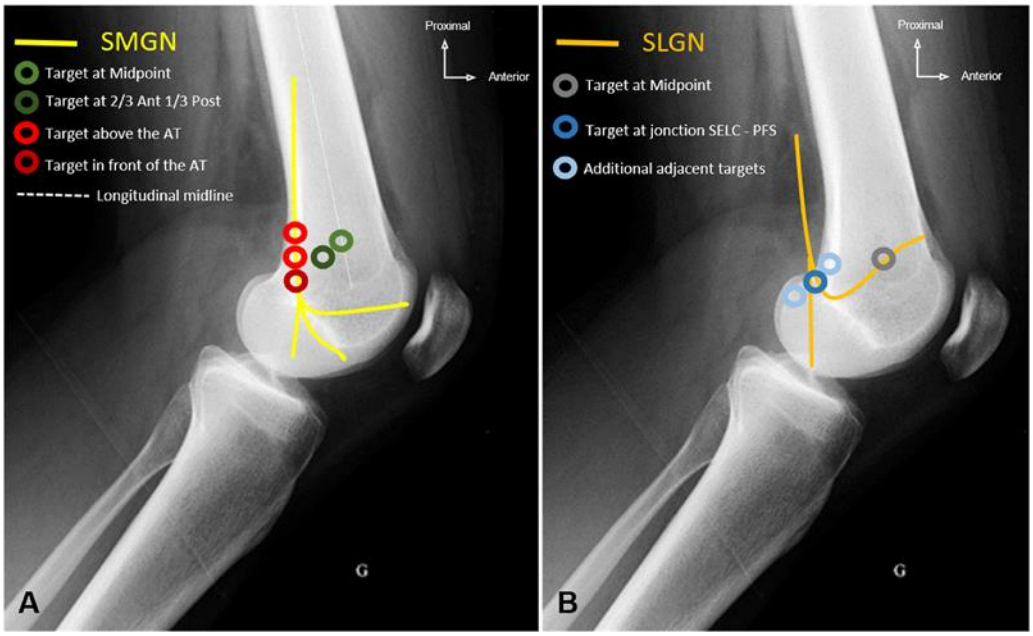

FIGURE 6 Summary of the different targets with the main course of the nerves, on lateral radiographs. (A) A lesion performed above or just in front of the AT would capture the SMGN whereas classical target would not. (B) Due to the variability of the bony contact of the SLGN, a palisade of lesions (3 blue circles) would improve the capture rate of the SLGN and all its terminal branches. SLGN, superior lateral genicular nerve; SMGN, superior medial genicular nerve.

Even though clinical studies have shown positive results [10, 14, 24], these would probably be enhanced with better anatomical targets. When looking carefully at a

few recent anatomical studies that support the current landmarks, there is one striking remark. The illustration of their dissections does not allow to identify either the origin and the course of the genicular nerves [115] or their ending at the level of the knee [23]. This is a huge bias since it is not easy to visually discriminate between very small nerves and vessels in a cadaver, a fortiori in an embalmed cadaver. To illustrate that, we did a direct dissection through a "window" at the site of the current target for the SLGN and we found a structure that closely resembled a nerve (figure 7A). Based on that, we would have concluded that the current target was accurate. But when we realized a total dissection of that branch until its origin, we realized that it was a vessel (figure 7B). The "figure 3" presented in recent anatomical study of Vanneste et al [115] illustrates that possible bias. Based on the dissections presented on that figure, it is not possible to be certain that the highlighted structures are genicular nerves. This could be misleading as it maintains the doubt among physicians about the real need to improve the current landmarks. To avoid confusion, we suggest that further studies conducted to demonstrate a genicular nerve should include either dissection of the nerve since its original trunk (which is big and easily identifiable) to its termination at the level of the knee, or vascular injection to highlight the small vessels, or histological analysis. Only such a rigorous methodology shared by all the researchers, would irrefutably demonstrate the best targets.

It is worth reporting that a volume of 0.1ml (10 times less than what is currently used for prognostic nerve blocks) dyed lidocaine spreads beyond the limits of the larger RF lesion. This may explain why a prognostic genicular nerve block using a local anesthetic volume of 1ml for subsequent RFA eligibility does not improve

the treatment success [75]. Based on the findings of our pilot study, we should use a volume of 0.1 ml or less.

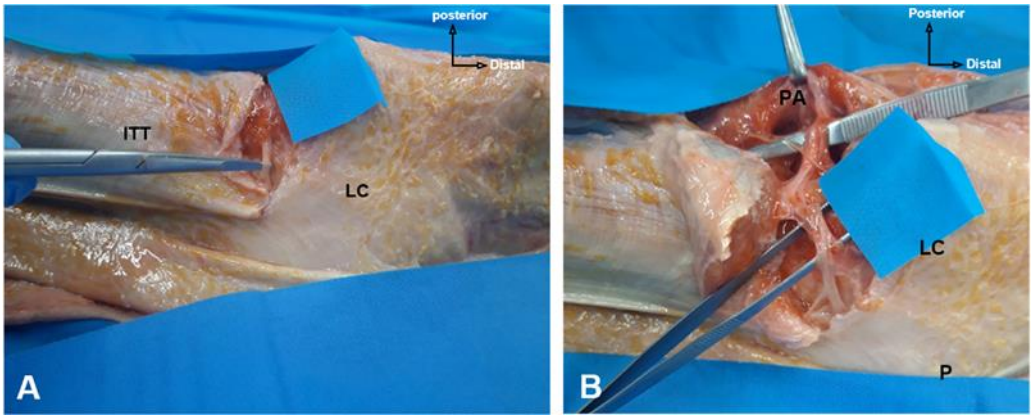

FIGURE 7 (A) Lateral view of the knee, the vastus lateral muscle and the fascia lata are left in place: Dissection performed through a "window" directly at the level of the current target for SLGN. A transversal structure that resemble a nerve is found. (B) Same view on the same knee: when performing a complete dissection of that "nerve" (supposed to be the SLGN) to check for its origin, it is rather the superior lateral genicular artery originating from popliteal artery. LC, lateral condyle; ITT, iliotibial tractus covering vastus lateralis muscle; P, patella; PA, popliteal artery.

This study has some limitations. First, the accuracy of cannula placement would have been more definitely assessed if the RF lesions were directly appreciated during dissection. This was not possible despite a rigorous methodology to

simulate clinical conditions (fresh warmed cadavers, injection of fluids...). However, the use of non-diffusible ink to create just a black mark, rather that injecting fluids like in other studies [12, 100, 103, 115], is a reliable alternative. Secondly, a larger sample size would have allowed to create a more exhaustive figure map representing the entire spectrum of variations of the target points, especially for the SLGN, which was the only nerve to have less than 100% accuracy with revised targets. Nonetheless, our methodology for the exact localization of target points for each nerve on AP and lateral fluoroscopic image seems to be the most robust and would be of great interest for physicians in their daily practice.

Conclusion

This study found that the revised targets are more accurate than current targets for RFA of the SLGN and SMGN. In addition, the revised targets are 100% accurate for the RFN and the IPBSN, which are not targeted by the current procedure. The current technique, targeting only 3 nerves, based on confusing anatomical foundations, definitely needs to be improved. Our map presents the localization of exact target points to accurately capture the SLGN and SMGN, and provides an optimal design to guide needle placement during GN-RFA. Further studies must be conducted to compare the effectiveness and safety of both techniques for RF ablation of the genicular nerves in patients suffering from chronic knee pain.

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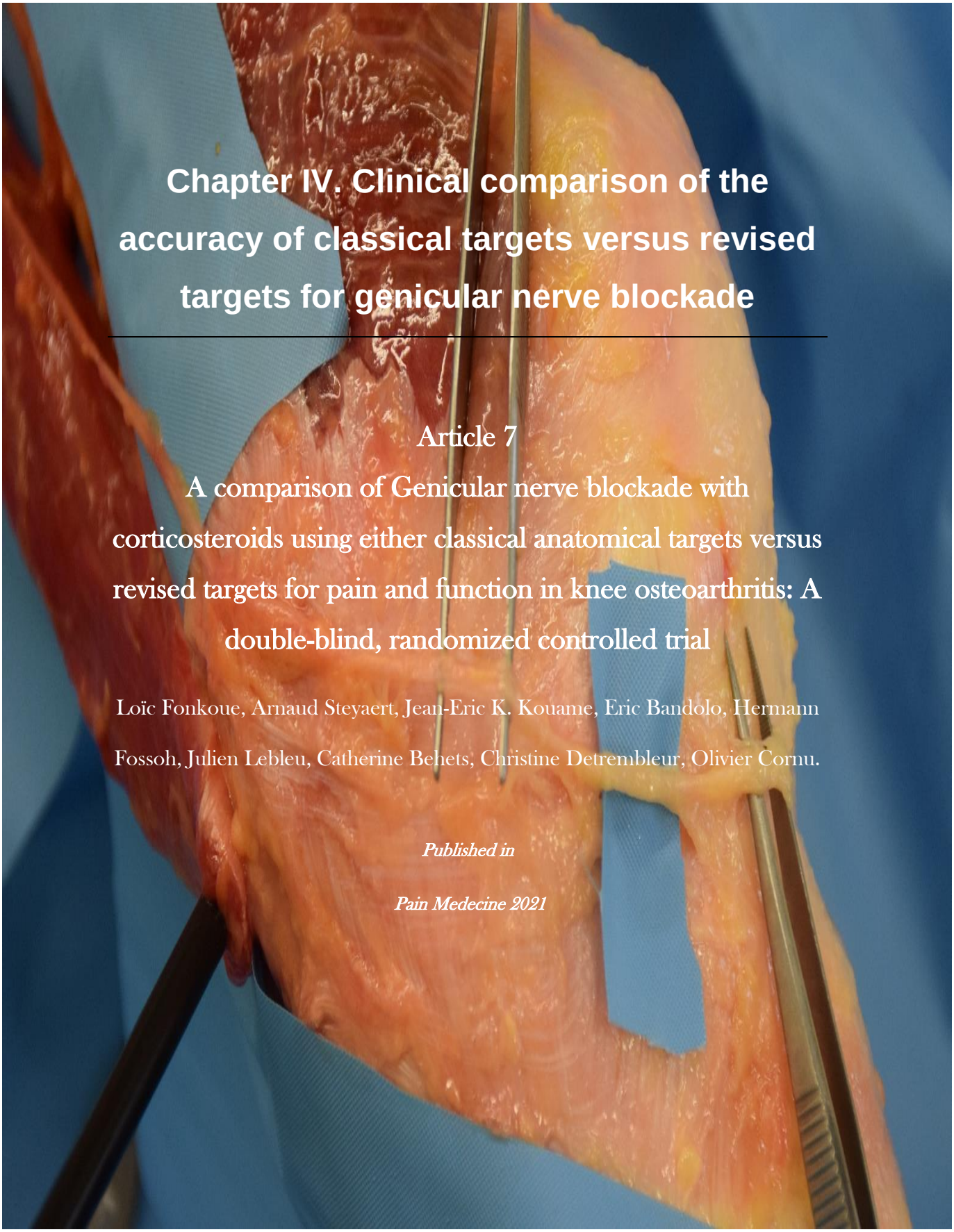

Chapter IV. Clinical comparison of the accuracy of classical targets versus revised targets for genicular nerve blockade

Article 7

A comparison of Genicular nerve blockade with corticosteroids using either classical anatomical targets versus revised targets for pain and function in knee osteoarthritis: A double-blind, randomized controlled trial

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4.1 Abstract

Objective. Compare the effectiveness of genicular nerve blockade (GNB) using classical anatomical targets (CT) versus revised targets (RT) in patients suffering from chronic knee osteoarthritis pain

Design. Double-blinded randomized controlled trial.

Setting. Pain medicine center of a teaching hospital.

Methods. We randomly assigned 55 patients with chronic knee osteoarthritis pain to receive a GNB (using a fluid mixture of 2ml: lidocaine 1% + 20mg triamcinolone) with either classical targets (CT-group, n=28) or revised targets (RT-group, n=27). Numeric rating pain scale (NRS), Oxford knee score (OKS), Western Ontario and McMaster Universities osteoarthritis index score (WOMAC), Quantitative analgesic questionnaire (QAQ) and global perceived effects were assessed at baseline, and at 1-hour, 24-hours, 1, 4 and 12 weeks post intervention.

Results. The RT-group showed greater reduction in NRS mean score at 1-hour post-intervention (2.4±2.1 vs 0.4±0.9, 95% confidence interval (CI) [0.0 – 0.8] vs [1.6 – 3.2], $p<0.001$). The proportion of patients achieving more than 50% knee pain reduction was higher in the RT-group at each follow up interval, yet these differences were statistically significant only at 1-hour post intervention (82.1% [95% CI=63.1 – 93.9] vs 100% [95% CI=97.2 – 100] $p = 0.02$). Both protocols resulted in significant pain reduction and joint function improvement up to 12 weeks post intervention.

Conclusion. The revised technique allowed more pain relief as well as greater proportion of successful responders at 1-hour post intervention. The large volume injected during therapeutic GNB could have compensated the lack of precision of the classical anatomical targets, mitigating differences in outcomes between both techniques.

4.2 Introduction

Knee osteoarthritis is one of the leading causes of global disability [135]. It is associated with chronic knee pain, and joint stiffness. There are several conservative treatments in the early stages, including oral analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), viscosupplementation, intra-articular corticosteroid injections, and physical therapy. In cases of failure of conservative treatment or advanced stages of the disease, total knee arthroplasty (TKA) remains the gold standard treatment. However, many patients do not progress to TKA and of those that do, 15 to 40% continue to suffer from refractory knee pain after TKA [8]. Therefore, whether for patients suffering from knee OA in whom conservative treatments have failed, not eligible for surgery (comorbidities, refusal), suffering from persistent pain after TKA or living in regions of the world with limited access to TKA, the problem of chronic knee pain remains a prominent challenge for patients and physicians worldwide.

For a decade, radiofrequency ablation (RFA) has been a promising technique to treat intractable knee OA pain [10, 64, 65]. Therapeutic genicular nerve blockade

(GNB) using corticosteroids and local anesthetic have shown up to six months comparable effectiveness to RFA in persistent pain after TKA [4], but controversial effectiveness in knee OA pain [68, 106, 120]. GNB and RFA aim to selectively inhibit the sensory nerves supplying the knee joint capsule, therefore relieving knee pain and improving function. RFA's success relies on precise needle placement near the targeted nerves, based on accurate anatomical targets [4, 14, 24, 136]. However, given the propensity of the injectate to diffuse, the need for very precise anatomical landmarks seems less necessary for GNB than for RFA. Recently, experimental cadaveric studies have demonstrated that the original anatomical foundations and the current targets are incomplete and somewhat inaccurate [16, 101, 132]. Based on those anatomical updates, revised targets have been proposed and were found to be more accurate than classical targets in a cadaveric model [103, 126]. However, since the standard procedure has been used for a decade with some effectiveness [4, 68, 106, 120], studies are necessary to compare the effectiveness and safety of the revised technique versus the classical one in patients with painful knee OA.

This randomized double-blinded clinical trial aimed to compare the effects on pain and function of fluoroscopic-guided therapeutic GNB using classical anatomical targets versus revised targets in patients suffering from chronic knee OA pain.

4.3 Methods

Study design

This prospective, randomized, double-blinded clinical study with a parallel-group design was approved by our Regional Ethics Committee for Human Health Research (agreement number: CE 0-771/CRERSHC/2019) and study protocol was registered in Pan African clinical trial registry www.pactr.org (PACTR202004822698484). All the patients provided a written informed consent prior to inclusion in the study. The study was conducted from May 2019 to May 2020 at a single pain clinic within a tertiary care hospital. Two techniques (classical versus revised targets) of fluoroscopic-guided GNB (using a fluid mixture of local anesthetic plus corticosteroid) were compared in patients suffering from chronic pain from knee OA.

Patients

Consecutive patients presenting to study investigators with chronic knee OA pain were eligible for this study. The inclusion criteria were: chronic knee pain lasting over 3 months that was unresponsive to conservative treatments (oral analgesics, NSAIDs, intra-articular injections with corticosteroids, or viscosupplementation), moderate to severe knee pain (≥ 5/10 on a Numeric Rating Scale), and radiological confirmation of tibio-femoral OA (Kellgren-Lawrence grade 2-4 as evaluated by a radiologist). Exclusion criteria were: uncontrolled psychiatric or neurological illness, viscosupplementation or intra-articular injection with corticosteroids less than 3 months before inclusion, inability to write, speak or read in English or

French, systemic inflammatory conditions that affected the knee, uncontrolled diabetes, pregnancy, cancer, lumbar radiculopathy, and anticoagulant treatment.

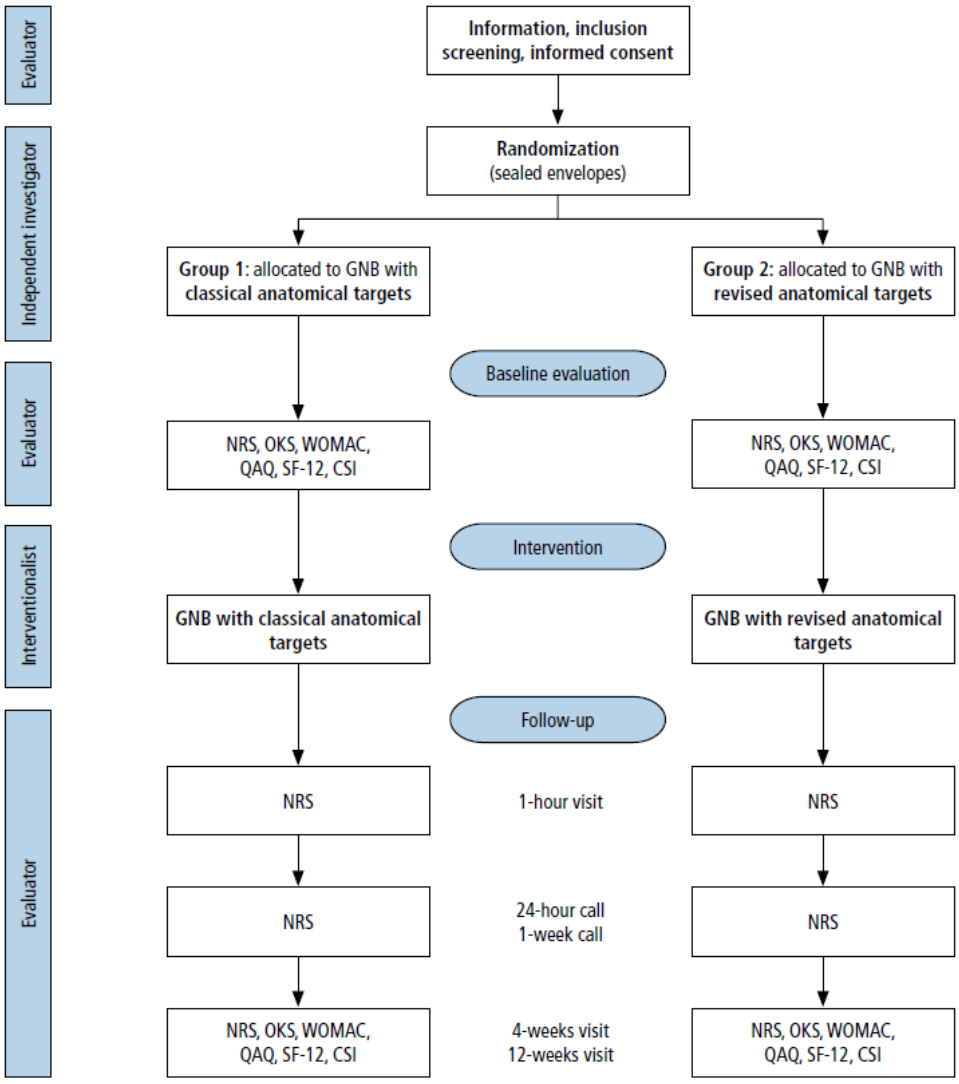

Figure 1: Study flowchart

Randomization

Enrolled patients were randomized in a 1:1 scheme into one of the two treatments groups: patients in the classical targets group (CT-Group) underwent GNB with classical anatomical targets and those in the revised targets group (RT-Group) GNB with revised anatomical targets (figure 1). A randomization by blocks of 4 sealed envelopes with random draw without replacement was made to assign each patient to one of the two groups while ensuring the balance between both groups. Independent research personnel, who were not involved in the interventions or evaluations, conducted the randomization process. A single interventionist (with four years of experience in GNB and RFA), who was not involved in the evaluation process, conducted all the interventions. Just before the intervention, the interventionist opened the sealed envelope to reveal the participant group assignment. The randomization sequence was concealed throughout the study from the participants, the investigator who conducted all the evaluations (evaluator), and all other care providers. Neither the patient, nor the investigator, were aware of what intervention the patient received.

Interventional procedures

All participants underwent a single treatment session. No premedication or sedatives were administered. Participants were placed in supine position on a fluoroscopy table with a pillow under the popliteal fossa to provide 30° flexion. Under sterile conditions, skin and subcutaneous tissues superficial to the targeted nerves were anesthetized with 1ml of 1% lidocaine.

The GNB was performed under fluoroscopic guidance, using 22-gauge spinal needles. The targets depended on the group assignment (figure 2 and 3). Participants were blinded for the type of intervention they received (GNB with classical targets or revised targets). A surgical drape prevented the participant from seeing the injection procedure, and the fluoroscopy screen was positioned out of the participant's view.

CT-Group: classical targets [10, 11, 64, 66]

The target site for the superior medial genicular nerve (SMGN) was located at the confluence of the medial femoral shaft and the condyle in the anterior-posterior (A-P) view, and at the midpoint of the femur in the true lateral view.

The target site for the superior lateral genicular nerve (SLGN) was located at the confluence of the lateral femoral shaft and the condyle in the A-P view, and at the midpoint of the femur in the true lateral view.

The target site for the inferior medial genicular nerve (IMGN) was located at the confluence of the medial tibial shaft and the tibial condyle in the A-P view, and at the midpoint of the tibia in the lateral view.

To ensure that each participant remained blinded to group allocation, the interventionist simulated an injection for the recurrent fibular nerve (RFN) and the infrapatellar branch of the saphenous nerve (IPBSN): the needle was placed as described below, but 2ml saline was injected, without any medication.

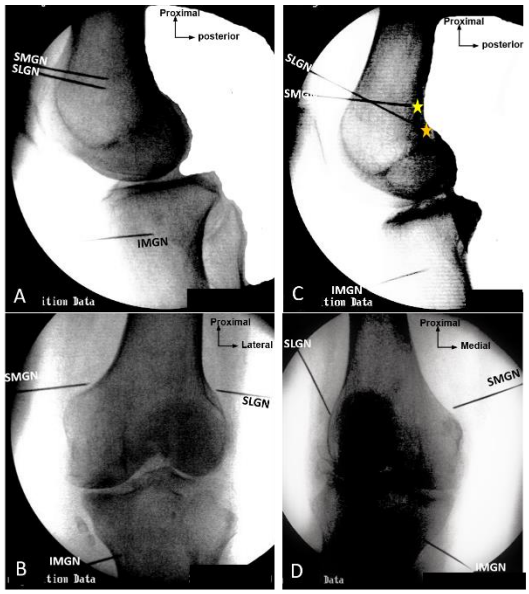

Figure 2. Anterior/posterior and lateral fluoroscopic images of the final needle position for genicular nerve blockade targeting the SMGN, SLGN, and IMGN. (A) and (B) Classical targets. (C) and (D) Revised targets. SMGN, superior-medial genicular nerve; IMGN, inferior-medial genicular nerve; SLGN, superior-lateral genicular nerve, yellow star, position of the needle tip for the SMGN; orange star, position of the needle tip for the SLGN.

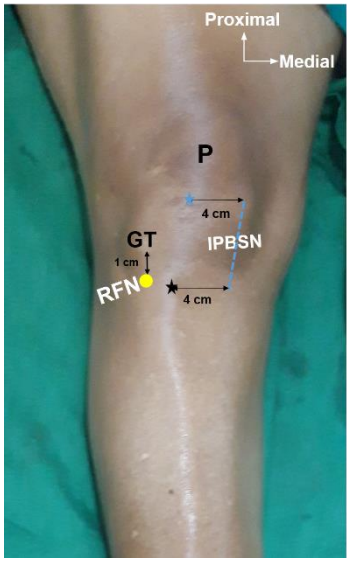

Figure 3: Clinical landmarks for the RFN and IPBSN (without imaging). IPBSN, infrapatellar branch of the saphenous nerve; RFN, recurrent fibular nerve; P, patella; GT, Gerdy's tubercle; black star, tibial tuberosity; blue star, apex of the patella; yellow circle, target point for RFN; blue dashed line, treatment line for the IPBSN.

RT-Group: revised targets [103, 126]

For the SMGN, the needle was advanced towards the superior edge of the medial condyle on A-P view. Subsequently, the C-arm was rotated to have a true lateral view, with both condyles superimposed. The tip of the cannula was adjusted to fit in front or above the adductor tubercle.

For the SLGN, the needle was advanced towards the superior edge of the lateral femoral condyle on the A-P view. Then, in the true lateral view, the needle tip was adjusted to fit the target site located at the junction between the superior edge of the lateral condyle and the posterior femoral cortex, 2 to 3 mm from the bone.

For the IMGN, the needle was fitted at the confluence of the medial tibial shaft and the tibial condyle in the A-P view, and at the midpoint of the tibia in the lateral view, in contact of the bone. These targets were unchanged from the CT group.

For the recurrent fibular nerve (RFN), a longitudinal line was drawn below the Gerdy's tubercle (GT). The needle was inserted 1cm below the inferior edge of the GT and advanced until the tip touched the bone.

For the infrapatellar branch of the saphenous nerve (IPBSN), we drew a longitudinal line (which correspond to the target line), 4 cm medially to the patella apex, connecting both transversal lines passing by the patella apex and the top of the tibial tuberosity. The needle was inserted longitudinally at the proximal end of the target line and advanced all along until its distal end, deeply in the subcutaneous tissue. No imaging was used for RFN and IPBSN [103].

Regardless of group assignment, after verification of correct needle placement, we performed a gentle aspiration before administering the medication, to avoid intravascular injection. Then, a volume of 2 ml of fluid mixture of lidocaine 1% (1.5 ml) plus 20 mg of triamcinolone (0.5 ml of triamcinolone 40 mg/ml) was injected at each target site. The injection sites were bandaged identically in both groups.

All the participants were advised to continue using their previously prescribed medications if needed, according to the intensity of their pain. Any additional therapy was prohibited for the 12 weeks post intervention.

Assessment and study outcomes

A single physician, who was blinded for the group allocation, performed all pre-intervention (baseline) and post-intervention evaluations. Baseline measurements were collected on the day of the intervention. Post interventional evaluations were made after 1 and 24 hours, and at 1, 4 and 12 weeks following the study intervention. The evaluation after 24 hours and 1 week were made by telephone, and the remaining by a personal interview. The following items were evaluated: pain intensity (NRS, Numeric rating scale), knee function (OKS, Oxford knee Score; WOMAC, Western Ontario and McMaster Universities osteoarthritis index score), analgesic consumption (QAQ, quantitative analgesic questionnaire), quality of life (SF-12, 12-item short form health survey), central sensitization to pain (CSI, central sensitization inventory) and patient satisfaction (GPES, global perceived effect scale). Patients were asked to report any adverse effects (AE) at

each evaluation period or at any other time during the study. We also assessed post-procedural muscle palsy or anesthesia in the territory of the CFN.

The NRS is used by patients to evaluate the intensity of their pain on a scale of 0 (no pain) to 10 (unbearable pain) [137, 138]. The OKS questionnaire consists of 12 multiple-choice questions (5 possible answers), yielding a total score within the range of 0 to 48. A score of 40 to 48 indicates a satisfactory function of the knees whereas scores of 0 to 19 indicate a severe loss of function [139]. The WOMAC questionnaire consists of 24 multiple choice questions to assess disability in three subscales, including pain (five items), joint stiffness (two items) and physical function (17 items) [140]. Higher score on the WOMAC indicates worse pain, stiffness, and functional limitation. The SF-12 consists of 12 MCQ assessing physical and mental health. The global perceived effect (GPES) is assessed on a 7-point scale (1 = worst ever, 2 = much worse, 3 = worse, 4 = not improved but not worse, 5 = improved, 6 = much improved and 7 = best ever) [141]. The QAQ is designed to comprehensively document patient-reported chronic pain medication use, generate scores to quantify and compare it and tracking changes in medication use over time [142]. The higher the score, the higher the pain medication use. The CSI consists of 25 MCQ assessing symptoms related to central sensitization to pain; a score over 40/100 indicate a higher probability of central sensitization [143].

The primary outcome was the mean changes of NRS score from baseline to 1 hour, 4 and 12 weeks after the intervention. Secondary outcomes included the proportion of successful responders (reduction of at least 50% from baseline NRS score [10, 64, 65]), mean changes in knee function (OKS and WOMAC), mean

changes in pain medication consumption (QAQ score), subjects' perception of treatment effect (GPES), and changes in the quality of life (SF-12).

Statistical analysis

The power analysis was guided by prior randomized control trials assessing the efficacy of GNB or RFA with similar primary endpoints [4, 10, 106, 120]. Sample size calculation was based on the primary outcome of difference in the mean changes of NRS score between the two groups at 4 weeks after the intervention. For a precision of 1.7 (minimal clinically important difference) and a standard deviation of 1.3 [138], assuming 2-sided significance level of 5% and a power of 90%, a minimum of 13 patients per group would be needed. However, as the technique is new and to comply with the sample size of recently published studies on therapeutic genicular nerve blockade, we chose to increase the number of enrolled patients [106, 120]. Data were analyzed using SPSS version 25.0 software package (SPSS Inc., Chicago, IL, USA). The quantitative variables were tested for normality using the Kolmogorov-Smirnov test. Quantitative demographic data were presented as mean and standard deviation if they were normally distributed and compared between groups using independent sample t test, whereas non parametric data were presented as median (inter quantile range) and compared between groups using Mann Whitney U test. Mean changes in outcome measurements scores among baseline and post-interventional assessments within and between both groups were compared using two-way repeated measures analysis of variance (ANOVA), with post-hoc Bonferroni tests for multiple

comparisons. Categorical data were presented as counts and percentages, and compared using Chi-square test or Fischer exact test as appropriate. A p-value < 0.05 was considered as statistically significant.

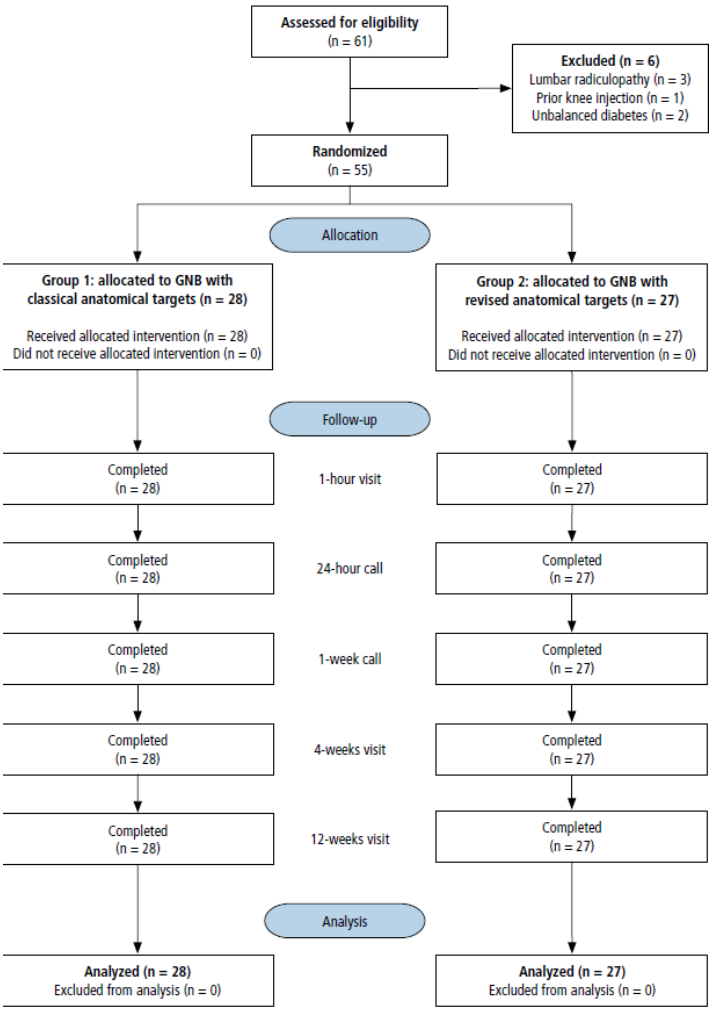

Figure 4: CONSORT diagram.

4.4 Results

Table 1. Baseline characteristics per group

	GNB with classical targets (n = 28)	GNB with revised targets (n = 27)	*p*-value
Age (years)	61.6 ± 9.7	61.1 ± 12.9	0.85
Sex distribution (M/F)	1 (3.6%)/ 27 (96.4%)	6 (22.2%)/ 21(77.8%)	0.05
Body mass index (Kg/m²)	32.9 ± 7.1	29.8 ± 6.2	0.09
Treatment sites (unilateral/bilateral)	11 (39.3%) / 17 (60.7%)	12 (46.4%) / 15 (55.6%)	0.74
Duration of knee pain (months)	41.7 ± 32.7	43.3 ± 41.3	0.86
Kellgren-Lawrence Grade			0.46
2	4 (14.3%)	7 (25.9%)	
3	11 (39.3%)	11 (40.7%)	
4	13 (46.4%)	9 (33.4%)	
NRS score	8.54 ± 1.55	8.41 ± 1.65	0.76
Central sensitization index	30.5 ± 13.5	24.8 ± 16.1	0.16
OKS	19.7 ± 8.3	21.1 ± 7.6	0.70
WOMAC	41.6 ± 16.1	36.1 ± 12.8	0.16
SF-12 score			
Physical	33.36 ± 8.52	34.32 ± 6.69	0.64
Mental	40.89 ± 10.26	42.89 ± 9.18	0.44
QAQ score	3.5 ± 2.5	4.9 ± 3.3	0.08

Quantitative data are presented as mean ± SD, categorical data as number (percentage).

GNB, genicular nerve blockade; NRS, numeric rating pain scale; OKS, Oxford knee score; WOMAC, Western Ontario and McMaster Universities osteoarthritis index score; SF-12, 12-items short form health survey, QAQ, quantitative analgesic score. *P* values comparing baseline characteristics between both groups.

Study population

From the sixty-one patients who fulfilled the inclusion criteria for this study, six were excluded (3 with lumbar radiculopathy, 2 with unbalanced diabetes, 1 with prior steroid injection within 3 months) (CONSORT diagram, figure 4). The remaining 55 patients agreed to participate in the study and were randomized into the two treatment groups: GNB with classical targets (28 patients) and GNB with revised targets (27 patients). The treatment was successfully conducted in all participants, and all of them completed the follow-up. There were no significant baseline differences between both treatment groups regarding age, body mass index (BMI), knee OA severity, pain score, pain duration, OKS, WOMAC score, CSI score, and analgesic consumption (Table 1). All participants were Black Africans, and most of them were female and obese.

Pain intensity

There was a significant effect of group allocation ($F(1, 1) = 5.75$, $Mse = 15.35$, $p = 0.02$) and time within groups ($F(3.27, 173.66) = 170.75$, $Mse = 3.93$, $p < 0.001$) for the mean changes of the NRS scores. There was no significant interaction between time and group allocation for the mean changes of the NRS score ($F(3.27, 173.66) = 1.96$, $Mse = 3.93$, $p = 0.115$). Within both groups, mean pain NRS were significantly reduced at all time-points relative to baseline (Figure 5). Patients in the RT-group trended toward greater reduction in NRS mean score compared to patients in the CT-group, but this difference was significant only at 1-hour post-intervention ($p < 0.001$) (Table 2 and figure 5).

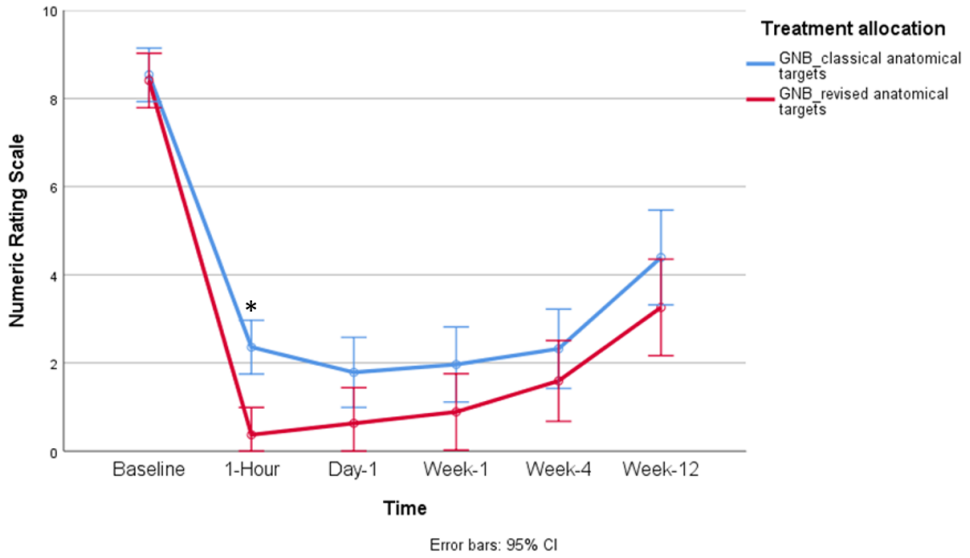

Figure 5: Numeric rating scale knee pain evolution in both groups. Error bars represent 95% confidence intervals; * $p<0.05$.

Positive responders

The proportion of patients achieving more than 50% knee pain reduction tended to be higher in the revised target groups at each follow up interval, yet this difference was statistically significant only at 1-hour post intervention (82.1% *vs* 100%, $p = 0.028$). At 3-months post procedure, 63% (17/27) of patients in the revised targets group against 43% (12/28) in the classical targets group met this successful outcome criteria ($p = 0.11$). We did not find an association between the proportion of successful responders and the presence of central sensitization at each follow up interval.

Table 2. Functional outcomes in both groups

	GNB with classical targets (n = 28)	GNB with revised targets (n = 27)	*p*-value
NRS score			
Baseline	8.5 ± 1.5 (7.9 – 9.1)	8.4 ± 1.6 (7.7 – 9.0)	0.760
1-Hour post-intervention	2.4 ± 2.1 (1.6 – 3.2)	0.4 ± 0.9 (0.0 – 0.8)	**<0.001**
Day-1	1.8 ± 2.6 (0.78 – 2.8)	0.6 ± 1.4 (0.7 – 1.24)	0.046
Week-1	2.0 ± 2.7 (0.9 – 3.0)	0.9 ± 1.6 (0.3 – 1.6)	0.082
Week-4	2.3 ± 1.6 (1.29 – 3.35)	1.7 ± 2.0 (0.82 – 2.5)	0.260
Week-12	4.4 ± 2.6 (3.4 – 5.38)	3.2 ± 3.1 (2.1 – 4.6)	0.140
Positive responders			
1-Hour post-intervention	23 (82.1%) (63.1 – 93.9)	27 (100%)(97.2 – 100)	**0.028**
Day-1	23 (82.1%) (63.1 – 93.9)	25 (92.6%)(75.7 – 99.1)	0.226
Week-1	21 (75%)(55.1 – 89.3)	25 (92.6%)(75.7 – 99.1)	0.080
Week-4	20 (71.4%)(51.3 – 86.8)	24 (88.9%)(70.8 – 97.6)	0.099
Week-12	12 (42.9%)(24.5 – 62.8)	17 (63.0%)(42.4 – 80.6)	0.111
OKS score			
Baseline	19.7 ± 8.3 (16.5 – 22.9)	21.1 ± 7.6 (18.0 – 24.2)	0.703
Week-4	39.2 ± 9.1 (35.3 – 43.1)	42.0 ± 7.5 (39.0 – 45.0)	0.260
Week-12	34.7 ± 11.4 (30.3 – 39.2)	38.4 ± 9.6 (34.5 – 42.3)	0.208
WOMAC total score			
Baseline	41.6 ± 16.1 (35.3 – 47.9)	36.1 ± 12.8 (32.0 – 42.0)	0.169
Week-4	14.6 ± 16.0 (8.4 – 20.8)	6.0 ± 4.6 (4.3 – 8.0)	**0.033**
Week-12	7.4 ± 6.1 (5.1 – 9.8)	4.7 ± 5.1 (2.9 – 7.0)	0.082
QAQ score			
Baseline	3.5 ± 2.5 (2.6 – 4.5)	4.9 ± 3.3 (3.6 – 6.2)	0.083
Week-4	0.8 ± 1.5 (0.2 – 1.3)	0.5 ± 1.5 (-0.1 – 1.07)	0.260
Week-12	1.4 ± 2.1 (0.6 – 2.2)	1.6 ± 2.6 (0.6 – 2.6)	0.144
SF-12 Physical score			
Baseline	33.36 ± 8.52 (39.8 - 46.5)	34.31 ± 6.69(44.1– 49.6)	0.648
Week-4	43.14 ± 8.64 (39.8 - 46.5)	46.84 ± 6.85(44.1– 49.6)	0.085
Week-12	40.35 ± 9.10 (36.7 – 43.9)	42.33 ± 8.34 (39.0-45.7)	0.405
SF-12 Mental score			
Baseline	40.89 ± 10.26	42.90 ± 9.18	0.449
Week-4	49.03 ± 8.89 (45.6 – 52.5)	52.28 ± 7.05 (49.5-55.1)	0.140
Week-12	46.31 ± 9.97 (42.4 – 50.1)	51. 05 ± 7.67 (48.0-54.1)	0.054
GPES			
Week-4	5.7 ± 1.4 (5.1 – 6.2)	6.2 ± 1.1 (5.8 – 6.6)	0.137
Week-12	5.2 ± 1.74 (4.5 – 5.9)	5.8 ± 1.4 (5.2 – 6.4)	0.147

Quantitative data are presented as mean ± SD 95% CI, categorical data as number (percentage) 95% CI.
GNB, genicular nerve blockade; NRS, numeric rating pain scale; OKS, Oxford knee score; WOMAC, Western Ontario and McMaster Universities osteoarthritis index score; SF-12, 12-items short form health survey, QAQ, quantitative analgesic score; GPES, global perceived effect. *P* values comparing outcome measures between both groups.

Oxford Knee score

There was no significant effect of group allocation on the mean changes in OKS (F(1,1)= 1.67, Mse = 165.8, $p = 0.202$). Within each group, there was a significant effect of time (F(2, 104)= 138.42, Mse = 44.47, p<0.001). There was no interaction between time and group allocation (F(2,104)=0.41, Mse 44.47, p=0.41). Within both groups, the OKS improved at 4 and 12 weeks compared to baseline (figure 6).

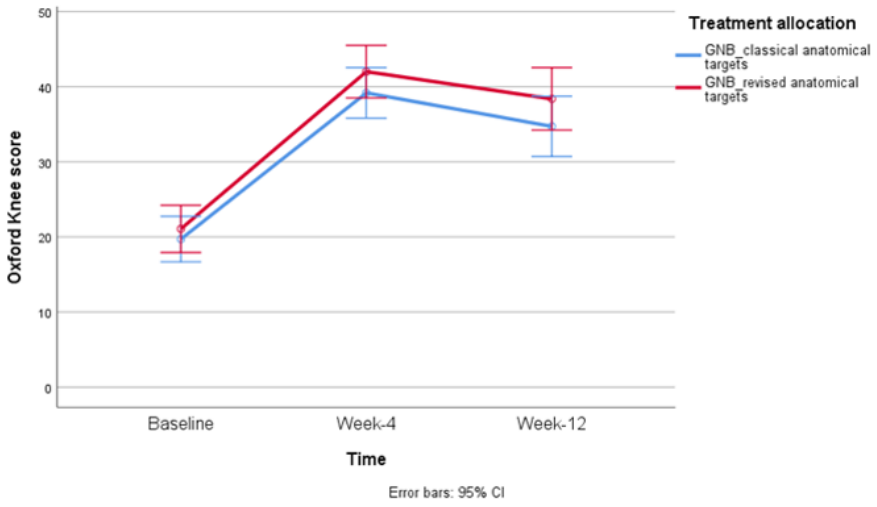

Figure 6: OKS evolution in both groups. Error bars represent 95% confidence intervals; * $p<0.05$.

WOMAC score

In both groups, there was a significant improvement in WOMAC total score ($F(2,106)=213.6$, Mse = 81.85, $p<0.001$) at 4 and 12 weeks (figure 7). Intergroup comparison showed a significant difference in WOMAC score improvement ($F(1,53)= 251.4$, Mse = 222.4, $p = 0.020$). Post hoc tests with Bonferroni's correction showed that the WOMAC score improved significantly more in the RT-group at 4-week follow-up ($p = 0.03$).

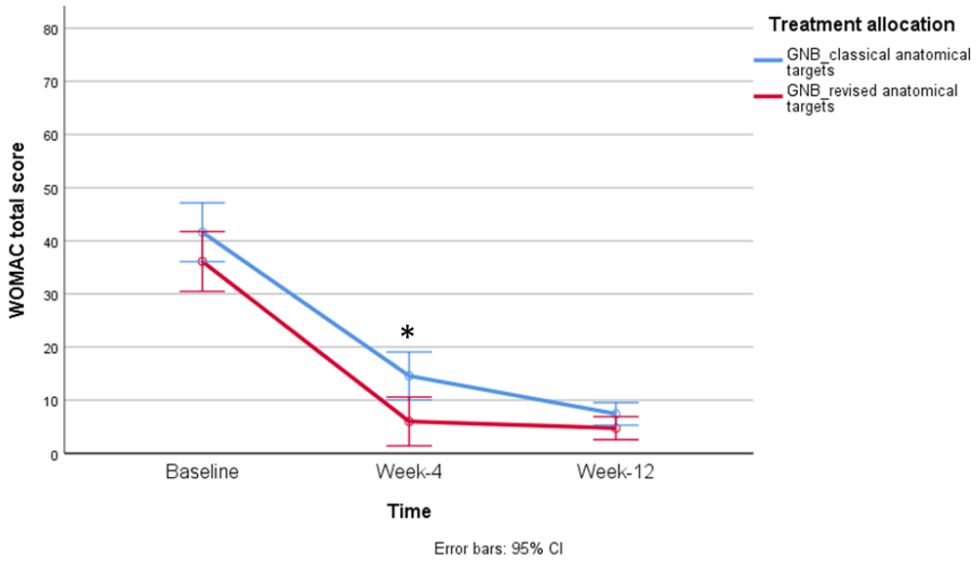

Figure 7: WOMAC score evolution in both groups. Error bars represent 95% confidence intervals; * $p<0.05$.

Pain medication consumption

There was a reduction of analgesic consumption at follow up in both groups ($F(1.6, 84.21) = 41.96$, Mse = 5.85, $p<0.001$). No significant difference was found in QAQ score in both groups ($F(1,53)=106.1$, Mse = 6.98, $p = 0.302$).

SF-12 Scale

Compared to baseline, the SF-12 physical and mental scores improved significantly in both groups at 4 and 12 weeks. There was no significant effect of group allocation on changes in SF-12 physical ($F(1,53) = 1.41$, Mse = 143.07, $p = 0.241$) and mental scores ($F(1,53) = 2.84$, Mse = 161.06, $p = 0.098$).

Global perceived effect

There was an improvement in patient global impression of change within both groups at 4 and 12 weeks. The GPE score was not significantly different between both groups at 4 and 12 weeks (Table 2)

Adverse Events

During the intervention, no major adverse events (AE) was reported. Five participants (3 in the revised targets group) experienced mild AE within the hour after the intervention: dizziness, nausea or malaise. No cardiac or respiratory dysfunction was observed in these patients. These symptoms disappeared spontaneously after 30 minutes. No patient presented transient blockade of the CFN after the procedure. Regardless of group allocation, no motor dysfunction

was observed and all the patients resumed their normal activities after the procedure.

5.5 Discussion

To our knowledge, this is the first randomized clinical trial comparing the effectiveness of GNB using two techniques based on different anatomical targets. Patients in both groups demonstrated significant improvements in pain intensity, analgesic consumption, quality of life and knee function. Compared to the patients in the classical targets group, patients who benefited from GNB with the revised targets reported significantly less pain one hour after the procedure and better WOMAC score four weeks later. There were no significant differences in OKS, QAQ, SF-12 and GPEs between both groups.

One hour after the procedure, pain intensity was significantly lower and the proportion of responders was significantly higher in the revised target group. This marked difference is most likely due to the immediate effect of lidocaine, a local anesthetic with a rapid onset but a short half-life. Since anatomical studies have shown that the revised targets are more accurate and target more nerves [126], we believe that immediately after the block the knee was better "anesthetized" with the revised than with the classical targets. In addition, the revised protocol involved more injection sites, thus more lidocaine, which may account for more immediate pain relief. As the effect of lidocaine wears off quickly, the difference becomes less important. On the other hand, the onset of action of triamcinolone ranges from

two hours up to one or two days after the intervention. However, corticosteroids have a local but also a systemic action and tend to diffuse more readily when mixed to anesthetics, which dilutes the crystalline suspension [144]. This could explain the short-term versus long-term discrepancy as they may have mitigated a possible difference in results between both groups over time.

In this study, both protocols resulted in statistically significant pain reduction up to three months post procedure. Moreover, the function, analgesic consumption, satisfaction and quality of life were also globally improved up to three months after the procedure. In two recent studies conducted by the same authors, the effect of injection of a total of 6 ml of lidocaine + 20 mg triamcinolone at 3 the sites of classical targets (2 ml of lidocaine + 6.6 mg of triamcinolone per site) lasted for only one month after the procedure [106, 120]. However, in another study, injection of only the IPBSN with a fluid mixture of 20mg methylprednisolone and 5 ml 1% ropivacaine resulted in pain reduction, from a baseline median score of 8/10 to 0 or 1/10 over 6 months after intervention, in nine out of 16 patients with persistent medial pain after TKA [54]. In a RCT focusing on persistent pain post TKA, GNB with 2 ml of 0.25% levobupivacaïne plus 0.5 ml of triamcinolone (20 mg) per target site resulted in a statistically significant drop of NRS scores from baseline to 1 month and 6 months after the procedure, similar to the effect of RFA [4]. In a patient with knee OA pain, Demir et al. [9] reported that the VAS pain score improved after the GNB (with 2 ml of lidocaine + 20 mg triamcinolone per site using the classical targets) and dropped from 80 mm to 10 mm by week 4, and 0 mm at 24 weeks. Therefore, we can suggest that the shorter effect in Kim et al

studies could be due to the amount of corticosteroids in their injections, which was three times smaller than that used in other studies.

Similar to previous clinical studies assessing genicular nerve blockade [4, 106, 120], we injected a total volume of 2 ml of a fluid mixture (local anaesthetic + corticoids) at each target site. These relatively high volumes could also explain the relatively small differences in outcome between both techniques. In a recent study performing GNB with classical targets, injection of 2 ml of solution at the midpoint of the junction between epiphysis and diaphysis resulted in large diffusion, covering all the surface of the metaphysis from anterior border to posterior border, as illustrated on their "figure 1C" [106]. Cushman et al. made the same demonstration by injecting 1 ml of contrast medium [124]. With such a diffusion, for example, the SMGN, which descend posteriorly, would be captured by an injection performed at the midpoint of the femoral metaphysis on the lateral view. The former study also illustrated that an injection of 0.5 ml spreads beyond the boundaries of typical RF lesion [124]. This explains the high false positive rate of genicular nerves blocks in predicting successful outcome of subsequent RFA [75, 124]. Based on cadaveric experiments but not yet demonstrated in clinical studies, the volume to be injected per target site should not be more than 0.1 ml for prognostic nerve blockade [126]. However, when performing therapeutic genicular nerve blockade, using large volumes of local anaesthetics plus corticoids seems justified. Unfortunately, with such volumes, both approaches did not result in significantly different pain relief.

This study shows that the new technique is clinically feasible, effective and safe. The injection of the RFN with the revised technique did not affect the common fibular nerve. As the pain relief last several months, therapeutic GNB could be proposed as a treatment option for knee OA pain when RFA is not available. Although the differences in outcome with the classical technique for GNB were relatively small, they could be more important when it comes to RFA, where we need more precision in the anatomical positioning because of the small volume of RF lesions. During the GNB, the large volume injected could have compensated to some extent for the anatomical imprecision of the classical landmarks.

This study has some limitations. The volume injected for therapeutic GNB did not allow to clearly discriminate the effects of the anatomical precision of the targets in both techniques. No sham-controlled trials have been performed which demonstrate the efficacy of therapeutic GNB. Patient-reported outcome are highly subjective. The administration of large amount of glucocorticoids could theoretically provoke serious complications, e.g. suppression of the pituitary axis system. Skin penetration without anesthetic administration (for RFN and IPBSN in the CT group) could have led to greater post-procedural pain. Finally, the monocentric design of this study could limit generability of the results.

Conclusion

In this study, we report that GNB using a volume of 2 ml of lidocaine plus triamcinolone 20 mg per target site resulted in significant pain reduction in both

groups, up to 3 months post intervention. The revised technique allowed significant more pain relief as well as greater proportion of successful responders at 1-hour post intervention. The mean WOMAC total score was significantly more improved with revised technique at 4-weeks. Both techniques resulted in reduction of analgesic consumption, improvement of quality of life and global perceived effect, without statistically significant difference between groups. The large volume injected during therapeutic GNB could have compensated to some extend the lack of precision of the classical anatomical targets. A similar study comparing RFA with both techniques is expected.

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Conflicts Of Interest. The authors declare no conflicts of interest.

General discussion

Thesis summary

The main objective of this PhD thesis was to develop and validate accurate anatomical targets for GNB and RFA to treat chronic knee OA pain. In the first part, systematic anterograde anatomical dissections of all the nerve branches supplying the knee joint capsule were performed, which allowed identification of five constant genicular nerves and their respective anatomical landmarks. The vascular pattern of arteries accompanying these consistent genicular nerves was assessed through meticulous anatomical dissections, since these arteries are commonly used as landmarks to target the nerve that runs alongside them during ultrasound-guided interventions. This first part found preeminent discrepancies in the anatomical bases that support GNB and RFA for chronic knee OA pain. In the second part, the accuracy of revised targets for fluoroscopic-guided GNB was tested on cadavers under clinical-like conditions, which showed 100% accuracy for the SMGN, IMGN, RFN, and IPBSN and 90% for the SLGN. A new protocol for ultrasound-guided genicular nerve RFA with revised anatomical targets was developed and assessed in fresh cadaveric knees. The proportions of nerve capture were 100% for the SMGN, IMGN, RFN and IPBSN, and 95% for the SLGN. In the third part, we compared the accuracy of the current targets for genicular nerve RFA with the revised targets in cadavers under clinical-like conditions. The revised targets demonstrated more accuracy than the current targets, and they

accurately targeted more genicular nerves. In the last part, a double-blind randomized control trial compared current anatomical targets and the revised targets for GNB in patients with chronic knee OA pain. Although the revised targets demonstrated greater pain relief and functional improvement at all follow-up times, the difference was only statistically and clinically significant one-hour post-intervention. This was probably due to the large volume that was injected and the adjunction of corticoids to local anesthetics. The difference in clinical outcome is expected to be clearer with RFA, where anatomical precision is of paramount importance.

Discrepancies and convergences on nerve supply to the knee joint capsule, and their implications for GNB and RFA

Although all the authors agree that the nerves supplying the knee joint are branches of the femoral, obturator, and sciatic nerves, following the Hilton's law ("the same truncks of nerves, whose branches supply the groups of muscles moving a joint, furnish also a distribution of nerves to the skin over the insertions of the same muscles; and the interior of the joint receives its nerves from the same source")[92], there is no consensus concerning the topographic distribution of the main trunks or about the number, origin, ending, or nomenclature of the nerve branches. Discrepancies between these original studies could be explained by inter-individual anatomical variations, as well as by methodological issues and knowledge at the time of the study. Very recent anatomical studies, including those comprised in the current thesis, show more points of convergence than of divergence. Although we still observe some differences in origin, course, and nomenclature of the nerve branches to the knee joint capsule, most descriptions from very recent authors converge and appear to be increasingly clear. However, a major issue persists concerning the application of this better anatomical knowledge to the choice of accurate targets for RFA to treat chronic knee pain. This is currently the crux of the debate. Therefore, our approach aimed to make a continuous link between anatomical updates, identification and validation of accurate targets for the constant nerves, and application in clinical practice. We hope that such a prospective, and almost complete scientific process would allow the scientific community and

pain physicians to better converge, with the ultimate goal of improving the outcome of these interventions.

One of the first and most extensive anatomical studies of the nerve supply to the human knee was published by Gardner [21] (1948), who had considered previous descriptions from Ellis (1840 and 1882), Cruveilhier (1844), Rudinger (1857), Sappey (1877), Fick (1904), Drüner (1927), and Jelersky (1930). Then, from 1948 to 2011, the latter of which marks the first introduction of RFA to treat chronic knee pain, there were only three anatomical studies of the nerve distribution to the human knee joint. Anatomical studies on this subject have regained interest in recent years, due to the critical importance of accurate and faithful anatomical descriptions of the nerve branches innervating the knee joint capsule, which influences the success of promising interventions for regional anesthesia and chronic knee pain control. Therefore, from 2015 to date, almost ten anatomical studies have been published [12, 16, 17, 20, 23, 84, 88, 100], which included dissection of a total 102 cadaveric knees for this purpose. In addition, throughout this thesis, we thoroughly dissected no less than 63 cadaveric lower limbs in total. This provided a proper understanding of the nerve supply to the knee, which has implications for image-guided interventions for knee pain.

Almost all the articular branches to the knee joint capsule have at some point been described by one study or another, but accounts in classical anatomical and orthopedic textbooks are brief and simplified, sometimes to the point of inaccuracy. It is striking to note that descriptions of the sensory branches supplying the knee capsule are skimmed over in most classical anatomical and orthopedic textbooks.

Topographic subdivision of the nerve supply to the knee joint capsule

Although territories of the sensory branches innervating the knee capsule overlap, almost all the authors divided its innervation into different topographic aspects to facilitate understanding and clinical relevance. Like Kennedy et al. [22], some authors have identified two distinct groups of afferents nerves supplying the knee: the anterior and posterior group. This can be confusing, since some articular nerves of the anterior group were described as branching from nerves located posteriorly and vice-versa. Other authors divided the knee capsule into three parts: anteromedial, anterolateral, and posterior [21]. Other authors divided the knee into two aspects: the anterior capsule with four quadrants (superior-lateral, superior-medial, inferior-lateral and inferior-medial [16]) and the posterior capsule with three parts (supero-medial, supero-lateral, and inferior [84]). In our studies, we also divided the anterior knee capsule into four quadrants, but we did not divide the posterior capsule because we found no consistent pattern of topographic distribution in the articular nerve branches to the posterior capsule.

The superior-medial quadrant of the anterior knee capsule (Table 1)

All the studies indicate that the superior-medial quadrant is essentially innervated by the branches of the nerve to the vastus medialis. All authors described transmuscular branches from the NVM reaching the capsule, but only a few authors identified its intra-fascial branch. This is its direct branch to the knee capsule, which is found in all specimens in our successive studies, as well as the two other most recent studies [16, 20]. This can be explained by the

fact that dissection of this branch is difficult and requires special skills because of its intra-fascial course. Moreover, if the fascia of the vastus medialis muscle is removed before identifying and tracing this nerve up to its end, it would no longer be possible to identify it. We (as well as these authors) named it the superior-medial genicular nerve because we found it to be the main and only constant nerve at the superior-medial aspect of the knee capsule. Some authors described the contribution of the obturator, tibial and saphenous nerves, but this lacked any photographic illustration. The popular description on which identification of neural targets for RFA was based states that the SMGN branches from the tibial nerve and follows the superior-medial genicular artery. There is no single dissection illustration of this, and there is no single specimen where this pattern was found and presented to the readers. We did not find such a nerve, which aligns with very recent robust anatomical studies.

Table 1. Nerve branches to the superior-medial quadrant of anterior knee capsule among studies

Authors (n, year)	Nerves branches (number)	Origin	Course	Consistency
Gardner (11, 1948)	Articular branch from the NVM (1)	NVM, the most distal of its branches	Turns around the edge of the VM muscle	Yes, similar course in all joints
	SMGN (1)	TN (3 cases) or PON (4 cases)	Accompanies the SMGA	7/11
Kennedy et al. (15, 1982)	Articular branch of the NVM (1)	NVM	Bifurcates beneath the medial retinaculum	NR
Horner et al. (45, 1994)	Medial reticular nerve	Terminal branch of NVM	Courses in the substance of VM (90%) or superficial to its fascia (10%)	45/45
Hirasawa et al. (10, 2000)	Minor articular Branches from NVM	NVM from FN	Pierce the VM muscle and distribute to the capsule	NR
	Articular branch from tibial nerve	Tibial nerve	Following superomedial popliteal vessels to innervate the articular capsule	NR
Franco et al. (8, 2015)	Supero-medial genicular branch	NVM	Deep surface of VM, coming in close proximity to the junction of medial epicondyle and shaft of femur	In every specimen (8/8)

Burckett-St Laurent et al. (20, 2016)	Intramuscular branches of NVM (1-3)	NVM, at distal third of the AC	After leaving the AC, courses obliquely from medial to lateral through the belly of VM towards anterior capsule superior to patella and medial capsule	20/20
	Extramuscular branch of NVM (1)	NVM, at distal third of the AC	Courses along the medial border of the VM towards Medial retinaculum and medial aspect of the knee capsule	7/20 (35%)
	Deep genicular nerves: medial genicular nerve and anterior genicular nerve	Deep plexus of mixed NVM and SN at distal third of AC	Deep to the VM along the femur towards anteromedial aspect of the joint capsule	18/20 (90%)
Orduna-valls et al. (25, 2017)	Medial retinacular nerve	NVM	Courses within the fascia of the vastus medialis	25/25 (100%)
	Intramuscular articular nerves	NVM	Course through the VM muscle	High variability
Tran et al. (15, 2018)	Medial branch of NVI	NVI from femoral nerve	Courses along antero-medial aspect of femur between VI and VM, towards anterior-medial joint capsule	All the specimens (15/15)

	Articular branches of NVM (2-3)	NVM, from femoral nerve	Course intramuscularly towards anterior region of the supero-medial quadrant	All the specimens (15/15)
	SMGN	Femoral nerve	Courses deep to Sartorius and distally follows AMT with DGA, towards posterior-medial knee capsule	All the specimens (15/15)
Fonkoue et al. (63, 2018- 2020)	SMGN (1)	NVM (direct articular branch)	Courses within the fascia of VM, run with an artery from DGA on the AMT towards adductor tubercle	All the specimens (63/63)
	Transmuscular articular branches from NVM (0-3)	NVM (indirect articular branches)	Course through the belly of the muscle	Highly variable
	A small branch from SN	SN, in the AC	Courses on the AMT towards the superior-medial aspect of the capsule	Inconstantly found

NVM, nerve to the vastus medialis; SMGN, superior-medial genicular nerve; TN, tibial nerve; PON, posterior branch of obturator nerve; SMGA, superior-medial genicular artery; VM, vastus medialis muscle; NR, not reported; FN, femoral nerve; AC, adductor canal; SN, saphenous nerve; NVI, nerve to the vastus intermedium; VI, vastus intermedium muscle; AMT, adductor magnus tendon; DGA, descending genicular artery; NR, non-reported

The inferior-medial quadrant of the knee capsule (Table 2)

As shown on Table 2, two major nerves are regularly described at the inferior-medial quadrant of the anterior knee capsule: the inferior-medial genicular nerve and the infrapatellar branch of the saphenous nerve. We made the same observations in our studies. However, contrary to some recent authors [16] who continued to describe the IPBSN as a cutaneous nerve, with inconstant capsular twigs in a few specimens, we found (and provided multiple illustrations) that this nerve makes a major contribution to the innervation of the inferior-medial capsule in all specimens, as some other authors have also found [17, 20]. Therefore, treatment of this nerve for the very effective control of medial chronic knee pain seems essential. Many authors did not describe the IMGN [18-20, 22] or only described it as a branch of the saphenous nerve [23]. Once more, they did not show illustrations to support these particular findings. We described and illustrated, for the first time, the entire course of the IMGN, which was not a direct branch of the tibial nerve as usually described, but one of the two branches of bifurcation of the posterior articular nerve that had detached from the sciatic or tibial nerve. However, this is not of major clinical relevance because, 70 years ago, Gardner [21] accurately described the distal course of the nerve, which runs alongside with the SMGA, and passes beneath the MCL. This basis was correctly used to target the IMGN in RFA procedures.

Table 2. Nerve branches to the inferior-medial quadrant of anterior knee capsule among studies

Authors (year)	Nerves branches (number)	Origin	Course	Consistency
Gardner (11, 1948)	IPBSN (1)	Anastomosis between SN and ON in the AC	Variable proximal course; turn toward anteromedial joint capsule	5/11 cases
	IMGN (1)	PAN from TN	Accompanies the IMGA, deep to MCL	All the cases (11/11)
Kennedy et al. (15, 1982)	IPBSN	SN	Crosses the medial aspect of the tibia	NR
Horner (45, 1994)	IPBSN (2 or more)	SN	Courses toward anterolateral skin of the patella and antero-inferior knee capsule	45/45 (100%)
	AON (through subsartorial plexus)	ON	Perforates the AM and ramifying in AC to contribute to subsartorial plexus	5/45 (11.1%)
Hirasawa (10, 2000)	IPBSN	SN	Courses towards the skin and wide area covering capsule from medial to antero-inferior side of the knee	NR
Franco (8, 2015)	Infero-medial genicular branch	SN (subpatellar branch)	Runs anteriorly from the medial side of the knee in a trajectory close to the junction between MTC and tibial shaft	In every specimen (8/8)
Burckett-St Laurent et al. (20, 2016)	IPBSN	SN	Distributes just to the skin inferior to the patella	11/20 (55%)

Orduna-valls et al. (25, 2017)	IPBSN	SN	Distributes to innervate the knee in this region	25/25 (100%)
Tran et al. (15, 2018)	IPBSN	SN	Courses antero-inferiorly. Mainly cutaneous innervation but also few articular branches	3/15
	IMGN	Tibial nerve	Courses in a bundle with IMGV, inferior to MTC and deep to MCL	All the specimens (15/15)
Fonkoue et al. (63, 2018-2020)	IMGN (1)	Posterior articular branch from sciatic nerve or tibial nerve	Courses distally between PA and PV and divides in 2 branches. The medial branch runs with IMGV and passes beneath the MCL toward antero-inferior capsule	All the specimens (63/63)
	IPBSN	SN	Courses distally towards inferior-medial quadrant of the knee capsule	All the specimens (63/63)

IPBSN, infrapatellar branch of the saphenous nerve; IMGN, inferior-medial genicular nerve; SN, saphenous nerve, MTC, medial tibial condyle; MCL, medial collateral ligament; IMGV, inferior-medial genicular vessels; PA, popliteal artery; PV, popliteal vein; AON, anterior branch of the obturator nerve; PAN, posterior articular nerve; AC, adductor canal; TN, tibial nerve; AM, adductor magnus muscle; ON, obturator nerve.

The superior-lateral quadrant of the knee capsule (Table 3)

For most of the authors, the superior-lateral quadrant of the knee capsule is innervated by articular branches of the nerve to the vastus lateralis and the sciatic nerve or common fibular nerve. Discrepancies arise with regards to the number, course, consistency, and anatomical targets for RFA of the superior-lateral knee nerves. We found only one nerve with a consistent distal course that allowed accurate anatomical landmarks: the articular branch from the sciatic nerve or common fibular nerve. Although the nomenclature of this nerve varies between studies (e.g., the SLGN, lateral articular branch of CFN, lateral retinacular nerve, long articular nerve), it is indeed the same nerve with a constant course across the studies. Almost all the robust anatomical studies found this nerve in 100% of specimens, just as we did. Moreover, it is the most illustrated nerve of the superior-lateral aspect of the knee. We aligned with recent authors, in calling it the superior-lateral genicular nerve.

Although the NVL is cited by all the studies, we did not find consistency in the course of the distal ending of this nerve. Many authors found high variability in the articular branches of this nerve [21] or found their contribution to be of minor importance [18]. Horner et al. [19] found no constant branch of the NVL reaching the capsule in any of the 45 specimens dissected, and Valls et al. [20] described the articular branches of the NVL to be variable, and localized at the distal level in 25% (4/16) of specimens. Conversely, a few authors found the articular branch of the NVL to be consistent, and suggested that this can be accurately captured by classical anatomical targets [16, 23]. We did not observe such findings. In addition, we found that the photographs illustrating the articular branches of the NVL penetrating the knee capsule are rare among studies, and when they are included, their course differs between

studies. Therefore, the articular branches of the NVL do not allow the establishment of a consistent target for RFA.

Table 3. Nerve branches to the superior-lateral quadrant of anterior knee capsule among studies

Authors (year)	Nerves branches (number)	Origin	Course	Consistency
Gardner (11, 1948)	Articular branches from the NVL (1-2)	NVL	Turn around the posterior edge of VL	11/11 cases. Variabilitity of articular branches
	Single articular branch from the CFN which sometime divides in 2 branchs	CFN or SCN	Superior branch deep to BF, then accompanies SLGA	10/11 cases.
Kennedy et al. (15, 1982)	Terminal portion of the NVL (1)	NVL	Passes beneath the VL muscle	NR
Horner (45, 1994)	SLGN (1): "lateral articular branch from sciatic nerve"	Sciatic nerve, 8-10 cm superior to joint line	Courses deep to BF and iliotibial band towards superolateral aspect of knee capsule	45/45 (100%)
	Articular branches of NVL	NVL from FN	Deep to VL, Appears to terminate near the edge of the muscle	No constant branch were found to reach the capsule
Hirasawa (10, 2000)	Minor articular branch from NVL	NVL, from FN	Pierces the VL muscle to distribute to the capsule	NR
	Superior articular branch from common fibular nerve (1)	CFN, as it ran down medially along the long head of BF	Courses deep to BF towards porterior and lateral side of articular capsule	NR

Franco (8, 2015)	Supero-lateral genicular branch	NVL	Deep surface of the VL, coming in close proximity to the junction of lateral epicondyle and shaft of femur	In every specimen (8/8)
	Lateral retinacular nerve	CFN at the lateral side of the joint	Distributes around the lateral aspect of the capsule	In ervery specimen (8/8)
Orduna-valls et al. (25, 2017)	Articular branches of the NVL	NVL	Run through fascia between VL and VI. Distally, run above the posterior aspect of VL and provides branches to antero-lateral capsule	Viariable, localized at distal level in 4/16 specimens
	Lateral retinacular nerve	CFN at the level of gastrocnemius	Runs lateral deeper into the long head of biceps femoris	NR
Tran et al. (15, 2018)	Articular branch from the NVL	NVL	Deep to anterior-medial border of VL and superf to muscle belly of VI	15/15
	Lateral branch from NVI	NVI, from FN	LB crosses femur obliquely, within VI	All the specimens (15/15)
	SLGN	Sciatic (5/15) or CFN (10/15)	Lay deep to the VI, coursing along postero-lat aspect of femur. If CFN, it was short and coursed superiorly to join SLGV just before entering knee capsule	15/15

	Long articular branch from CFN	CFN, just inferior to bifurcation of sciatic nerve	Followed the CFN distally to sup border of LFC. It coursed anteroinferiorly and divided into 2-3 articular branches	All the specimens (15/15)
Fonkoue et al. (63, 2018- 2020)	SLGN	Sciatic nerve (fibular contingent) or CFN	Courses deep to the biceps femoris toward the lateral femoral condyle and divides into 2 terminal branches: LRN and descending branch	All the specimens (63/63)
	Articular branches from NVL (1-2)	NVL	Deep surface of VL	Inconstant

NVL, nerve to the vastus lateralis; CFN, common fibular nerve; SCN, sciatic nerve; VL, vastus lateralis muscle; SLGA, superior-lateral genicular artery; SLGN, superior-lateral genicular nerve; FN, femoral nerve, BF, biceps femoris muscle, NR, non-reported.

The inferior-lateral quadrant of the knee capsule (Table 4)

It emerges from all the studies that the recurrent fibular nerve is the most consistent nerve supplying the inferior-lateral quadrant of the knee capsule. Discrepancies appear with regards to the inferior-lateral genicular nerve, which for some authors, is a branch of the SLGN passing beneath the lateral collateral ligament (LCL) alongside the inferior-lateral genicular artery [16]. Meanwhile, for other authors, it is a branch of the CFN or sciatic nerve that has detached from the popliteal fossa [18, 21]. Like many other authors [20, 23], we did not find this branch. However, we found an inconstant branch that had detached from the CFN at the level of the joint line, running inferior-laterally toward the fibular head, and distributing to the ligaments and fascia around the fibular head. We did not trace a branch joining the ILGA and running with it beneath the LCL, nor detached from this nerve, nor from the SLGN. Gardner found it occasionally, some authors [21, 22] described an inferior articular nerve that had detached from the CFN with a termination similar to ours, and some others [20, 23] did not even describe it. Only Tran et al. [16] clearly indicated that they had found an ILGN running with ILGA beneath the LCL in all their specimens. Other authors were somewhat evasive about the termination of this branch of the CFN and did not display any illustration. If this nerve was as constant as they said, with such a clear course allowing easy targeting, it would have been clearly identified by at least one of the other recent robust anatomical studies. Therefore, in view of this controversy, their results should be taken with caution and further specific studies are needed from other authors. Otherwise, they should provide irrefutable photographic proofs of their findings.

Table 4. Nerve branches to the inferior-lateral quadrant of anterior knee capsule among studies

Authors (year)	Nerves branches (number)	Origin	Course	Consistency
Gardner (11, 1948)	Inferior branch of the single articular branch of CFN	CFN	Descend with ILGA	Occasionally
	Recurrent fibular nerve	CFN	Accompany blood vessels which supplies anterolateral portion of the tibia	11/11
Kennedy et al. (15, 1982)	Lateral articular nerve	CFN at joint line postero-superiorly to fibular hear	Joins the inferior portion of the lateral capsule and LCL	NR
	Recurrent fibular nerve (1)	CFN (uppermost division around the fibular head	Ascends the anterior surface of the tibia	NR (most common findings)
Horner (45, 1994)	Inferior lateral articular nerve	CFN within popliteal space, near joint line	Courses deep to BF tendon, ends near the fibular head deep to ilitibial band	"Constant" (45/45)
	Recurrent fibular nerve	CFN, distal to the fibular head	Courses towards infero-lateral aspect of the capsule and proximal tibiofibular joint	"Constant" (45/45)

Hirasawa (10, 2000)	Inferior articular branch from CFN	CFN, As it ran down to the origin of the lateral head of gastrocnemius	Extended to fibular head, ran with infero-lateral popliteal vessels towards inferolateral side of articular capsule	NR
Franco (8, 2015)	Infero-lateral (recurrent) branch	CFN, inferior the femoral head	Split into superficial and deep branches and provides a recurrent branch to the infero-lateral capsule	"In every specimen" (8/8)
Orduna-valls et al. (25, 2017)	RFN	CFN, adjacent to head of fibula	Distributes to the infero-lateral aspect of the capsule	NR
Tran et al. (15, 2018)	ILGN	Long articular branch from CFN	Coursed inferiorly with ILGV deep to LCL and turned anteriorly just inferior to LFC	"All the specimens" (15/15)
	RFN	CFN, inferior to fibular head	Coursed antero-superiorly around the neck of fibula towards the inferior-lateral capsule	"All the specimens" (15/15)
Fonkoue et al. (63, 2018- 2020)	RFN	CFN, at the level of fibular neck	Ascends with the recurrent tibial artey towards antero-inferior capsule	All the specimens (63/63)
	ILGN	CFN, at the level of femoro-tibial joint line	Courses laterally and ends near the fibular head, not found with ILGV.	Inconstant

CFN, common fibular nerve; ILGA, inferior-lateral genicular artery; LCL, lateral collateral ligament; BF, biceps femoris; ILGN, inferior-lateral genicular nerve; LFC, lateral femoral condyle; ILGV; inferior-lateral genicular vessels; NR, non-reported.

The posterior aspect of the knee capsule (Table 5)

The development of posterior knee joint analgesic blocks has aroused interest in the innervation of the posterior knee joint capsule. However, the anatomical description of the origin, course and distribution of the nerve branches innervating the posterior capsule remains imprecise and rarely illustrated. There are very few photographic illustrations of the nerve branches entering the posterior knee capsule in the literature. There is a general agreement that branches from the sciatic nerve (TN and/or CFN) and the obturator nerve innervate the posterior knee joint capsule. Discrepancies appear with regards to the precise description of these branches. Since its first description by Rudinger et al., most of the authors described a popliteal plexus from which twigs detach to innervate the posterior capsule. However, the origin of the nerve branches forming the popliteal plexus varies across studies, and no photographic illustrations are shown. Some authors described a popliteal plexus constituted by the posterior articular nerve (a single large branch from the tibial nerve of the tibial contingent of the sciatic nerve) and a branch from the posterior obturator nerve [21, 22]. Others asserted that the plexus was formed by multiple articular branches from the tibial nerve and the terminal portion of the PON [19, 20]. Some authors described an inconstant contribution of the anterior branch of the obturator nerve and saphenous nerve [21, 22]. In a recent study that focused solely on the innervation of the posterior capsule, Tran et al. [84] described a popliteal plexus that was constituted by two branches from the tibial nerve (superior and inferior) and articular branch from the PON. Contrary to all previous authors, they provided some photographic illustrations of their findings. However, they did not show the origin or termination of these branches in the posterior capsule (the popliteal

vessels and/or the gastrocnemius muscle are still in situ in their illustrations), and there is no identifiable plexus on these photographs. In this thesis, we found that the posterior capsule is innervated by the constant posterior articular nerve (from the tibial contingent of sciatic nerve or from the tibial nerve), variable direct articular branches from the tibial nerve (0-3), an inconstant branch accompanying the femoral vessels through the adductor hiatus (anastomotic branch from AON + SN), and an inconstant branch from the PON passing through the adductor magnus muscle to join the popliteal fossa. However, we did not find a clearly identifiable "popliteal plexus" and we have not succeeded in tracing these branches of the ON in the popliteal fossa until their penetration in the knee capsule. Nevertheless, since precise targeting of articular nerves penetrating the posterior capsule for RFA (as is the case with the anterior capsule) is not contemplated, these anatomical details are of little clinical relevance. The iPACK (Interspace between the Popliteal Artery and the Capsule of the posterior Knee) block is a recent procedure that targets the articular branches that innervate the posterior knee joint by administering local anesthetic into the interspace between the popliteal artery and the posterior capsule of the knee. Due to the large volume that is injected and its wide diffusion, this does not require precise identification of small articular branches or a supposed "popliteal plexus" to provide analgesia after a TKA.

Table 5. Nerve branches to the posterior aspect of the knee joint capsule among studies

Authors (year)	Nerves branches (number)	Origin	Course	Consistency
Gardner (11, 1948)	Single large branch with variable number of ending branches (Sometimes 2 separate branches or more)	TN or SCN	Form a dense plexus with similar branches of ON in popliteal fossa	"Usual finding"
	Articular branch of ON	PON (8 cases) AON (1 case)	Through the AM to join popliteal fossa Anastomosis with a branch of SN in AC, which passes with PV through adductor hiatus	9/11
Kennedy et al. (15, 1982)	Posterior articular nerve	Tibial nerve, at variable level above or within the popliteal fossa	Courses laterally, wrapping around PV, descend into fatty substance of popliteal plexus	"Most consistent and largest nerve supplying the knee"
	Terminal portion of ON	PON (usually) or AO or AO + SN(occasionally)	Accompany femoral vessels into the popliteal fossa and distributes into popliteal plexus	NR
Horner (45, 1994)	Terminal branch of PON	PON	Courses within Hunter canal fascially bound to PA, and enter the popliteal space and distributes to popliteal plexus	NR

	Porterior articular branches (1-5)	Tibial nerve	Contributes to popliteal plexus	NR
Hirasawa (10, 2000)	Articular branches of tibial nerve	Tibial nerve	Pierces adipose tissue within popliteal fossa	NR
Burckett-St Laurent et al. (20, 2016)	Anastomotic branch from AON and SN	AON + SN	Runs with femoral vessels towards popliteal fossa	2/20
Orduna-valls et al. (25, 2017)	Articular branches of TN (variable number)	Tibial nerve	Distribute to the posterior aspect of the capsule	NR
	Articular branch of PON	PON	Passes through the adductor magnus to reach the popliteal fossa	"Not verified in specimen dissected"
Tran et al. (15, 2019)	Articular branch from PON	PON	Run deep to adductor longus, on the anterior surface of AM towards adductor hiatus with FV. At the level of MFC, it divided into 2-3 branches to the supero-medial aspect of posterior capsule	15/15
	Articular nerve from CFN or sciatic nerve	CFN (8/15) or sciatic nerve (3/15)	Divides into anterior (SLGN) and posterior branch. PB courses lateraly to PV and distributes to posterior-lateral capsule	11/15
	Branches of the Tibial nerve : superior branch and inferior branch	Tibial nerve	SB: course distally, between popliteal artery and vein IB: transverse short course, and divides into 3-5 branches	SB: 7/15 IB: 15/15

			They supply entire posterior knee capsule	Popliteal plexus (SB + IB + PON): 7/15
Fonkoue et al. (63, 2018-2020)	Direct articular branches from tibial nerve (1-2)	Tibial nerve	Pierces the popliteal fat to supply the posterior capsule	"Consistent"
	Articular branches of ON	PON AON + SN	Passes through the AM to join the popliteal fossa Anastomosis between small branches from AON and SN, which passes through the adductor hiatus with femoral vessels	"Inconstant"
	Posterior articular branch from SLGN	SLGN from Sciatic nerve or CFN	Detaches from the proximal part of SLGN in the popliteal fossa to supply the superior-lateral aspect of posterior capsule	"Consistent"
	Lateral articular branch of the PAN	Posterior articular nerve from Sciatic or Tibial nerve	Lateral branch of bifurcation of the PAN; dives lateraly into the inferior-lateral aspect of the popliteal fossa.	"Consistent"

TN, tibial nerve; SCN, sciatic nerve; PON, posterior obturator nerve; AON, anterior obturator nerve; AM, adductor magnus; SN, saphenous nerve; AC, adductor canal; PV, popliteal vessels; PA, popliteal artery; CFN, common fibular nerve; PB, posterior branch; SB, superior branch; IB, inferior branch; SLGN, superior-lateral genicular nerve.

Synthetic diagram of the innervation of the knee joint capsule

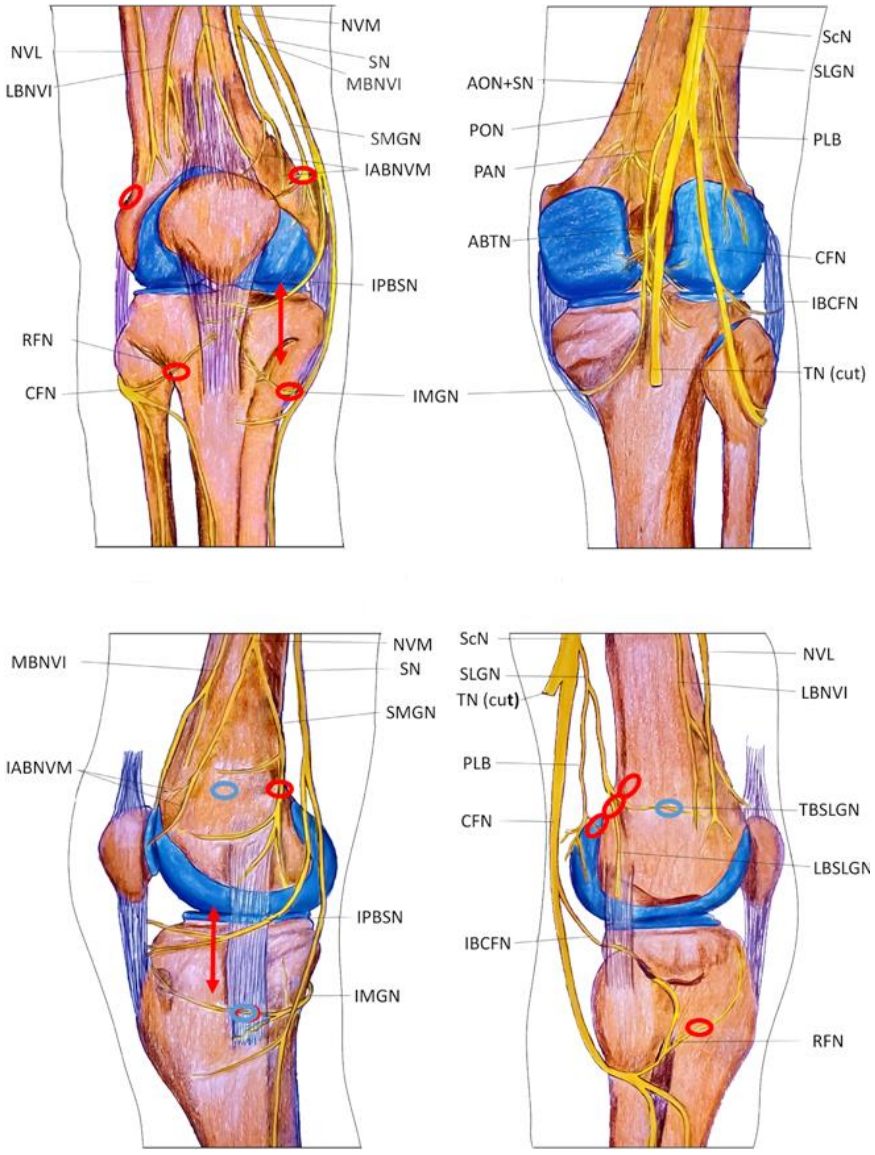

Figure 4. Summary of the nerve supply to the knee joint capsule and targets for GNB/RFA. NVL, nerve to the vastus lateralis; LBNVI, lateral branch of the

nerve to the vastus intermedius; RFN, recurrent fibular nerve; CFN, common fibular nerve; NVM, nerve to the vastus medialis SN, saphenous nerve; MBNVI, medial branch of the nerve to the vastus intermedius; SMGN, superior-medial genicular nerve; IABNVM, indirect articular branches from the nerve to the vastus medialis; IPBSN, infrapatelar branch of the saphenous nerve; IMGN, inferior-medial genicular nerve; AON+SN, branch from anterior obturator nerve + saphenous nerve (inconstant) PON, posterior obturator nerve; PAN, posterior articular nerve; ABTN, articular branch from tibial nerve; ScN, sciatic nerve; SLGN, superior-lateral genicular nerve; PLB, posterior-lateral branch; IBCFN, inferior branch from common fibular nerve; TN, tibial nerve; TBSLGN, tranverse branch of the SLGN; LBSLGN, longitudinal branch of the SLGN. Red oval shapes represent lesions with our revised targets; Blue oval shapes represent lesions with the classical targets; red double arrows represent the treatment line for IPBSN.

Methodological issues with identifying the accurate anatomical targets for GNB and RFA

Choi et al. [10] provided the original anatomical targets for genicular nerve RFA 10 years ago, based on anatomical literature and dissection of two knees. The method that allowed identification of these classical targets was not clearly described, and no accuracy validation study was performed. These authors based their choice of targets on the literature, which explains that the *"SLGN, SMGN, and IMGN accompanying genicular vessels pass close to epicondyles of the femur and tibia; except the IL genicular nerve, which runs laterally above the head of the fibula, and does not pass near the lateral epicondyle of the tibia"[10].* Therefore, their targets included "*the SLGN, SMGN and IMGN which pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle*." They confirmed this anatomical description on anatomical dissections of only two specimens, which were very questionable. They positioned the electrode tips parallel to the genicular nerve and next to the periosteum of the target sites to comply with the main principles of RF neurotomy, which include "*a correct placement of the electrode parallel to the target nerve*" [10]. Their targets have been considered accurate because they found that RFA relieved chronic knee OA pain to some extent, assuming that this pain relief was due to focal ablation of the targeted nerves. Therefore, their description has been widely used for this procedure, with relatively appreciable results in most of the studies. Despite appreciable clinical outcomes among studies, some authors queried the anatomical foundations and targets used for RFA of the genicular nerves,

resulting in subsequent anatomical studies, which found that the anatomical foundations were somewhat inaccurate. However, these authors concluded that the classical targets are sound and accurate, without any anatomical validation study [16, 23]. Yet, it remains to be understood that, for such a small lesion, the accuracy of the target and the capture of a nerve could be the same despite differences in origin, course, and termination of this same nerve between studies. Analysis of the methods and photographs that are provided in different studies reveals that very few of them described a scientific process to identify the targets or to test their precision, and there are some methodological differences with our studies, which could explain their paradoxical conclusions:

- Systematic anterograde dissection: We performed dissection of all the branches of the femoral, sciatic, and obturator nerves, from their origin, and traced their course until their endings to identify those reaching the knee joint capsule. We believe this is the correct method to identify articular nerves. Some studies did the same and displayed the entire course of the nerve [16, 17, 84]. The results of these robust studies were similar to ours. Conversely, in other studies, the photographs provided suggest that they did not perform a systematic anterograde dissection and do not allow identification of either the origin or termination (or both) of the genicular nerves [20, 23, 115]. In Articles 2 and 6, we have shown that, in donated bodies for science, the small genicular vessels can sometimes be confused with nerves. Therefore, without entire dissection, it is difficult for the researcher and the reader to confirm that the structure displayed at the level of the knee joint is really a nerve, or if the nerve that is displayed from its origin actually reaches the articular capsule. The original procedure that is described by Choi et

al. [10] seems to have targeted the superior-lateral, superior-medial, and inferior-medial genicular arteries. In this thesis, we have shown that the trunks of two of these three nerves are not accompanied by homologous arteries, as initially postulated.

- Starting dissection by removing the cutaneous tissue and fascia: Such a procedure has probably prevented many authors from identifying the entire course of the SMGN, since it has an essential intra-fascial trajectory. This, coupled with non-systematic anterograde dissection, is probably the reason why most of the studies failed to identify the most constant nerve supplying the supero-medial quadrant of the knee capsule. In all our anatomical studies, as well as the most recent anatomical studies, this nerve was found in all the specimens [16, 20].

- Identification of neural targets: The process of identifying neural targets for genicular nerve RFA was somewhat weak in most of the published studies. Only Franco et al. [23] fixed stainless steel onto the course of the nerves and performed radiographs to identify the targets for fluoroscopic-guided RFA. However, the authors did not dissect the consistent genicular nerves that are well known today, but rather the nerve of the vastus lateralis (considered the SLGN), the nerve of the vastus medialis (considered the SMGN), and the IPBSN (considered the IMGN). Tran et al. [16] recently provided a famous figure map of nerves that supply the knee joint capsule to guide cannula placement during RFA procedures. Based on this figure map, they argue that the classical targets are correct, and in their letter to the editor in response to Article 3 of this thesis, they paradoxically did not agree with any revision of the classical targets to comply with the updated anatomical

knowledge to which they have greatly contributed. Yet, Tran et al.'s [16] frequency map was not designed to provide or assess accurate landmarks for fluoroscopic-guided GNB and RFA. As they stated in their method, "*The course of each nerve was traced and consolidated onto a three-dimensional skeletal model to generate a frequency map of the innervation of the anterior knee joint capsule.*" If the aim is to provide accurate landmarks for GNB/RFA, this method is not robust enough because the transcription of the real trajectory of each nerve from the dissection to the three-dimensional skeletal model can introduce bias, especially regarding accuracy. In order to generate a robust and reliable frequency map that could enable identification of accurate landmarks or assessment of the targets validated by cadaveric studies, it would be necessary, for example, to fix slender stainless-steel wires along the course of each nerve during dissection, and then proceed to imaging (radiographs or CT scan) to obtain a reliable projection of the nerve trajectory for fluoroscopic-guided procedures. Then, all images would be computerized to generate a robust frequency map with less bias, which would be accurate and relevant for physicians. Until then, the frequency map traced by Tran et al. could be misleading with respect to precise fluoroscopic landmarks. In their most recent cadaveric study on five specimens, Tran et al used a more robust technique to evaluate the nerve capture using classical landmarks [145]. A deployed marker was positioned at the precise location of a RF cannula tip and subsequent dissection was performed to assess nerve capture rate. However, there are still significant methodological flaws that make their results questionable. For example, looking closely at most of their dissections figures, the deployed markers are not located

at the classical target points for the SLGN and SMGN (midpoint of the femoral shaft) but clearly located far anteriorly, which constitutes a huge biais. Therefore, the results of their new study are somewhat contradictory to those of their previous articles [16, 130].

In our successive studies, we fixed Kirshner wires (Article 1), stainless steel (Article 4), or radio-opaque thumbtacks (Article 6) onto the constant genicular nerves at their precise target points just before distribution to the articular capsule, and then we performed radiographs or ultrasound scanning to identify the targets for each of the nerves. We believe that only such a robust method can provide sound and precise landmarks for RFA.

- Anatomical validation of neural targets: We found few validation studies for the targets of GNB and RFA [12, 20, 100, 115]. The common point of all these studies is that, since they injected a volume of aqueous dyed solution (as we did in Article 3 of this thesis), their results are only applicable to GNB and not RFA. In Articles 4 and 6, we developed a new method to simulate small RFA lesions, which allowed accurate assessment of the nerve capture rate at a specific target point. In addition to the bias that was due to the large diffusion, the injections performed in some studies [20] were too proximal. Although some may have been applicable to regional anesthesia, this was surely not appropriate for the treatment of chronic knee pain, which requires distal targeting of the sensory articular branches. Moreover, the photographs of their dissections were too proximal, which not allowed visualization of the targeted nerve reaching the capsule [20], or only distal "through a window," which could not allow the researcher or the reader to identify the origin of the structure that had been captured.

Thus, we could not be sure that it was really a small nerve and not a small vessel [115].

Are we moving toward better anatomical targets for GNB and RFA?

The answer to this question is undoubtedly yes, as demonstrated in Article 6 of this thesis and suggested by the recent studies that propose new anatomical targets based on anatomical updates [102, 104, 146-148]. However, these other targets have not been developed according to a rigorous methodology and have not been validated. Nevertheless, we must recognize that it is difficult to change a technique that seems to work, even if everyone agrees that the anatomical bases are questionable, and that the technique's results can be improved. We are convinced that the anatomical landmarks proposed in this thesis will constitute the starting point of new studies, which will ultimately lead to a consensual revision of the anatomical targets. This thesis would thus find its full relevance. The five-target-nerve technique that is proposed in this thesis captures the constant nerves that were found in our successive pieces of research and that were gleaned from the global objective analysis of all the original anatomical studies. Inhibiting five nerves rather than three, out of approximately 11 to 13 that innervate the knee joint capsule, would, in our opinion, better reduce afferent impulses from the knee, but without canceling them either. This could have disastrous consequences, due to suppression of proprioception. This raises the question of the optimal number of nerves to target; why did we propose five but not six or four? This is simply a question of the nerves that have been identified without ambiguity in each specimen, whose anatomical landmarks were constant and targetable throughout this thesis. Any research seeking to provide accurate anatomical targets for GNB and RFA would have to adhere to such methodological rigor. This will certainly

facilitate evolution toward better anatomical landmarks, which we hope will subsequently achieve definitive consensus.

Is the pain relief reported after RFA for knee OA pain really related to genicular nerve ablation?

To date, all the studies have reported effective relief (greater than 50%) of knee OA pain after RFA in a significant proportion of participants and over a period of three months to one year [4, 10, 14, 24, 25, 52, 53, 55-57, 60, 64, 65, 67, 69, 72, 76, 85, 105, 123, 149]. However, it is extraordinarily striking to notice that the outcomes are similar, despite clear differences in the number of targeted nerves (ranging from one to six, according to the published studies) and especially considering the anatomical positioning of the electrodes was sometimes grossly distant, even with the classical technique, which obviously rendered them unable to capture the nerve. This is curious and calls into question the theory of nerve ablation justifying pain relief. Based on this thesis, the classical technique has shown an accuracy of 0% on the superior-medial geniculate nerve, 35% on the superior-lateral nerve, and 100% on the inferior-medial nerve. This poor precision contrasts with the clinical results reported, if we consider the pain relief related to the focal nerve lesion. In addition, with regards to the very limited volume of a RF lesion, and having meticulously dissected the knees throughout this thesis, it seems to us very unlikely that the anatomical imprecision observed in various clinical studies will result in the capture of target nerves because it requires millimetric precision. We could even assert that it is not possible to place the electrodes at such different locations as are presented in various studies, and hope to capture the same nerve with an infra-centimeter lesion. This seems illogical. Other RF modalities that are applied intra-articularly [63] or around the sciatic nerve [78] have been shown to relieve pain through a non-ablative mechanism.

In addition, reduction of the vascular supply to the knee has been proven to alleviate chronic knee OA pain [117]. Therefore, since we found that the classical targets would thermocoagulate the upper transverse artery, the superior-lateral and inferior-medial genicular arteries, this could have contributed to the pain relief that is reported in the studies. In light of this thesis, we believe that the pain relief observed in the studies that used classical anatomical targets was not primarily the result of the focal lesion of the target nerves. Instead, we believe this was multifactorial (*e.g.,* a psychological response to the procedure, which is performed in the impressive context of an operating room that has a lot of devices, the non-ablative effect of RF, reduction of vascular supply). Only one study involving 28 patients demonstrated the superiority of RFA against placebo on knee pain [10]. Another study involving a sham group showed that RFA performed preoperatively had no benefit on pain relief in patients after their knee replacement surgery, compared to the sham group [66]. These authors attributed their findings to the high rate of non-responders (>26%) for cooled genicular nerve RFA, even with a positive prognostic genicular nerve block, the complexity of the knee innervation, and patient neuroanatomic variability. Central sensitization may also explain the absence of therapeutic response [150].

All the arguments that are outlined above call into question the ablative theory that is based on precision of anatomical targets, which has been accepted for this procedure until now. We believe, however, that better nerve targeting allowing effective ablation of more nerves could add to the pain relief that is associated with other mechanisms, which could therefore lead to better outcomes. This paves the way for a vast field of studies to elucidate these new research hypotheses. An animal model to explore RFA lesions *in vivo* could

also be developed. In addition, double-blind randomized control trials should be conducted, as follows:

- RFA using revised anatomical targets (or even classical targets) for the positioning of the RF electrodes versus random positioning (application of a periarticular RF with the same number of electrodes but without targeting a specific nerve).
- Intra-articular RFA versus periarticular RFA with accurate anatomical targets.
- RFA using classical anatomical targets (poor accuracy) versus revisited targets (better accuracy).
- RFA using revisited anatomical targets versus sham.
- RFA using different numbers of targets (e.g., ranging from two to six).

These future clinical studies would make it possible to better understand the mechanisms that actually lead to the relief of pain, which would contribute with the anatomical studies in this thesis, to ultimately improve the management of these patients.

Are we moving toward better outcomes with better anatomical targets?

The clinical trial carried out in this thesis, which compared GNB with the revised targets (which were shown to be anatomically more precise) to GNB with the classical targets, showed better pain relief with the revised technique immediately after the procedure. However, it did not endure over time. This difference was less marked than we had expected, given the important difference in the accuracy of the anatomical landmarks between both techniques. However, the large volume that was injected, allowing a large diffusion which could have corrected the anatomical imprecision, and the addition of corticosteroids, could explain this narrow difference between both techniques. The superiority of the immediate pain relief provided by GNB using the revised targets probably reflects the effect of the local anesthetic and therefore the procedure's anatomical precision. This could presage a better clinical outcome after RFA with revised targets because precision is purported to be the basis of this technique's success, if we still consider that the mechanism of action is essentially ablative. At the end of this thesis, we question this theory slightly because of the similarly satisfying results that were systematically reported in the clinical studies, independent of anatomical targets used. Nevertheless, these outcomes still need to be improved. Therefore, we believe that a real focal ablative lesion of the genicular nerves that is obtained with accurate anatomical targets would enhance the analgesic effect that is obtained by other mechanisms, which have not yet been elucidated. This is why we believe that the accurate anatomical targets developed in this thesis would improve the pain relief of patients, compared to the less-precise classical

technique. However, the clinically-reported difference might not be as substantial as that obtained anatomically.

It is worth raising the question whether radiofrequency denervation of the knee will not lead to Charcot-type joint. First, our procedure targets only 5 of the 13-16 nerves supplying the knee joint capsule and therefore, the deafferentation of this weight-bearing joint is partial. Second, the Charcot joint involves much more than reduced innervation; it occurs in chronically compromised vascularity, altered soft-tissue characteristics and peripheral neuropathy [11]. To date, no charcot-type joints have been reported following this procedure.

Conclusions

This thesis revisited the nerve supply to the knee joint capsule and provided sound anatomical foundations for GNB and RFA to treat chronic knee OA pain. It has improved understanding of the pattern of arteries that accompany the targeted genicular nerves, since the arteries can be used as landmarks during ultrasound-guided procedures. The thesis has also provided evidence that the current targets do not accurately capture two of the three commonly targeted genicular nerves. New protocols that target the five consistent nerves that supply the knee capsule, using accurate anatomical landmarks, were developed and validated for both fluoroscopic and ultrasound-guided GNB and RFA. The new protocol was shown to be more accurate than the classical protocol in cadaveric models, and it was associated with significantly better immediate pain relief in patients suffering from chronic knee OA pain treated by GNB. These findings are promising, and we hope that this new, ready-to-use protocol will guide pain physicians and provide more effective relief for patients with chronic knee pain. However, this thesis calls into question the theory that focal nerve lesions that are secondary to the anatomical precision of RF thermocoagulation are primarily responsible for the relief of pain that is systematically reported in clinical studies. This opens perspectives for further studies to explore alternative theories.

Appendix

Appendix 1: Questionnaire used for the clinical trial reported in part IV

Ce questionnaire est destiné aux patients atteints de gonarthrose douloureuse participant volontairement à cette étude clinique, visant l'amélioration de la prise en charge de ces douleurs. La complétion de ce questionnaire est anonymisée. Les investigateurs s'engagent non seulement à ne pas divulguer votre nom dans le cadre d'une publication ou d'une conférence, mais aussi à remplacer votre identité par des codes avant de transmettre vos données au gestionnaire de base de données collectées pour analyses. Le promoteur s'engage à utiliser les données collectées uniquement dans le cadre de l'étude à laquelle vous participez.

Merci de compléter ce questionnaire jusqu'au bout.

Date : ……/……/20….

Code identifiant patient : ……

Evaluation *Base* □ H_1 □ J_1 □ J_7 □ J_{30} □ J_{90} □

1. Echelle numérique d'évaluation de la douleur (NRS)

Sur une échelle de 0 (Aucune douleur) à 10 (douleur maximale imaginable) Veuillez indiquer l'intensité de votre douleur actuelle, votre meilleur et votre pire niveau de douleur ressenties au cours de la semaine écoulée

Echelle numérique (EN)

Pas de Douleur	0	1	2	3	4	5	6	7	8	9	10	Douleur maximale imaginable

Douleur actuelle : …….
Douleur minimale au repos : …….
Douleur maximale à l'effort: …….

2. Questionnaire d'Oxford pour le genou

Durant les 4 dernières semaines:

1 - Comment décririez vous la douleur que vous avez habituellement ressentie dans votre genou ?

O Aucune O Minime O Légère
O Modérée O Sévère

2- Avez-vous eu des difficultés pour vous laver et vous sécher le corps vous-même (des pieds à la tête) à cause de votre genou ?

O Aucune difficulté O Difficultés minimes O Difficultés modérées
O Difficultés majeures O Impossible à réaliser

3. Avez-vous des difficultés à cause de votre genou pour entrer ou sortir d'une voiture ou pour utiliser les transports en commun ?

O Aucune difficulté O Difficultés minimes O Difficultés modérées
O Difficultés majeures O Impossible à réaliser

4. Combien de temps pourriez-vous marcher avant que votre douleur de genou ne devienne importante? (avec ou sans canne)

O Aucune douleur />30mn O de 16 à 30mn O de 5 à 15mn
O Aux abords de la maison O Marche impossible

5. Après être resté assis (pour un repas par exemple), quel degré de douleur avez-vous ressenti en vous levant de la chaise à cause de votre genou ?

O Pas douloureux du tout O Légèrement douloureux O Modérmnt douloureux
O Très douloureux O Insupportable

6. Avez-vous boité en marchant à cause de votre genou?

O Rarement ou Jamais O Qqfois, ou juste au début O Souvent, en continu
O La plupart du temps O Tout le temps

7. Avez-vous pu vous mettre à genoux et vous relevez ensuite ?

O Oui, facilement O Avec difficulté légère O Avec difficulté modérée
O Avec difficulté majeure O Non, impossible

8. Avez-vous souffert de douleurs de votre genou au lit la nuit?

O Pas une nuit | O Seulement 1 ou 2 nuits | O Quelques nuits
O La plupart des nuits | O Chaque nuit

9. La douleur de votre genou vous a-t-elle gêné(e) dans votre travail ou vos activités habituelles (taches ménagères comprises) ?

O Pas du tout | O Un peu | O Modérément
O Fortement | O Tout le temps

10. Avez vous pensé que votre genou allait soudainement se dérober et vous faire chuter ?

O Rarement ou Jamais | O Qqfois, ou juste au début | O Souvent, en continu
O La plupart du temps | O Tout le temps

11. Avez-vous pu faire tout(e) seul(e) les courses pour la maison?

O Oui, facilement | O Avec difficulté légère | O Avec difficulté modérée
O Avec difficulté majeure | O Non, impossible

12. Avez-vous pu monter au moins un étage par les escaliers ?

O Oui, facilement | O Avec difficulté légère | O Avec difficulté modérée
O Avec difficulté majeure | O Non, impossible

3: Questionnaire WOMAC pour le genou

P : *les questions suivantes sont relatives au* ***degré de douleur*** *que vous ressentez actuellement en raison de l'arthrose de votre genou. Veuillez noter le degré de douleurs ressenties récemment*

Quelle est **l'intensité des douleurs lors des activités suivantes:**

1. Marcher sur le plat:					
	O Aucune	O Légère	O Modérée	O Sévère	O Extrême
2. Monter/Descendre les escaliers:					
	O Aucune	O Légère	O Modérée	O Sévère	O Extrême
3. Durant le décubitus nocturne au lit:					
	O Aucune	O Légère	O Modérée	O Sévère	O Extrême
4. Position assise ou au repos:					
	O Aucune	O Légère	O Modérée	O Sévère	O Extrême
5. Position debout:					
	O Aucune	O Légère	O Modérée	O Sévère	O Extrême

M : *Ces questions concernent* ***le degré de raideur articulaire*** *que vous ressentez actuellement en raison de l'arthrose de votre genou*

6. Quel est le degré de raideur de l'articulation lors du premier lever le matin :				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
7. Quel est le degré de raideur de l'articulation après une position assise, allongée ou au repos plus tard dans la journée :				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême

F : *Ces questions concernent vos aptitudes physiques. Il s'agit des possibilités pour vous déplacer et pour vaquer à vos occupations. Veuillez indiquer le* ***degré de difficulté*** *imputable actuellement à votre (vos) genou (x).*

Quel degré de difficultés ressentez-vous lors des activités suivantes…

(Les 7 questions entre parenthèses correspondent aux questions du score Womace dit "réduit")

8.Descendre les escaliers:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
9. (1) Monter les escaliers:				
O Aucun	**O Léger**	**O Modéré**	**O Sévère**	**O Extrême**

10. (2) Se lever d'un siège				
O Aucun	**O Léger**	**O Modéré**	**O Sévère**	**O Extrême**
11.Position debout:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
12.Se pencher à terre:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
13. (3) Marcher sur le plat:				
O Aucun	**O Léger**	**O Modéré**	**O Sévère**	**O Extrême**
14. (4) Monter/Descendre d'une voiture:				
O Aucun	**O Léger**	**O Modéré**	**O Sévère**	**O Extrême**
16. (5) Enfiler des chaussettes ou des bas:				
O Aucun	**O Léger**	**O Modéré**	**O Sévère**	**O Extrême**
17. (6)Se lever du lit:				
O Aucun	**O Léger**	**O Modéré**	**O Sévère**	**O Extrême**
18. Enlever des chaussettes ou des bas:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
19. Se tenir allongé(e) au lit:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
20.Entrer/Sortir d'une baignoire:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
21. (7) Position assise:				
O Aucun	**O Léger**	**O Modéré**	**O Sévère**	**O Extrême**
22.S'asseoir/se lever du siège des toilettes :				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
23.Activités domestiques lourdes:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême
24.Activités domestiques légères:				
O Aucun	O Léger	O Modéré	O Sévère	O Extrême

4: Evaluation quantitative de la prise d'analgésiques (Quantitative Analgesic Questionnaire)

a. Médicaments que vous avez récemment (4 dernières semaines) pris pour vos douleurs au(x) genou(x)

Nom du médicament :

1. …… Dosage (mg) : ……
2. ……..... Dosage (mg) : ……
3. ……..... Dosage (mg) : ……

Pour quel type de douleurs prenez-vous ces médicaments ? ……..

Combien de **jours par semaine** prenez-vous **habituellement** ces médicaments ? encerclez un nombre ci-dessous.

0 1 2 3 4 5 6 7

Lorsque vous vous prenez ce médicament, combien de **comprimés en moyenne** prenez-vous **par jour** ? encerclez un nombre ci-dessous pour chaque médicament

Médicament 1: 0 1 2 3 4 5 6 7 8 9 10 ou plus

Médicament 2: 0 1 2 3 4 5 6 7 8 9 10 ou plus

Médicament 3: 0 1 2 3 4 5 6 7 8 9 10 ou plus

☐ Je prends ce(s) médicament(s) de façon régulière

☐ Je ne prends ce(s) médicament(s) que lorsque j'en ai besoin

b. Utilisation des patchs analgésiques

Utilisez-vous des **patchs de Fentanyl** contre vos douleurs du genou ? OUI NON ☐ ☐

Si oui, Dosage : …….

Combien de jours par semaine en moyenne portez-vous le patch : …….

Utilisez-vous des **patchs de Buprenorphine** contre vos douleurs du genou **?** OUI NON ☐ ☐

Si oui, Dosage : …….

Combien de jours par semaine en moyenne portez-vous le patch : …….

c. Utilisation des topiques analgésiques

Utilisez-vous des **gels/pommades/crèmes** que vous **appliquez régulièrement** sur vos genoux contre la douleur ?

OUI ☐ NON ☐

Si oui, veuillez les lister :

……..

TOTAL QAQ SCORE : ……

5: QUESTIONNAIRE DE LA QUALITE DE VIE (forme abrégée) SF-12

1. Dans l'ensemble, pensez-vous que votre santé est :

☐ 1 Excellente ☐ 2 Très bonne ☐ 3 Bonne ☐ 4 Médiocre ☐ 5 Mauvaise

2. En raison de votre état de santé actuel, êtes-vous limité pour des efforts physiques modérés (déplacer une table, passer l'aspirateur, jouer aux boules) ?

☐ 1 Oui, beaucoup limité ☐ 2 Oui, peu limité ☐ 3 Non, pas du tout limité

3. En raison de votre état de santé actuel, êtes-vous limité pour monter plusieurs étages par l'escalier ?

☐ 1 Oui, beaucoup limité ☐ 2 Oui, peu limité ☐ 3 Non, pas du tout limité

Au cours de ces 4 dernières semaines, et en raison de votre état physique :

4. Avez-vous accompli moins de choses que vous auriez souhaité ?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

5. Avez-vous été limité pour faire certaines choses ?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

Au cours de ces 4 dernières semaines, et en raison de votre état émotionnel (comme vous sentir triste, nerveux ou déprimé) :

6. Avez-vous accompli moins de choses que vous auriez souhaité ?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

7. Avez-vous eu des difficultés à faire ce que vous aviez à faire avec autant de soin et d'attention que d'habitude?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

8. Au cours de ces 4 dernières semaines, dans quelle mesure vos douleurs physiques vous ont-elles limité dans votre travail ou vos activités domestiques ?

☐ 1 pas du tout ☐ 2 un petit peu ☐ 3 Moyennement ☐ 4 Beaucoup ☐ 5 Jamais

Les questions qui suivent portent sur comment vous vous êtes sentis au cours de ces 4 dernières semaines. Pour chaque question, indiquez la réponse qui vous semble la plus appropriée

9. Y'a-t-il eu des moments où vous vous êtes senti(e) calme et détendu(e) ?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

10. Y'a-t-il eu des moments où vous vous êtes senti(e) débordant(e) d'énergie ?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

11. Y'a-t-il eu des moments où vous vous êtes senti(e) triste et abattu(e) ?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

12. Au cours de ces 4 dernières semaines, y'a-t-il eu des moments où votre état de santé physique ou émotionnel vous a gêné dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances ?

☐ 1 Toujours ☐ 2 La plupart du temps ☐ 3 Souvent ☐ 4 Parfois ☐ 5 Jamais

6: INDICE DE SATISFACTION DU PATIENT

(QUESTIONNAIRE *PATIENT GLOBAL IMPRESSION OF CHANGE*)

Depuis le début de ce traitement, comment qualifierez-vous le **changement** (s'il existe) sur la **limitation de vos activités**, vos **symptômes**, vos **émotions** et tout ce qui fait votre **qualité de vie**, **en lien avec votre douleur** ?

Faites une croix dans la case de droite (une seule réponse possible)

1	Pas de changement ou c'est devenu pire	
2	Presque pareil, pratiquement pas d'amélioration	
3	Un peu mieux, mais pas de changement notable	
4	Plutôt mieux, mais le changement ne fait pas de réelle différence	
5	Mieux, le changement est modéré mais notable	
6	Mieux, avec sans aucun doute une amélioration réelle qui fait la différence	
7	Nettement mieux, une amélioration considérable qui fait toute la différence	

Inventaire de sensibilisation Centrale.

INVENTAIRE DE SENSIBILISATION CENTRALE: PARTIE A

Veuillez indiquer pour chaque situation la proposition la plus adaptée	Jamais	Rarement	Parfois	Souvent	Toujours
1. J'ai la sensation d'un sommeil non récupérateur quand je me réveille le matin	☐	☐	☐	☐	☐
2. Je ressens des raideurs et des douleurs musculaires	☐	☐	☐	☐	☐
3. Je fais des crises d'angoisse	☐	☐	☐	☐	☐
4. Je grince ou serre les dents	☐	☐	☐	☐	☐
5. J'ai des problèmes de diarrhée et/ou de constipation	☐	☐	☐	☐	☐
6. J'ai besoin d'aide pour effectuer mes activités quotidiennes	☐	☐	☐	☐	☐
7. Je suis sensible aux fortes lumières	☐	☐	☐	☐	☐
8. Je me fatigue très facilement lorsque je suis actif physiquement	☐	☐	☐	☐	☐
9. Je ressens des douleurs partout dans le corps	☐	☐	☐	☐	☐
10. J'ai des maux de tête	☐	☐	☐	☐	☐
11. Je ressens une gêne à la vessie et/ou des brûlures lorsque j'urine	☐	☐	☐	☐	☐
12. Je ne dors pas bien	☐	☐	☐	☐	☐
13. J'ai des difficultés de concentration	☐	☐	☐	☐	☐
14. J'ai des problèmes de peau tels que sécheresse, démangeaisons ou éruption cutanées	☐	☐	☐	☐	☐
15. Le stress aggrave mes symptômes physiques	☐	☐	☐	☐	☐
16. Je me sens triste ou déprimé	☐	☐	☐	☐	☐
17. J'ai peu d'énergie	☐	☐	☐	☐	☐
18. Je ressens des tensions musculaires dans la nuque et dans les épaules	☐	☐	☐	☐	☐
19. J'ai mal à la mâchoire	☐	☐	☐	☐	☐
20. Certaines odeurs, comme des parfums, me donnent des nausées et des étourdissements	☐	☐	☐	☐	☐
21. Je dois uriner fréquemment	☐	☐	☐	☐	☐
22. J'ai la sensation désagréable des jambes sans repos lorsque j'essaye de dormir le soir	☐	☐	☐	☐	☐
23. J'ai des difficultés à me souvenir de certaines choses	☐	☐	☐	☐	☐
24. J'ai eu des traumatismes au cours de mon enfance	☐	☐	☐	☐	☐
25. Je ressens des douleurs dans la région du bassin	☐	☐	☐	☐	☐

INVENTAIRE DES SYMPTOMES ASSOCIES A LA SENSIBILISATION CENTRALE: PARTIE B

Un médecin vous a-t-il diagnostiqué l'un des troubles suivants? *Pour chaque diagnostic, veuillez cocher **Oui** ou **Non** dans la colonne de droite et indiquer l'année du diagnostic*	OUI	NON	Année du diagnostic
1. Syndrome des jambes sans repos	☐	☐	
2. Syndrome de fatigue chronique	☐	☐	
3. Fibromyalgie	☐	☐	
4. Trouble de l'articulation temporo-mandibulaire (ATM)	☐	☐	
5. Migraines ou céphalées de tension	☐	☐	
6. Syndrome du côlon irritable	☐	☐	
7. Hypersensibilité chimique multiple	☐	☐	
8. Lésion de la nuque (y-compris le syndrome du coup du lapin, ou « whiplash syndrome »)	☐	☐	
9. Troubles anxieux ou attaques de panique	☐	☐	
10. Dépression	☐	☐	

VEUILLEZ VERIFIER QUE VOUS AVEZ BIEN FOURNI UNE REPONSE POUR CHACUNE DES QUESTIONS. MERCI DE VOTRE COLLABORATION.

Références patient : …… Date :……...

Avez-vous bien tout complété ?

Merci de votre participation

References

1. O'Neill TW, McCabe PS, McBeth J. *Update on the epidemiology, risk factors and disease outcomes of osteoarthritis.* Best Pract Res Clin Rheumatol 2018; **32**(2):312-326.
2. Felson DT, Naimark A, Anderson J et al. *The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study.* Arthritis Rheum 1987;**30**(8):914-8.
3. Gaught AM, Carneiro KA. *Evidence for determining the exercise prescription in patients with osteoarthritis.* Phys Sportsmed 2013;**41**(1):58-65.
4. Qudsi-Sinclair S, Borras-Rubio E, Abellan-Guillen J F, Padilla Del Rey M L, Ruiz-Merino G. A Comparison of Genicular Nerve Treatment Using Either Radiofrequency or Analgesic Block with Corticosteroid for Pain after a Total Knee Arthroplasty: A Double-Blind, Randomized Clinical Study. *Pain practice* 2017; *17*:578-588.
5. Diehl P, Gerdesmeyer L, Schauwecker J, Kreuz PC, Gollwitzer H, Tischer T. *Conservative therapy of osteoarthritis.* Orthopade 2013; **42**(2):125-39.
6. Filardo G, Kon E, Longo UG et al. *Non-surgical treatments for the management of early osteoarthritis.* Knee Surg Sports Traumatol Arthrosc 2016; **24**(6):1775-85.
7. Hrnack SA, Barber FA. *Managing the pain of knee osteoarthritis.* Phys Sportsmed 2014; **42**(3):63-70.
8. Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain* 2011;*152*:566-572.
9. Sullivan M, Tanzer M, Reardon G, Amirault D, Dunbar M, StanishW. *The role of presurgical expectancies in predicting pain and function one year following total knee arthroplasty.* Pain 2011;**152**(10):2287-93.
10. Choi WJ, Hwang SJ, Song JG et al. Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double-blind randomized controlled trial. *Pain* 2011; *152*:481-487.
11. Kidd VD, Strum SR, Strum DS, Shah J. Genicular Nerve Radiofrequency Ablation for Painful Knee Arthritis: The Why and the How. *JBJS Essent Surg Tech* 2019; *9(1)*e10.

12. Yasar E, Kesikburun S, Kilic C, Guzelkucuk U, Yazar F, Tan AK. Accuracy of Ultrasound-Guided Genicular Nerve Block: A Cadaveric Study. *Pain Physician* 2015;*18*:E899-904.
13. Kim SY, Le PU, Kosharskyy B, Kaye AD, Shaparin N, Downie SA. Is Genicular Nerve Radiofrequency Ablation Safe? A Literature Review and Anatomical Study. *Pain Physician* 2016; *19*:E697-705.
14. Bhatia A, Peng P, Cohen SP. Radiofrequency Procedures to Relieve Chronic Knee Pain: An Evidence-Based Narrative Review. *Reg Anesth Pain Med* 2016; *41*:501-510.
15. McCormick ZL, Walega DR. *Third-Degree Skin Burn from Conventional Radiofrequency Ablation of the Inferiomedial Genicular Nerve.* Pain Med 2018; 19(5):1095-1097.
16. Tran J, Peng PWH, Lam K, Baig E, Agur AMR, Gofeld M. Anatomical Study of the Innervation of Anterior Knee Joint Capsule: Implication for Image-Guided Intervention. *Reg Anesth Pain Med* 2018; *43*:407-414.
17. Burckett-St Laurant D, Peng P, Giron Arango L et al. The Nerves of the Adductor Canal and the Innervation of the Knee: An Anatomic Study. *Reg Anesth Pain Med* 2016;*41*:321-327.
18. Hirasawa Y, Okajima S, Ohta M, Tokioka T. Nerve distribution to the human knee joint: anatomical and immunohistochemical study. *Int Orthop* 2000; *24*:1-4.
19. Horner G, Dellon AL. Innervation of the human knee joint and implications for surgery. *Clin Orthop Relat Res* 1994;221-226.
20. Orduna Valls JM, Vallejo R, Lopez Pais P et al. Anatomic and Ultrasonographic Evaluation of the Knee Sensory Innervation: A Cadaveric Study to Determine Anatomic Targets in the Treatment of Chronic Knee Pain. *Reg Anesth Pain Med* 2017;*42*:90-98.
21. Gardner E. *The innervation of the knee joint.* Anat Rec 1948; 101:109.
22. Kennedy JC, Alexander IJ, Hayes KC. Nerve supply of the human knee and its functional importance. Am J Sports Med 1982; 10,6:329-335
23. Franco CD, Buvanendran A, Petersohn JD, Menzies RD, Menzies LP. Innervation of the Anterior Capsule of the Human Knee: Implications for Radiofrequency Ablation. *Reg Anesth Pain Med* 2015; *40*:363-368.
24. Jamison DE, Cohen SP. Radiofrequency techniques to treat chronic knee pain: a comprehensive review of anatomy, effectiveness, treatment parameters, and patient selection. *J Pain Res* 2018;*11*:1879-1888.
25. Gupta A, Huettner DP, Dukewich M. *Comparative Effectiveness Review of Cooled Versus Pulsed Radiofrequency Ablation for the*

Treatment of Knee Osteoarthritis: A Systematic Review. Pain Physician 2017; **20**(3):155-171.

26. Brown GA. *AAOS clinical practice guideline: treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition.* J Am Acad Orthop Surg, 2013; **21**(9):577-9.
27. Goldman DT, Piechowiak R, Nissman D, Bagla S, Isaacson A. *Current Concepts and Future Directions of Minimally Invasive Treatment for Knee Pain.* Curr Rheumatol Rep, 2018; **20**(9):54.
28. Bijlsma JW, Berenbaum F, Lafeber FP. *Osteoarthritis: an update with relevance for clinical practice.* Lancet; 2011; **377**(9783):2115-26.
29. Sawitzke AD, Shi H, Finco MF et al. *Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT.* Ann Rheum Dis 2010; **69**(8):1459-64.
30. Clegg DO, Reda DJ, Harris CL et al. *Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis.* N Engl J Med 2006;**354**(8):795-808.
31. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. *Intraarticular corticosteroid for treatment of osteoarthritis of the knee.* Cochrane Database Syst Rev 2006;(2):Cd005328.
32. Jevsevar DS. *Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition.* J Am Acad Orthop Surg 2013; **21**(9):571-6.
33. Rabago, D, Patterson J J, Mundt M et al. *Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial.* Ann Fam Med 2013; **11**(3):229-37.
34. Feeley BT, Gallo RA, Sherman S, Williams RJ. *Management of osteoarthritis of the knee in the active patient.* J Am Acad Orthop Surg 2010; **18**(7):406-16.
35. Laupattarakasem W, Laopaiboon M, Laupattarakasem P, Sumananont C. *Arthroscopic debridement for knee osteoarthritis.* Cochrane Database Syst Rev 2008;(1):Cd005118.
36. Usenbo A, Kramer V, Young T, Musekiwa A. *Prevalence of Arthritis in Africa: A Systematic Review and Meta-Analysis.* PLoS One 2015; **10**(8):e0133858.
37. Schwartzler C, Natta D, Detrembleur C. *État des connaissances sur la gonarthrose dans les peuples d'Afrique : Une revue narrative de la littérature.* DIAL, Faculté des sciences de la motricité, Université catholique de Louvain, Mémoire de Master en sciences de la moticité, 2020.

38. Felson DT. *The sources of pain in knee osteoarthritis.* Curr Opin Rheumatol 2005; **17**(5):624-8.

39. Biedert RM, Sanchis-Alfonso V. *Sources of anterior knee pain.* Clin Sports Med 2002; **21**(3):335-47.
40. Biedert RM, Stauffer E, Friederich NF. *Occurrence of free nerve endings in the soft tissue of the knee joint: A histologic investigation.* Am J Sports Med 1992; **20**(4):430-3.
41. Biedert R, Lobenhoffer P, Lattermann C, Stauffer E, Müller W. *Free nerve endings in the medial and posteromedial capsuloligamentous complexes: occurrence and distribution.* Knee Surg Sports Traumatol Arthrosc 2000; **8**(2):68-72.
42. Wyke B. *The neurology of joints.* Ann R Coll Surg Engl 1967; **41**(1):25-50.
43. Grönblad M, Korkala O, Liesi P, Karaharju E. *Innervation of synovial membrane and meniscus.* Acta Orthop Scand 1985; **56**(6):484-6.
44. Wojtys EM, Beaman DN, Glover RA, Janda D. *Innervation of the human knee joint by substance-P fibers.* Arthroscopy 1990;**6**(4):254-63.
45. Witoński D, Wagrowska-Danilewicz M, Raczyńska-Witońska G. *Distribution of substance P nerve fibers in osteoarthritis knee joint.* Pol J Pathol 2005; **56**(4):203-6.
46. Kellgren JH, Samuel EP. *The sensitivity and innervation of the articular capsule.* J Bone Joint Surg Br 1950; **32**:84 - 92.
47. Felson DT, Chaisson CE, Hill CL et al. *The association of bone marrow lesions with pain in knee osteoarthritis.* Ann Intern Med 2001; **134**(7):541-9.
48. Sowers MF, Hayes C, Jamadar D et al. *Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee osteoarthritis.* Osteoarthritis Cartilage 2003; **11**(6):387-93.
49. Emshoff R, Brandlmaier I, Gerhard S, Strobl H, Bertram S, Rudisch A. *Magnetic resonance imaging predictors of temporomandibular joint pain.* J Am Dent Assoc 2003; **134**(6):705-14.
50. Hill CL, Gale DG, Chaisson C E et al. *Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis.* J Rheumatol 2001; **28**(6):1330-7.
51. Tun K, Cemil B, Gurcay AG et al. *Ultrastructural evaluation of Pulsed Radiofrequency and Conventional Radiofrequency lesions in rat sciatic nerve.* Surg Neurol 2009; **72**(5):496-501.

52. Ikeuchi M, Ushida T, Izumi M, Tani T. *Percutaneous radiofrequency treatment for refractory anteromedial pain of osteoarthritic knees.* Pain Med 2011; **12**(4):546-51.
53. Bellini M, Barbieri M. *Cooled radiofrequency system relieves chronic knee osteoarthritis pain: the first case-series.* Anaesthesiol Intensive Ther 2015; **47**(1):30-3.
54. Clendenen S, Greengrass R, Whalen J, O'Connor MI. Infrapatellar saphenous neuralgia after TKA can be improved with ultrasound-guided local treatments. *Clin Orthop Relat Res* 2015;*473*:119-125.
55. Menzies RD, Hawkins JK. *Analgesia and Improved Performance in a Patient Treated by Cooled Radiofrequency for Pain and Dysfunction Postbilateral Total Knee Replacement.* Pain Pract 2015; **15**(6):E54-8.
56. Shen WS, Xu XQ, Zhai NN, Zhou ZS, Shao J, Yu YH. Radiofrequency Thermocoagulation in Relieving Refractory Pain of Knee Osteoarthritis. Am J Ther 2017;24:693-700.
57. El-Hakeim EH, Elawamy A, Kamel EZ et al. Fluoroscopic Guided Radiofrequency of Genicular Nerves for Pain Alleviation in Chronic Knee Osteoarthritis: A Single-Blind Randomized Controlled Trial. *Pain physician* 2018; *21*:169-177.
58. Protzman NM, Gyi J, Malhotra AD, Kooch JE. *Examining the feasibility of radiofrequency treatment for chronic knee pain after total knee arthroplasty.* Pm r 2014; **6**(4):373-6.
59. Cosman ER Jr, Cosman ER Sr. *Electric and thermal field effects in tissue around radiofrequency electrodes.* Pain Med 2005; **6**(6): 405-24.
60. Iannaccone F, Dixon S, Kaufman A. *A Review of Long-Term Pain Relief after Genicular Nerve Radiofrequency Ablation in Chronic Knee Osteoarthritis.* Pain Physician 2017; **20**(3):E437-e444.
61. Smith HP, McWhorter JM, Challa VR. *Radiofrequency neurolysis in a clinical model. Neuropathological correlation.* J Neurosurg 1981; **55**(2):246-53.
62. Slappendel R, Crul BJ, Braak GJ et al. *The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study: no difference between 40 degrees C and 67 degrees C treatments.* Pain 1997; **73**(2):159-63.
63. Sluijter ME, Teixeira A, Serra V, Balogh S, Schianchi P. *Intra-articular application of pulsed radiofrequency for arthrogenic pain--report of six cases.* Pain Pract 2008; **8**(1):57-61.
64. McCormick Z L, Reddy R, Korn M et al. Cooled Radiofrequency Ablation of the Genicular Nerves for Chronic Pain due to Knee Osteoarthritis: Six-Month Outcomes. *Pain Med* 2017;*18*:1631-1641.

65. Davis T, Loudermilk E, DePalma M, et al. Prospective, Multicenter, Randomized, Crossover Clinical Trial Comparing the Safety and Effectiveness of Cooled Radiofrequency Ablation With Corticosteroid Injection in the Management of Knee Pain From Osteoarthritis. *Reg Anesth Pain Med* 2018, *43*, 84-91.
66. Walega D, McCormick Z, Manning D, Avram M. Radiofrequency ablation of genicular nerves prior to total knee replacement has no effect on postoperative pain outcomes: a prospective randomized sham-controlled trial with 6-month follow-up. *Reg Anesth Pain Med* 2019;44:646–651.
67. Ahmed A, Arora D. *Ultrasound-guided radiofrequency ablation of genicular nerves of knee for relief of intractable pain from knee osteoarthritis: a case series.* Br J Pain 2018; **12**(3):145-154.
68. DemIr Y, Guzelkucuk U, Tezel K, AydemIr K, Taskaynatan MA. A Different Approach to the Management of Osteoarthritis in the Knee: Ultrasound Guided Genicular Nerve Block. *Pain med* 2017; *18*:181-183.
69. Erdem Y, Sir E. The Efficacy of Ultrasound-Guided Pulsed Radiofrequency of Genicular Nerves in the Treatment of Chronic Knee Pain Due to Severe Degenerative Disease or Previous Total Knee Arthroplasty. *Med Sci Monit* 2019; *25*:1857-1863.
70. Gonzalez SV, Macule F, Minguell J, Berge R, Franco C, Sala-Blanch X. Ultrasound-guided genicular nerve block for pain control after total knee replacement: Preliminary case series and technical note. Rev Esp Anestesiol Reanim 2017; *64*:568-576.
71. Wong J, Bremer N, Weyker PD, Webb CA. Ultrasound-Guided Genicular Nerve Thermal Radiofrequency Ablation for Chronic Knee Pain. *Case Rep Anesthesiol* 2016;8292450.
72. Akbas M, Luleci N, Dere K, Luleci E, Ozdemir U, Toman H. Efficacy of pulsed radiofrequency treatment on the saphenous nerve in patients with chronic knee pain. J Back Musculoskelet Rehabil 2011;*24*:77-82.
73. Cosman ER, Dolensky JR, Hoffman RA. Factors that affect radiofrequency heat lesion size. *Pain Med* 2014;*15*:2020-2036.
74. Cedeno DL, Vallejo A, Kelley CA, Tilley DM, Kumar N. Comparisons of Lesion Volumes and Shapes Produced by a Radiofrequency System with a Cooled, a Protruding, or a Monopolar Probe. *Pain physician* 2017;*20*:E915-e922.
75. McCormick Z L, Reddy R, Korn M et al. Prospective Randomized Trial of Prognostic Genicular Nerve Blocks to Determine the Predictive Value for the Outcome of Cooled Radiofrequency Ablation

for Chronic Knee Pain Due to Osteoarthritis. *Pain Med* 2018;*19*:1628-1638.

76. Rojhani S, Qureshi Z, Chhatre A. *Water-Cooled Radiofrequency Provides Pain Relief, Decreases Disability, and Improves Quality of Life in Chronic Knee Osteoarthritis.* Am J Phys Med Rehabil, 2017; 96(1):e5-e8.
77. Vas L, Pai R, Khandagale N, Pattnaik M. *Pulsed radiofrequency of the composite nerve supply to the knee joint as a new technique for relieving osteoarthritic pain: a preliminary report.* Pain Physician 2014; 17(6):493-506.
78. Djibilian Fucci ER, Pascual-Ramírez J, Martínez-Marcos A, Mantecón JM. *Ultrasound-guided sciatic nerve pulsed radiofrequency for chronic knee pain treatment: a novel approach.* J Anesth 2013; 27(6):935-8.
79. Masala S, Fiori R, Raguso M, Morini M, Calabria E, Simonetti G. *Pulse-dose radiofrequency for knee osteoartrithis.* Cardiovasc Intervent Radiol 2014; 37(2):482-7.
80. Ren H, Jin H, Jia Z, Ji N, Luo F. *Pulsed Radiofrequency Applied to the Sciatic Nerve Improves Neuropathic Pain by Down-regulating The Expression of Calcitonin Gene-related Peptide in the Dorsal Root Ganglion.* Int J Med Sci 2018; 15(2):153-160.
81. Jeletsky A. *On the innervation of the capsule and epiphysis of the knee joint.* Vestn. Khir 1931; 22:74.
82. Burgener J. *A contribution to the macroscopic anatomy of the innervation of the knee capsule (author's transl).* Anat Anz 1982; 151(4):393-400.
83. Samuel EP. *The innervation of the articular capsule of the knee joint.* J Anat 1949; 83:80.
84. Tran J, Peng PWH, Gofeld M, Chan V, Agur AMR. *Anatomical study of the innervation of posterior knee joint capsule: implication for image-guided intervention.* Reg Anesth Pain Med 2019; 44(2):234-238.
85. McCormick ZL, Walega DR. *Achieving Meaningful Success in Studies of Genicular Nerve Radiofrequency Ablation.* Pain Med 2018; 19(10):2093-2094.
86. Lash D, Frantz E, Hurdle MF. Ultrasound-guided cooled radiofrequency ablation of the genicular nerves: a technique paper. Pain Manag 2020; DOI 10.2217/pmt-2019-0067.
87. Sari S, Aydin ON, Turan Y, Ozlulerden P, Efe U, Kurt Omurlu I. *Which one is more effective for the clinical treatment of chronic pain in knee osteoarthritis: radiofrequency neurotomy of the genicular*

nerves or intra-articular injection? Int J Rheum Dis 2018; 21(10):1772-1778.
88. Bendtsen TF, Moriggl B, Chan V, Borglum J. The Optimal Analgesic Block for Total Knee Arthroplasty. *Reg Anesth Pain Med* 2016; *41*:711-719.
89. Dellon AL. *Partial Knee Joint Denervation for Knee Pain: a review.* Orthop Muscul Syst 2014; 3(1):167.
90. Radnovich R, Scott D, Patel AT et al. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. Osteoarthritis cartilage 2017; 25(8):1247-1256
91. Hu E, Preciado J, Dasa V, Mussell J. Development and validation of a new method for locating patella sensory nerves for the treatment of inferior and superior knee pain. *J Exp Orthop* 2015; *2*:16.
92. Hilton J. *On Rest and Pain: A Course of Lectures on the Influence of Mechanical and Physiological Rest in the Treatment of Accidents and Surgical Diseases, and the Diagnostic Value of Pain. Edited by Jacobson WHA, FRCS, George Bell and Sons London* 1891; p165
93. Elazab EEB. Morphological study and relations of the fascia vasto-adductoria. Surg Radiol Anat 2017;(39)10:1085-1095
94. Kalthur SG, Sumalatha S, Nair N, Pandey AK, Sequeria S, Shobha L. Anatomic study of infrapatellar branch of saphenous nerve in male cadavers. Ir J Med Sci 2015; 184(1):201-206
95. Henry BM, Tomaszewski KA, Pekala PA et al. *The Variable Emergence of the Infrapatellar Branch of the Saphenous Nerve.* J Knee Surg, 2017; 30(6):585-593.
96. Ackmann T, Von During M, Teske W, et al. Anatomy of the infrapatellar branch in relation to skin incisions and as the basis to treat neuropathic pain by cryodenervation. Pain physician 2014; 17(3):E339-348
97. Koch G, Kling A, Ramamurthy N, et al. Anatomical risk evaluation of iatrogenic injury to the infrapatellar branch of the saphenous nerve during medial meniscus arthroscopic surgery. Surg Radiol Anat 2017; 39(6):611-618
98. Drüner L, *Ueber die Beteiligung des nervus obturatorius an der Innervation des Kniegelenks.* Z. F. Anat. U. Entwick-I 1927; 82: 388.
99. Macalou D, Trueck S, Meuret P et al. Postoperative analgesia after total knee replacement: the effect of an obturator nerve block added to the femoral 3-in-1 nerve block. Anesth Analg 2004; 99(1):251-254.

100. Sutaria RG, Lee SW, Kim SY, Howe R, Downie SA. Localization of the Lateral Retinacular Nerve for Diagnostic and Therapeutic Nerve Block for Lateral Knee Pain: A Cadaveric Study. *Pm r* 2017; *9*:149-153.
101. Fonkoue L, Behets C, Kouassi KJE et al. Distribution of sensory nerves supplying the knee joint capsule and implications for genicular blockade and radiofrequency ablation: anatomical study. *Surg Radiol Anat 2019*;41(12):1461-1471.
102. Roberts SL, Stout A, Dreyfuss P . Review of Knee Joint Innervation: Implications for Diagnostic Blocks and Radiofrequency Ablation. *Pain Med* 2020; 21(5):922-938.
103. Fonkoue L, Behets C W, Steyaert A et al. Accuracy of fluoroscopic-guided genicular nerve blockade: a need for revisiting anatomical landmarks. *Reg Anesth Pain Med 2019;44:950–958.*
104. Conger A, Cushman DM, Walker K et al. Novel Technical Protocol for Improved Capture of the Genicular Nerves by Radiofrequency Ablation. *Pain Med* 2019;20(11):2208-2212
105. Sari S, Aydin ON, Turan Y et al. Which imaging method should be used for genicular nerve radio frequency thermocoagulation in chronic knee osteoarthritis? J Clin Monit Comput 2017; *31*:797-803.
106. Kim DH, Lee MS, Lee S, Yoon SH, Shin JW, Choi SS. A Prospective Randomized Comparison of the Efficacy of Ultrasound- vs Fluoroscopy-Guided Genicular Nerve Block for Chronic Knee Osteoarthritis. *Pain physician* 2019; *22*:139-146.
107. Huang D, Wang HW, Xu DC, Wang HG, Wu WZ, Zhang HR. An anatomic and clinical study of the adductor magnus tendon-descending genicular artery bone flap. *Clin Anat 2011; 24*(1):77-83.
108. Xu Q, Zheng X, Li Y, Zhu L, Ding Z. Anatomical Study of the Descending Genicular Artery Chimeric Flaps. *J Invest Surg 2019;* 1-6.
109. Ziegler T, Kamolz LP, Vasilyeva A, Schintler M, Neuwirth M, Parvizi D. Descending genicular artery. Branching patterns and measuring parameters: A systematic review and meta-analysis of several anatomical studies. *J Plast Reconstr Aesthet Surg 2018; 71*(7):967-975.
110. Weitgasser L, Cotofana S, Winkler M et al. Detailed vascular anatomy of the medial femoral condyle and the significance of its use as a free flap. *J Plast Reconstr Aesthet Surg 2016; 69*(12):1683-1689.
111. Sananpanich K, Atthakomol P, Luevitoonvechkij S, Kraisarin J. Anatomical variations of the saphenous and descending genicular artery perforators: cadaveric study and clinical implications for vascular flaps. *Plast Reconstr Surg 2013; 131*(3):363e-372e.

112. Hugon S, Koninckx A, Barbier O. Vascularized osteochondral graft from the medial femoral trochlea: anatomical study and clinical perspectives. *Surg Radiol Anat 2010; 32*(9):817-825.
113. Garcia-Pumarino R, Franco JM. Anatomical variability of descending genicular artery. *Ann Plast Surg 2014; 73*(5): 607-611.
114. Dubois G, Lopez R, Puwanarajah P, Noyelles L, Lauwers F. The corticoperiosteal medial femoral supracondylar flap: anatomical study for clinical evaluation in mandibular osteoradionecrosis. Surg Radiol Anat 2010; 32(10):971-7.
115. Vanneste B, Tomlinson J, Desmet M, Krol A. Feasibility of an ultrasound-guided approach to radiofrequency ablation of the superolateral, superomedial and inferomedial genicular nerves: a cadaveric study. *Reg Anesth Pain Med* 2019; 44:966–970.
116. Le Corroller T, Lagier A, Pirro N, Champsaur P. Anatomical study of the infrapatellar branch of the saphenous nerve using ultrasonography. *Muscle Nerve 2011; 44*(1):50-54.
117. Bagla S, Piechowiak R, Hartman T, Orlando J, Del Gaizo D, Isaacson A. Genicular Artery Embolization for the Treatment of Knee Pain Secondary to Osteoarthritis. J Vasc Interv Radiol 2020; 31(7):1096-1102.
118. Crawford DC, Miller LE, Block JE. *Conservative management of symptomatic knee osteoarthritis: a flawed strategy?* Orthop Rev 2013; 5(1):e2.
119. Lavand'homme P, Thienpont E. Pain after total knee arthroplasty: a narrative review focusing on the stratification of patients at risk for persistent pain. *Bone Joint J* 2015;*97-b*:45-48.
120. Kim DH, Choi SS, Yoon SH, Lee et al. Ultrasound-Guided Genicular Nerve Block for Knee Osteoarthritis: A Double-Blind, Randomized Controlled Trial of Local Anesthetic Alone or in Combination with Corticosteroid. *Pain Physician* 2018; *21*:41-52.
121. Hernandez-Gonzalez L, Calvo CE, Atkins-Gonzalez D. Peripheral Nerve Radiofrequency Neurotomy: Hip and Knee Joints. *Phys Med Rehabil Clin N Am* 2018; *29*:61-71.
122. Fonkoue L, Behets C, Kouassi KJE et al. Distribution of sensory nerves supplying the knee joint capsule and implications for genicular blockade and radiofrequency ablation: anatomical study. *Surg Radiol Anat 2019*;41(12):1461-1471.
123. Baysal PK, Baysal O, Erkilinc A et al. Is saphenous nerve radio frequency an effective treatment for advanced gonarthrosis in elders

with cardiac comorbidity? *J Back Musculoskelet Rehabil* 2018;*31*:113-118.
124. Cushman DM, Monson N, Conger A, Kendall RW, Henrie AM, McCormick ZL. Use of 0.5 mL and 1.0 mL of Local Anesthetic for Genicular Nerve Blocks. *Pain Med* 2019; *20*:1049-1052.
125. Mata J, Valenti P, Hernandez B, Mir B, Aguilar JL. Study protocol for a randomised controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain. *BMJ open* 2017;*7*:e016377.
126. Fonkoue L, Behets CW, Steyaert A et al. Current versus revised anatomical targets for genicular nerve blockade and radiofrequency ablation: evidence from a cadaveric model. *Reg Anesth Pain Med* 2020; DOI 10.1136/rapm-2020-101370.
127. Tran J, and Peng P. *Hip and Knee Joint Denervation*. In *Ultrasound for Interventional Pain Management*, P. Peng et al. (eds.), Editor. 2020, Springer Nature: Switzerland p. 333-355.
128. Fonkoue L, Behets CW, Steyaert A, Kouassi, KJE; Detrembleur C, Cornu, O . *Anatomical Study of the Descending Genicular Artery and Implications for Image-Guided Interventions for Knee Pain.* Clin Anat 2020 Sep 13. doi: 10.1002/ca.23680.
129. Gong W, Wang A, Fan KA. simple and novel ultrasound-guided approach for infrapatellar branch of the saphenous nerve block. J Clin Anesth 2019;*57*:22-23.
130. Tran J, Agur A, Peng P. *Revisiting the anatomical evidence supporting the classical landmark of genicular nerve ablation.* Reg Anesth Pain Med 2020; 45(5):393-394.
131. Roberts SL. *The importance of precise, validated bony landmarks for blocks and radiofrequency ablation.* Reg Anesth Pain Med 2019; doi: 10.1136/rapm-2019-100879.
132. Fonkoue L, Behets CW, Steyaert A, Kouassi, KJE; Detrembleur C, Cornu, O. Anatomical evidence supporting the revision of classical landmarks for genicular nerve ablation. *Reg Anesth Pain Med* 2020;45(8):672-673.
133. Vallejo R, Benyamin R, Tilley DM, Kelley CA, Cedeno DL. An ex vivo comparison of cooled-radiofrequency and bipolar-radiofrequency lesion size and the effect of injected fluids. *Reg Anesth Pain Med* 2014;*39*:312-321.
134. Lee CH, Derby R, Choi HS, Lee SH, Kim SH, Kang YK. The efficacy of two electrodes radiofrequency technique: comparison study using a

cadaveric interspinous ligament and temperature measurement using egg white. *Pain physician* 2010;*13*:43-49.
135. Cross M, Smith E, Hoy D et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73(7):1323-30.
136. Koshi E, Cheney CW, Sperry BP, Conger A, McCormick ZL. *Genicular Nerve Radiofrequency Ablation for Chronic Knee Pain Using a Three-Tined Electrode: A Technical Description and Case Series.* Pain Med 2020;21(12):3344-3349
137. Price D D, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;*17*:45-56.
138. Farrar JT, Young JPJr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; *94*:149-158.
139. Murray DW, Fitzpatrick R, Rogers K et al. The use of the Oxford hip and knee scores. *J Bone Joint Surg Br* 2007; *89*:1010-1014.
140. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15:1833-1840.
141. Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. *Am J Obstet Gynecol* 2003; *189*:98-101.
142. Robinson-Papp J, George MC, Wongmek A et al. The Quantitative Analgesic Questionnaire: A Tool to Capture Patient-Reported Chronic Pain Medication Use. *J Pain Symptom Manage* 2015;*50*:381-386.
143. Neblett R, Cohen H, Choi Y et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain* 2013;*14*:438-445.
144. Cardone DA, Tallia AF. Joint and soft tissue injection. Am Fam Physician 2002; 66(2): 283-8.
145. Tran J, Peng P, Agur A. Evaluation of nerve capture using classical landmarks for genicular nerve radiofrequency ablation: 3D cadaveric study. Reg Anesth Pain Med 2020;45(11): 898-906.
146. Sperry BP, Conger A, Kohan L, Walega DR, Cohen SP, McCormick ZL. A Proposed Protocol for Safe Radiofrequency Ablation of the Recurrent Fibular Nerve for the Treatment of Chronic Anterior Inferolateral Knee Pain. Pain Med 2020; doi: 10.1093/pm/pnaa291.

147. McCormick ZL, Cohen SP, Walega DR, Kohan L. Technical considerations for genicular nerve radiofrequency ablation: optimizing outcomes. Reg Anesth Pain Med 202; doi: 10.1136/rapm-2020-102117.
148. Koshi E, Cheney CW, Sperry BP, Conger A, McCormick ZL. *Genicular Nerve Radiofrequency Ablation for Chronic Knee Pain Using a Three-Tined Electrode: A Technical Description and Case Series.* Pain Med 2020;21(12):3344-3349
149. Santana P, Vanlinthout LE, Moreno MA, Van Zundert J, Rodriguez HF, Novalbos RJP. Analgesic Effect and Functional Improvement Caused by Radiofrequency Treatment of Genicular Nerves in Patients With Advanced Osteoarthritis of the Knee Until 1 Year Following Treatment. Reg Anesth Pain Med 2017;42(1):62-68.
150. Lavand'homme P, Thienpont E, and Cornu O. Preoperative sensory knee denervation and postoperative pain after total knee arthroplasty. Reg Anesth Pain Med 2019; doi: 10.1136/rapm-2019-100834.