

Unveiling Sex- and Side-Specific Variations in Genicular Nerve Targeting: Implications for Precision in Nerve Ablation Therapy

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Abstract

Background: Genicular nerve radiofrequency denervation, blocks, and neurolysis are effective techniques for pain from knee osteoarthritis (OA) by targeting specific sensory nerves. However, anatomical variability related to laterality and sex may influence targeting accuracy. This study systematically evaluated these factors to optimise procedural precision.

Methods: Twenty-seven frozen lower limbs (10 bilateral: 6 females and 4 males; 7 unilateral: 5 males and 2 females; mean age 84.5 ± 10.8 years) were dissected from the proximal thigh to the knee following colored latex injection. Nerve diameters and distances from genicular nerves to relevant bony landmarks were measured and compared by sex and side using standard statistical tests ($p < 0.05$).

Results: No significant differences were observed in the distances from the target points to the bony landmarks between either men and women or left and right sides. These were larger, on average, in males than in females, except for the distance from the superomedial genicular nerve (SMGN) to the medial condyle. The inferomedial genicular nerve (IMGN) measured diameter at the target point was statistically larger in females than in males [$p=0.04$ (CI; -0.39 - 0.05)]. Interestingly, 44.4% of the superolateral genicular nerve (SLGN) showed no proximity to vascular supply at the target point, which is necessary for ultrasound-assisted targeting.

Conclusion: Although minor dimensional differences exist, sex- and laterality-based anatomical variations do not significantly influence genicular nerve targeting for pain interventions. These findings support the applicability of current targeting protocols across sexes and sides for effective knee OA pain management.

Keywords: *genicular nerve ablation, anatomical variations, radiofrequency ablation, chronic knee pain, sex.*

Introduction

Osteoarthritis (OA) is the most prevalent joint disease and is projected to rank as the fourth cause of disability globally. In particular, knee OA contributes to 83% of the overall OA burden and ranks as the second most common reason for pain-related consultations at pain clinics, following lumbar pains caused by osteoarthritis [1]. Over the years, there has been tremendous progress in treatment modalities for chronic knee pain, such as pain medications, physiotherapy, visco-supplementation, bracing, and knee replacement. Emerging alternative procedures for chronic pain management, such as radiofrequency denervation, genicular blockade and neurolysis, are all based on the theory that cutting the innervation of a painful structure can relieve pain and restore function [2,3]. These techniques require a proper understanding of the genicular nerve anatomy and precision of constant landmarks to target these nerves for optimal pain relief [4,5]. Genicular nerves are branches of the femoral, sciatic, and obturator nerves that relay sensory innervation of the knee joint. In most studies, the targeted constant genicular nerves during genicular nerve block are the superolateral genicular nerve (SLGN), superomedial genicular nerve (SMGN), inferomedial genicular nerve (IMGN), recurrent fibular nerve (RFN), and infrapatellar branch of the saphenous nerve (IPBSN) [6–9].

Generally, these nerve targets are considered identical on both sides of the body. However, anatomical variations, such as the position, number of branches and size of the genicular nerves, may lead to differences in the targeting and response. Some studies suggest that there may be anatomical differences between sexes, particularly in the pelvic and lower extremity regions [10,11]. American and Swedish authors reported that one-third of the population had a leg length discrepancy of ≥ 1 cm [10,11]. These differences could influence the size and location of the genicular nerves. Furthermore, women are known to have a different fat distribution and anatomical structure in the knee area [12], possibly affecting nerve location and targeting. On the other hand, men may have larger muscle mass around the knee joint, potentially influencing nerve accessibility during the procedure [10,11]. To our knowledge, no study has focused on sex and left-right differences in genicular nerve targets.

We hypothesised that anatomical variations in genicular nerve targets are influenced by both sex and laterality. Specifically, we expected to find measurable differences in the location, size, branching pattern and vascular proximity of key genicular nerves between males and females, as well as between left and right knees. Such differences could partly explain the variability in clinical outcomes of genicular nerve-targeted procedures. Therefore, this article compares the genicular nerve targets in the left and right as well as in male and female knees.

Materials and methods

We used 27 fresh frozen limbs from bodies generously donated to the Pole of Morphology of Université Catholique de Louvain according to Belgian laws and regulations. This research was conducted with the approval of the University's Research Ethics [IRB00008535, Brussels, Belgium]. The limbs included 10 bilateral ones (four male and six female pairs) and seven unilateral ones (5 males and 2 females) (Table 1). After thawing, the femoral artery of each lower limb was flushed with lukewarm normal saline and then injected with coloured latex under continuous manual pressure [13]. The injection of coloured latex enabled us to easily differentiate small nerve branches from arterial blood vessels and evaluate the connection between nerve distribution and the vascular pattern. This also helped us determine the proximity of certain arterial branches with target nerves, which could facilitate their identification. We carried out the dissection 48 hours after the vascular injection to allow the latex to solidify.

As previously described, we used the same dissection protocol and standard instruments for each specimen [14]. Each lower limb was dissected from proximal to distal. Starting from the femoral triangle, we identified the femoral nerve, then the obturator nerve anterior and medial, and finally the sciatic nerve on the posterior aspect. These nerves were dissected right up to their various articular branches. We analysed five consistent genicular nerve branches in each limb: superior lateral genicular nerve (SLGN), superior medial genicular nerve (SMGN), inferior medial genicular nerve (IMGN), recurrent fibular nerve (RFN) and infrapatellar branch of the saphenous nerve (IPBSN) following the revised targets described by Fonkoue et al. [14]. The area where the nerve pierces the periosteum before entering the capsule was considered a suitable and stable target point. We systematically measured with a calliper and compared the following parameters between left and right sides, as well as between male and female subjects: nerve origin and course, vascular relationships, distances from the nerve to surrounding bony landmarks at the target point and, finally, nerve cross-sectional diameter at the target point. Three different linear measurements were obtained using a digital calliper with a resolution of 0.01 mm and an accuracy of ± 0.02 mm from two investigators and averaged.

Statistical analysis was performed using SPSS 28.0 (Chicago, Illinois, USA). The various distances were described as mean $\pm$ standard deviation (SD) for data with normal distribution; otherwise, they were presented as the median and interquartile range (IQR). The chi-square or Fisher exact tests were used to compare proportions, and the Student t-test or non-parametric equivalents (Mann-Whitney U test) were used to compare quantitative variables. A p -value < 0.05 was set as the level of significance difference.

Results

Genicular branches of the femoral nerve

Overall, the dissection of the femoral nerve included the following articular branches to the knee capsule: the superomedial genicular nerve (SMGN) via the nerve to the vastus medialis (NVM) and the infrapatellar branch of the saphenous nerve (IPBSN), as well as branches from the nerve to the vastus intermedius (NVI), and the nerve to the vastus lateralis (NVL).

The articular branch of the nerve to the vastus medius (NVM) SMGN (Figure 1A-C). In all the dissected limbs, the NVM was a constant branch of the femoral nerve that originated alongside three major branches, as seen above. The NVM ran beneath the fascia of the vastus medius along its medial border. Distally, it gave 3-5 muscular branches and continued anteriorly to the tendon of the adductor magnus, progressing distally toward and anterior to the adductor tubercle as the SMGN. This nerve had a constant vascular proximity with the articular branch of the descending genicular artery. The SMGN innervated the medial anterior-superior quadrant of the knee via two to three articular branches. This nerve was present in all our specimens except one knee, where the SMGN originated from the saphenous nerve as it exited the adductor canal anterior to and along the adductor magnus tendon, but had no impact on the targeting landmarks. This was observed on the right knee of a male specimen with bilateral knees (Figure 1B). No significant gender-related differences existed in the nerve trajectory of the SMGN and target points.

The articular branch of the saphenous nerve, IPBSN. The saphenous nerve was consistently identified as a direct branch of the femoral nerve in all specimens. The infrapatellar branch of the saphenous nerve (IPBSN) was the primary genicular branch of the saphenous nerve, terminating between the apex of the patella and the tibial tuberosity. Three distinct patterns regarding its pathway were observed. The most prevalent one (pattern 1, Figure 1A), representing 17(63.0%) overall, involved the IPBSN emerging distally after the saphenous nerve exited the adductor canal at the medial aspect of the distal third of the thigh. In this case, it typically travelled posteriorly and beneath the sartorius for most of its course before either perforating it distally or exiting anteriorly or posteriorly to the sartorius muscle tendons before gaining the anterior medial knee. For the second variant found in 6(22.2%) knees (pattern 2, Figure 1B), the IPBSN detached from the saphenous nerve proximally, just before the adductor canal, and took a course outside of it. In the third pattern, 4(14.8%) (pattern 3), the IPBSN detaches high at the proximal 1/3 of the thigh from its origin with the femoral nerve and descends along the sartorius muscles (Figure 1C). The IPBSN emerged variably around the sartorius muscle either at the anterior border (7.4%), through the muscle (40.8%), or at the posterior border (48.1%) before curving in the subcutaneous layer from posteromedial

to anterior. It then directed itself towards the inferior-medial aspect of the knee, providing innervation for the region between the tibial tuberosity and the apex of the patella. There were no sex or laterality specificities in the IPBSN knee insertion patterns among dissected knees. Five (50%) bilateral knees (two males and three females) had symmetric patterns and exit points of the IPBSN (Table 2). Importantly, despite the variability in IPBSN pathways, we found no difference in the target reference points, suggesting a stable and predictable anatomical landmark for nerve-targeting procedures.

Articular branches of the nerves to the vastus intermedius (NVI) and vastus lateralis (NVL). These nerves both branched from the femoral nerve and were present in all specimens, with no major sex or left-right discrepancy. They both innervated the superior and superolateral capsule.

The NVL coursed deep to the medial border of the vastus lateralis and superficial to the muscle belly of the vastus intermedius and ran obliquely close to the periosteum at the metaphyseal region to innervate the anterolateral aspect of the superior knee pouch via two articular branches.

The NVI coursed deep within the VI muscle, close to the femoral periosteum, gives two major articular branches: the medial and the lateral branches (Figure 2).

Articular branches from the sciatic nerve

The sciatic nerve provided the following branches to the knee: the superolateral genicular nerve (SLGN), the inferolateral genicular nerve (ILGN), the inferomedial genicular nerve (IMGN), the recurrent fibular nerve (RFN), and the posterior genicular nerve. The SLGN, IMGN, and RFN were the only consistent nerves observed in all our dissections.

The superolateral genicular nerve: The superolateral genicular nerve (SLGN) originated from the common fibular division of the sciatic nerve as it descends obliquely along the lateral side of the popliteal fossa to the head of the fibula, close to the medial margin of the Biceps femoris muscle. It lies between the tendon of the Biceps femoris and the lateral head of the Gastrocnemius muscle. At the posterolateral junction of the metaphysis, the SLGN divides into two articular branches as it pierces the periosteum down to the capsule. This nerve was constant in all knees with no sex or laterality specificities (Figure 3).

The inferolateral genicular nerve: The inferolateral genicular nerve (ILGN) originates either directly from the common fibular branch of the sciatic nerve or as a branch of the SLGN. It coursed deep to the lateral collateral ligament, moving anteriorly before innervating the inferior-lateral knee capsule. This nerve showed variability; among bilateral knee samples, three subjects exhibited the ILGN in at least one knee, while only one showed the

ILGN bilaterally. Meanwhile, two out of the seven unilateral knees exhibited the ILGN (Figure 4). This nerve had an overall 22.2% presence in presence among all samples.

The recurrent fibular nerve. This nerve was a constant branch of the CFN of all specimens with no group specificities. It coursed anteriorly around the fibular neck from the CFN, through about 1cm below Gerdy's tubercle, and it pierced the periosteum and terminated in 1-3 articular branches responsible for the innervation of the inferior-lateral aspect of the knee capsule. (Figure 3 and Figure 4).

Inferomedial genicular nerve. This nerve was constant in all specimens. It took its origin from the tibial nerve in the popliteal fossa. It coursed around the tibial medial condyle at the metaphyseal area, meeting the genicular vessels to form the inferior medial neurovascular bundle, then deep to the medial collateral ligament. It innervated the inferior medial quadrant of the knee via two or three branches (Figure 5).

Targeting five constant genicular nerves: gender and side specificities and arterial proximity

Bony Landmarks. The SMGN, SLGN, RFN, IMGN and IPBSN were the most consistent nerves in all specimens, with easy accessibility for genicular nerve-specific procedures like neurolysis or nerve ablation. We found no differences according to the laterality of various measured bony landmarks among the 10 bilateral knees dissected (Table 3). When comparing gender and laterality, the distances between target points and various landmarks did not differ significantly (Table 4).

Genicular nerve diameters at the target site. The diameter of the IMGN at the target site was statistically larger in females. There was no significant sex-related difference in the mean diameters for the SLGN, SMGN, IPBSN, and RNF measured at the target site (Table 5). As shown in Table 5, there was no significant difference in the diameter of the targeted genicular nerve at the target site between the left and right knees among the 10 bilateral knees.

Gender-based comparison of arterial proximity to the target nerve at the target site. We also analysed vascular variations that could help with targeting. All the SMGN, IMGN and RFN showed arteries near the nerves at the target point. Of the five targeted nerves, the SLGN target site showed the least arterial presence (46.15% in males and 42.86% in females) (Table 6). There was no significant sex-related difference for arterial proximity. No differences were found between male and female knees for the distance between the origin of the descending genicular artery (DGA) and the joint line (Table 7).

Laterality-based comparison of arterial proximity to the target site. Regarding Du Bois' classification of the descending genicular artery (DGA), 50% of bilateral knees showed symmetrical DGA patterns. No difference was observed in the distance of the origin of the DGA relative to the joint line between the left and right knees (Table

8). There was no left-right difference in our sample. Similarly, we observed 100% vascular proximity at the SMGN, RFN, and IMGN target sites in the bilateral knees. In contrast, the SLGN and IPBSN demonstrated the lowest association between the targeted nerve and arterial supply at the target; however, this difference was not statistically significant between left and right bilateral knees (Table 7).

Discussion

Genicular nerve targeting for chronic knee pain management has increased over the recent decade [15]. Theoretically, the success of pain control by genicular nerve ablation/block heavily depends on the precision of targeting and the number of targeted nerves. The success rates for genicular nerve targeting for pain management vary between 30% and 74% of OA patients at 6 months [7,16–21]. Outcomes appear to depend on both the precision of targeting and the number of ablated nerves. While some studies have shown no clear benefit of targeting five versus three nerves using fluoroscopic targeting [22], others demonstrated superior pain and functional improvement with five-nerve approaches with ultrasound guidance[23]. A recent meta-analysis also suggested sex-based differences, with women responding more favourably to ablation than men [24].

Even though many pain management teams use target-enhancing devices like fluoroscopy or ultrasonography, we still have some discrepancies in outcomes. This means many other factors may influence successful pain relief during this procedure. Recent studies have improved general knowledge of genicular nerve locations to help in targeting, but specific variations among patient groups have not yet been explored. Therefore, our study aimed to address this gap by comparing genicular nerve target points based on sex and laterality, with the goal of optimising outcomes across diverse patient populations.

Recent studies advocate five-nerve targeting, which increases pain relief as the more genicular territories are involved, the better the pain relief. This is why, in our study, we compared five frequently targeted nerves, i.e., SMGN, SLGN, IMGN, RFN, and IPBSN, which participate in the innervation of the anterior knee[4,5,25]. Some authors targeted the inferolateral genicular nerve (ILGN), but this nerve was not constant in our samples [26–28]. Moreover, this nerve was generally very inconsistent overall, making it a poor candidate for genicular nerve targeting procedures.

We found no significant difference in the targeting landmarks based on sex and laterality, as well as in the distances between the target points and the anatomical reference landmarks. The measured distances were, on average, greater in males than in females, except for the mean distance from the SMGN to the medial condyle, which was larger in females than in males. These differences were not statistically significant, even though some major

anatomic sex based structural differences could make us think otherwise, like the female lower limb alignment variations with greater Q angles than that of males, and the overall greater adipose tissue distributions around the knee in females [29–31].

The IMGN measured diameter at the target point was statistically larger in females than in males. We found no data about this observation in the literature. The ILGN was present in only 22% of knees, contrasting with higher frequencies in some prior reports, likely reflecting methodological differences [26]. There was no difference in the targets based on laterality.

Also, the SLGN showed the lowest vascular presence at the target site of 55.56%, which may reduce targeting accuracy under ultrasound guidance. The SMGN, IMGN and RFN had 100% vascular proximity at their target sites. Such variability may result in suboptimal outcomes, underscoring the need for adjunctive techniques—such as bony landmarks, hydrodissection, and diagnostic blocks to optimise outcomes. These consistent vascular supplies to regions innervated by specific sensory nerves make them good candidates for genicular nerve vascular embolisation procedures in chronic knee pain management. There was no laterality nor sex-based difference in the vascular proximity of the targeted nerves.

Furthermore, using chemical substances that can diffuse easily will readily hit the target nerves with the expected response (e.g., anaesthetic and phenol blocks) compared to cryo and radiofrequency targeting, which require more precise placement for optimal results.

In our study, we found the current genicular nerve targets to be compatible with targeting knees based on sex and laterality, but precautions must be taken when using vascular aid for ultrasound targeting, as this may be less accurate for the IPBSN and even more so for the SLGN.

A limitation of this study is that it is based on a relatively small sample of ten bilateral knees and seven unilateral knee specimens. This limited sample size might affect the generalizability of the findings. Although this sample size aligns with standards for anatomical research using cadavers, it limits our ability to capture the full spectrum of anatomical variations in the broader population. Therefore, the differences based on sex and side should be interpreted cautiously. They may not fully represent variations across different age groups, ethnicities, or health conditions. Additionally, applying these cadaver findings to living subjects, particularly regarding image-guided genicular nerve ablation, should be approached with caution. There could be differences in tissue properties and anatomical relationships in living bodies. Future studies with larger and more diverse samples, complemented by clinical and imaging data, are necessary to verify and expand upon these initial findings.

Conclusion

This study found no significant differences in targeting landmarks based on gender and laterality, and therefore recommends the same targeting protocols for sex and laterality. It confirmed the consistency of five genicular nerves for ablation procedures for chronic knee pain. Additionally, vascular proximity plays a crucial role in nerve targeting, but is not a suitable targeting aid for the SLGN. This study highlights the need for further clinical research to validate the efficacy of genicular nerve targeting, considering patient-specific variations. Future studies should aim to refine targeting strategies to optimise pain relief across diverse patient populations.

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Authors' Contributions

1. Gaspary Fodjeu: Conception and design, intervention, manuscript writing.
2. Loic Fonkoue: Conception and design, manuscript revision.
3. Catherine Behets: Project manager, conception and design, manuscript revision
4. Olivier Cornu: Conception and design, manuscript revision.

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Declarations

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