Study of "Rebound Pain" after Regional Anesthesia in Orthopaedic Surgery

A Process for Improving Regional Anesthesia in the Context of Personalised Ambulatory Care

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Thesis submitted for the Degree of PhD in Medical Sciences

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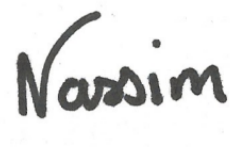

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Abbreviations

- **AB** : Ankle block

- **Anxa-1** : Annexin A1

- **AMPA** receptors : α-amino-3-hydroxy-5-methyl-4-isoxasolepropionate receptors

- **APAIS** : *Amsterdam Preoperative Anxiety and Information Scale,* a scale assessing preoperative anxiety and the patient's need for information.

- **CBFR study** (Short title of the study) : Comparative Blocks in Foot Surgery and Rebound Pain

- **CSI 9-item score** : Short 9-item version of the *Central Sensitization Inventory*, assessing symptoms related to central sensitization

- **DEXA** : Dexamethasone

- **DN2**: *Douleur Neuropathique en 2 questions,* a quick screening tool for neuropathic pain.

- **DN4** : *Douleur Neuropathique en 4 questions*, a validated questionnaire for detecting neuropathic pain.

- **h CRP** : high-sensitivity C-reactive protein

- **BMI** : Body Mass Index (kg/m²).

- **IV** : Intravenous, route of administration by direct injection into a vein.

- **NLR** : neutrophil-to-lymphocyte ratio

- **NMDA** : N-Methyl-D-Aspartate*, a glutamate receptor*

• **NRS score** : *Numerical Rating Scale*, 0–10 numeric scale for quantifying pain intensity.

• **NSAIDs** : *Non-steroidal anti-inflammatory drugs*

• **NTAP** : Night-time awakening pain.

• **PCS score – Pain Catastrophizing Scale** : Questionnaire measuring pain-related (rumination, magnification, helplessness).

• **PNB** : Peripheral nerve block

• **pPNS** : percutaneous peripheral nerve stimulation

• **PRPK study** (Short title of study) : Prospective Study on the Occurrence of Rebound Pain and the Predictive Role of Ketamine study

• **PSNB** : Popliteal sciatic nerve block

• **RA**: *Regional Anesthesia,* anesthetic technique blocking nerve conduction in a specific territory

• **RETRODEXA study (Short title) :** Retrospective analysis of the impact of intravenous dexamethasone dosing on the occurrence of rebound pain study

• **RP** : *Rebound Pain*, sudden resurgence of pain occurring after resolution of an effective peripheral nerve block.

• **VEDR study** (Short title of study): *Variability of the Effectiveness of Dexamethasone in Rebound Pain* study

PART I – GENERAL INTRODUCTION

1.1. Background and objectives

Over the past two decades, ambulatory surgery has become a standard approach, made possible by the development of minimally invasive techniques and optimised care pathways. These advances allow faster recovery, shorter hospital stays, and an overall improvement in the patient experience [1]. Today, more than half of surgical procedures are performed in an ambulatory setting, a growing trend across advanced healthcare systems [2], particularly in member countries of the OECD (Organisation for Economic Co-operation and Development) (Fig. 1.1).

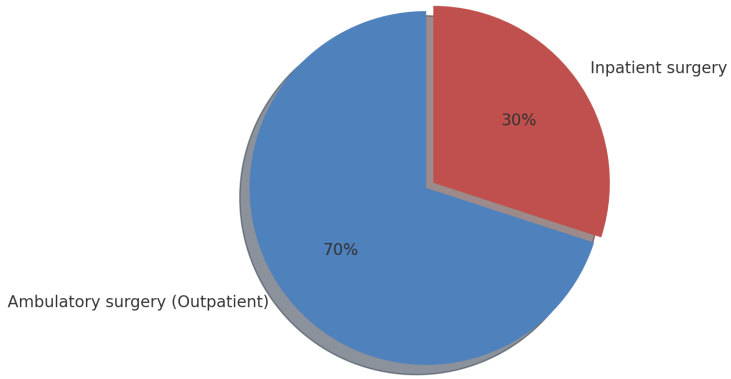

Figure 1.1 - ***Proportion of ambulatory versus inpatient surgery in OECD countries*** *(Health at a Glance 2023, OECD Publishing, Paris)*

Within this evolution, regional anesthesia (RA), and in particular peripheral nerve blocks (PNB), play a central role [1]. The advent of ultrasound guidance has profoundly reshaped practice, improving both the safety and effectiveness of these techniques [2]. By enabling real-time visualisation of anatomical structures and needle trajectory, ultrasound reduces the volumes and doses of local anesthetics required, increases block success rates, and lowers the risk of complications such as intravascular or intraneural injection [3,4] (Fig. 1.2).

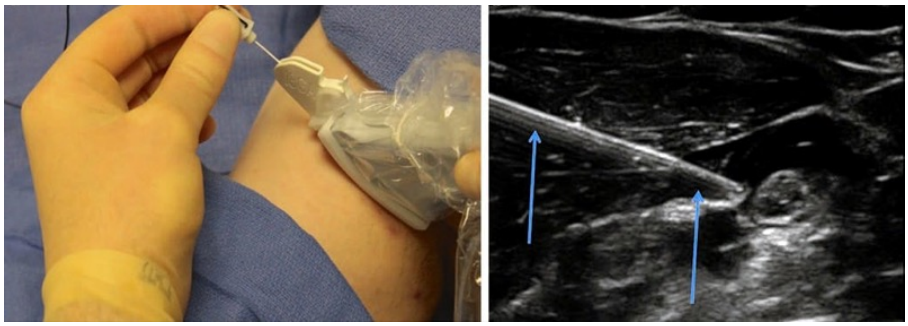

Figure 1.2 - ***Needle visibility during ultrasound-guided regional anesthesia.***

Ultrasound has also become a valuable teaching tool, enhancing training for junior practitioners and accelerating the acquisition of expertise [5]. Integrated into a multimodal pain management strategy, ultrasound-guided RA not only provides effective intraoperative anesthesia and prolonged postoperative analgesia but also reduces opioid consumption and facilitates faster recovery [6,7] (Fig. 1.3).

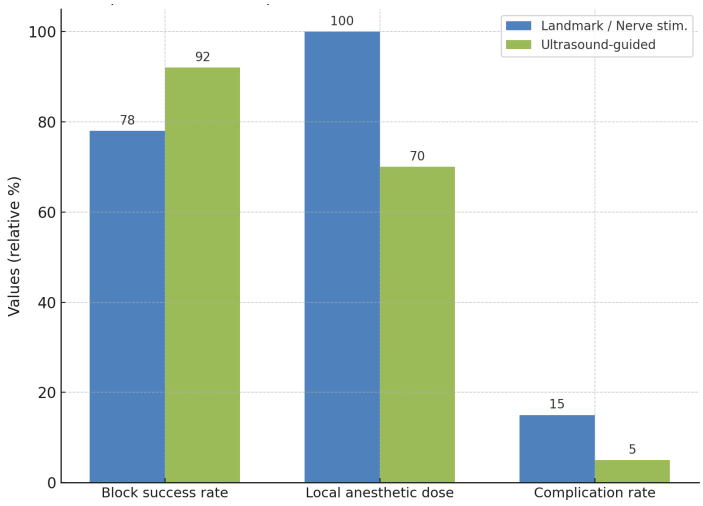

Figure 1.3 - ***Improvement of peripheral nerve blocks with Ultrasound Guidance*** *(Neal et al.* RAPM *2010; Ahmed et al.* Anesth Pain Med *2022)*

However, a paradoxical phenomenon may undermine these benefits: the onset of acute, severe, and often poorly controlled pain once the sensory block resolves, known as Rebound Pain (RP). This typically occurs at home, following discharge from ambulatory surgery, and remains insufficiently characterised [8,9]. The clinical implications of RP are significant. Several studies have shown that it is associated with a marked increase in opioid use, as patients abruptly compensate for the loss of block-induced analgesia [8]. It may also result in unplanned healthcare intervention, including unscheduled consultations or, more rarely, readmissions due to uncontrolled pain [9]. Beyond the acute phase, some evidence suggests that RP could be a risk factor for the transition to chronic postoperative pain, although current data are still limited and heterogeneous [7]. The abrupt and intense nature of RP also leads to considerable patient dissatisfaction, compromising both recovery quality and overall perioperative experience [10–12] (Fig. 1.4).

Given the clinical and organizational consequences associated with RP, this phenomenon is now recognized as a major research priority in regional anesthesia [13].

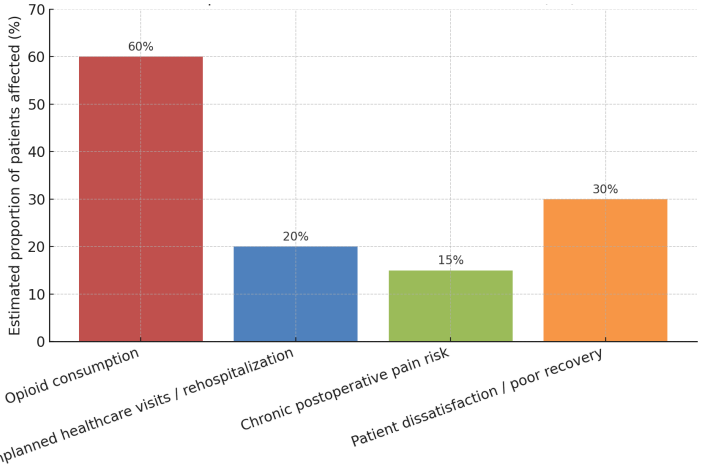

Figure 1.4 - ***Complications Associated with Rebound Pain*** *([8]. [7]. [9]. [12]).*

At present, the mechanisms underlying RP remain poorly understood. Several pathophysiological hypotheses have been proposed, including central sensitization phenomena, psychological factors, and local inflammatory processes [7,9]. A wide range of preventive strategies have been explored, from non-pharmacological approaches to pharmacological interventions. Yet, their effectiveness is inconsistent, and their applicability in routine clinical practice remains debated [14,15]. The issue is further complicated by marked inter-individual variability in both the intensity and duration of RP [9]. This heterogeneity points to the involvement of multiple pathophysiological mechanisms and individual susceptibility factors, biological, psychological,

or surgical, that are not yet fully elucidated [7]. It therefore highlights the need to identify predictive determinants more precisely and to develop standardised yet individualised management protocols in order to mitigate the clinical impact of Rebound Pain [8].

Based on these elements, this thesis aims to improve the understanding of the RP phenomenon following regional anaesthesia in ambulatory and short-stay orthopaedic surgery. It is grounded in complementary studies conducted in a progressive manner, the results of which are analysed in light of the existing literature. Beyond a purely descriptive approach, this work is structured around explicit and testable hypotheses, explored through prospective clinical and mechanistic investigations.

The first hypothesis is that RP represents a frequent and clinically relevant postoperative phenomenon following single-shot regional anaesthesia, with a measurable incidence and a heterogeneous clinical expression. We hypothesise that RP preferentially affects specific patient subgroups characterised by distinct demographic, surgical, psychological, or analgesic profiles, thereby allowing the prospective identification of patients at increased risk. [7,8,9].

The second hypothesis is that RP is not limited to the expected return of nociceptive afferent input upon resolution of the peripheral nerve block, but rather reflects the involvement of specific and interrelated pathophysiological mechanisms [9,10]. These mechanisms may include:

- An exacerbation of conscious pain perception, modulated by psychological factors such as high levels of anxiety and catastrophizing;

- An alteration of endogenous pain control, characterised by an imbalance between inhibitory and excitatory pathways promoting nociceptive transmission and involving central sensitisation phenomena;

- An exacerbation of the local inflammatory response at the surgical site during peripheral nerve block resolution, thereby contributing to peripheral sensitisation.

The third hypothesis is that RP may be, at least in part, prevented or attenuated through targeted perioperative strategies. We hypothesise that optimisation of pharmacological interventions and anticipatory multimodal analgesic strategies may reduce the incidence and severity of RP, while improving early postoperative pain control and functional recovery in ambulatory and short-stay surgical settings. [8,14,15]

Finally, the central hypothesis of this thesis is that integrating the clinical, psychological, and biological determinants of RP may enable the development of a more individualised approach to regional anaesthesia. Such a personalised strategy could optimise the benefit–risk balance of regional techniques and improve postoperative pain trajectories as well as patient-centred outcomes.

Overall, this work forms part of a broader effort to support the evolution of regional anaesthesia towards a model based on anticipation, prevention, and individualisation of care, in line with the principles of modern perioperative medicine and risk-stratified pain management [16].

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PART II – UNDERSTANDING AND CLINICAL CHARACTERISATION OF REBOUND PAIN

2.1. Definition of Rebound Pain

RP is characterised by a sudden, intense, and transient recurrence of pain following the resolution of an effective peripheral nerve block, occurring after an initial period of postoperative analgesic comfort. This phenomenon differs from a simple gradual return of nociception by its abrupt onset, which patients often perceive as disproportionate relative to their prior state.

Early descriptions of RP arose incidentally in clinical studies originally designed for other objectives such as evaluating block quality, measuring analgesic consumption, or monitoring overall postoperative pain, and were based on variable and rarely standardised definitions [1,2]. This methodological heterogeneity partly explains the discrepancies in reported incidence and complicates comparisons between studies.

To address this variability, Williams et al. proposed one of the first quantitative frameworks with the "*Rebound Pain Score"*, defined as the difference between the maximum pain score recorded within 12 hours after block resolution and the minimum score observed during the analgesic period [3]. This approach aimed to objectively quantify the loss of analgesia using a reproducible measure, independent of subjective assessment by the patient or clinician.

Barry et al. later refined this definition with a more pragmatic clinical approach: they described RP as the transition from well-controlled pain (NRS

≤ 3) during the block effect to severe pain (NRS ≥ 7) within 24 hours of block resolution, while excluding cases of incomplete block or technical failure [1].

More recent publications have adopted a stricter threshold for defining RP (i.e., NRS > 7 rather than ≥ 7) [4,5]. This choice allows for more specific identification of transient hyperalgesic episodes associated with RP, rather than simply expected pain following block resolution. A stricter threshold helps avoid including borderline scores of 7/10, which are common in practice and may reflect typical postoperative pain. It may also mitigate measurement variability (±1 point) and better distinguish situations where pain is disproportionate relative to the surgical procedure and multimodal analgesic regimen.

Thus, the evolution of the RP definition in recent years towards more operational criteria has improved diagnostic consistency in contemporary studies and enabled more reliable identification of affected patients.

2.2 Incidence of Rebound Pain

The reported incidence of RP varies widely in the literature, ranging from 30% to over 70%, depending on the adopted definitions, assessment criteria, surgical type, and anesthetic technique used [1–8]. This heterogeneity reflects the inherently multifactorial nature of RP, which arises from complex interactions among technical, contextual, psychological, and biological factors [1,9].

Most of the available data come from studies focusing on single-injection peripheral nerve blocks, particularly brachial plexus and femoral nerve blocks. However, similar phenomena have also been described following neuraxial anesthesia, whether spinal or epidural [10,11]. This observation suggests that RP may not be exclusive to peripheral blocks but rather represent a common mechanism related to the abrupt cessation of dense analgesia.

Conversely, the occurrence of RP appears markedly less frequent in studies employing continuous perineural catheters, likely due to a more gradual transition between peripheral analgesia and the restoration of nociception, thereby limiting reactive hyperalgesia [12,13].

It should also be emphasized that most published studies are based on single-center observational data, often retrospective and relying on self-reported pain scores [1,14]. Moreover, these data are frequently collected after discharge, outside a medicalized environment, introducing uncertainty regarding the reliability and standardization of patient-reported outcomes [15].

Such methodological limitations reduce comparability across studies and likely contribute to the substantial variability in reported incidences in the literature.

2.3 Risk factors for Rebound Pain

Several risk factors for RP have been identified in the literature, mainly from retrospective data [9,14].

In a large observational cohort, Barry et al. (2021) reported that certain patient profiles are more vulnerable to pain recurrence after block resolution. Notably younger age, female sex, bone surgery, pre-existing pain, and high pain catastrophizing scores [1] (Fig. 2.1).

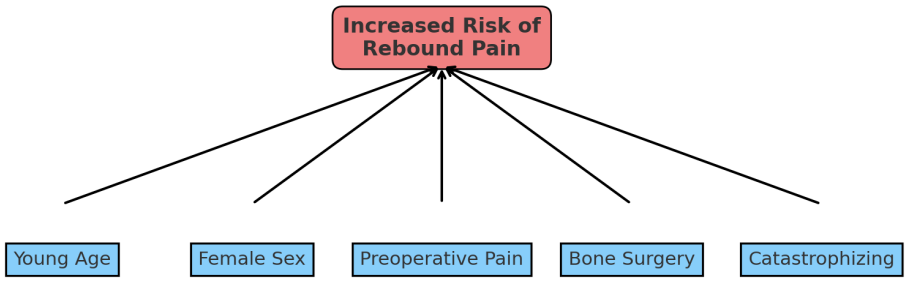

Figure 2.1 ***- Risk factors for increased Rebound Pain*** [1]

These findings are consistent with previous studies identifying several factors capable of amplifying postoperative nociceptive responses. Pre-existing pain may enhance the response to surgical injury by creating a state of peripheral and central sensitization sustained by local and systemic inflammatory activation [16,17].

Similarly, bone surgery (particularly major orthopedic procedures) elicits a strong inflammatory response and prolonged nociceptor stimulation [9].

These mechanisms may converge toward an exacerbation of pain at block resolution, contributing to the clinical manifestation of RP in some patients [18].

Female sex also emerges as a well-documented susceptibility factor. Women generally report higher pain scores and exhibit increased sensitivity to nociceptive *stimuli*, attributed to hormonal modulation, greater emotional reactivity, and sociocultural influences shaping pain perception [19,20].

Conversely, aging is associated with altered nociceptive processing, involving reduced sensory fiber density, slower nerve conduction, and lower responsiveness to local anesthetics, all of which raise the pain threshold and may explain the milder expression of RP in older patients [9,21].

Finally, pain catastrophizing, as assessed by the Pain Catastrophizing Scale, amplifies negative pain-related experiences, heightens attentional vigilance, and reinforces limbic activation, leading to higher pain scores and lower patient satisfaction [22,23].

Taken together, the initial data on RP confirm its complex and multifactorial nature but leave many uncertainties regarding its true incidence, risk factors, and underlying mechanisms. It therefore appeared essential to better characterize RP through prospective studies, aiming to refine its clinical description and improve understanding of its pathophysiological basis.

In this context, we conducted our first study, the PRPK study (Prevention of Rebound Pain with Ketamine), which was primarily designed to assess the

contribution of central mechanisms through the preventive use of ketamine, while prospectively documenting the RP phenomenon.

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2.4. The PRPK (Prevention of Rebound Pain with Ketamine) study

"*Evaluation of intraoperative ketamine on the prevention of severe Rebound Pain upon cessation of peripheral nerve block: a prospective randomized, double-blind, placebo-controlled study* "

Nassim Touil, Athanasia Pavlopoulou, Olivier Barbier, Xavier Libouton and Patricia Lavand'homme

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Background: Pain after resolution of peripheral nerve block, known as 'Rebound Pain', is a major problem in outpatient surgery. The primary objective was to evaluate the benefit of intraoperative ketamine at an anti-hyperalgesic dose on the incidence of Rebound Pain after upper limb surgery under axillary plexus block in ambulatory patients. The secondary objective was to better understand the Rebound Pain phenomenon (individual risk factors).

Methods: In this prospective, double-blind study, patients were randomized to receive either a single dose of i.v. ketamine (0.3 $mg \cdot kg^{-1}$) or a placebo. Preoperative mechanical temporal summation and central sensitization inventory were applied to question underlying central sensitization. Pain catastrophizing and Douleur Neuropathique 4 questionnaires were used. Rebound Pain was defined as performed on an outpatient setting pain intensity score >7 (numeric rating scale, 0-10) after block resolution. Postoperative pain was recorded at Days 1, 4, and 30 after discharge.

Results: A total of 109 subjects completed the study, and 40.4% presented with Rebound Pain. Ketamine administration did not reduce Rebound Pain incidence or intensity. Temporal summation and central sensitization inventory scores did not differ between subjects with and without Rebound Pain. The predictive risk factors were bone surgery (odds ratio [OR]=5.2; confidence interval [CI], 1.9-14.6), severe preoperative pain (OR=4.2; CI, 1.5-11.7), and high pain catastrophizing (OR=4.8; CI, 1.0-22.3). At Day 30, the average daily pain was higher in the Rebound Pain group involving neuropathic characteristics.

Conclusion: Ketamine at an anti-hyperalgesic dose showed no benefit on Rebound Pain development. Although central sensitization might not be involved, preoperative pain intensity, and catastrophizing stand as risk factors. Because Rebound Pain remains frequent despite adequate procedure-specific postoperative analgesia, future studies should focus on patient-specific pain management.

Introduction

Almost 50% of orthopaedic procedures are actually performed on an outpatient setting despite the fact that orthopaedic procedures stand among the most painful surgeries [1]. Peripheral nerve blocks (PNBs) are commonly used to offer comfortable surgical conditions associated to reduced recovery time [2]. However, postoperative pain follow-up is generally missing as the block wears off after patient discharge. Previous studies have highlighted the occurrence of important pain during the first 24 h after outpatient surgery and during the first days after hospital discharge [1]. Severe pain which occurs when a peripheral nerve block wears off has been referred to as Rebound Pain (RP) [3,4]. With the development of ambulatory surgery, the problem has recently had renewed interest [2,5–7]. Several studies have reported more RP in patients who received PNB for surgery in contrast with patients who had general anesthesia [8,9]. RP, which usually occurs during the first night at home, outside of a controlled healthcare setting, represents a relevant clinical problem. Besides patient suffering and lower satisfaction [10], RP may also cause unplanned use of medical resources [9]. In the recent literature, RP is generally mentioned as an under-recognized and poorly understood phenomenon [7,11]. Several causes have been hypothesized such as inadequate pre-emptive administration of multimodal analgesia, exaggerated state of hyperalgesia or personal inability to cope with pain [6,7].

Severe postoperative pain, including RP, occurs despite the use of recommended ‘procedure-specific’ analgesic treatment, which argues for the development of ‘individual-related’ pain management. The present study aimed to consider RP on an individual-related basis. Both psychological and

physiological mechanisms, that is, endogenous pain processing systems, are involved in the intensity of postoperative pain. The presence of exacerbated endogenous excitatory processes (e.g. facilitation of N-methyl-D-aspartate [NMDA] receptor activation) increases postoperative hyperalgesia caused by local tissue injury [12]. Moreover, some individuals who display such a pro-nociceptive pain modulation profile might be at risk of experiencing higher pain relative to injury [13]. Ketamine is a non-selective inhibitor of NMDA receptors that displays analgesic, anti-hyperalgesic, and anti-inflammatory properties [14]. Low doses of ketamine may supplement loco-regional analgesic techniques [15,16] and modulate postoperative pain severity [14]. The first aim of the study was to assess the benefit of intraoperative administration of ketamine (at an anti-hyperalgesic dose) on the incidence of RP after upper limb surgery under axillary plexus block. The secondary aim was to determine the incidence of RP after upper limb surgery and to better understand the risk factors associated with its development in ambulatory patients.

Methods

This prospective randomised double-blinded study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethical Committee of the Cliniques Universitaires Saint-Luc, Brussels, Belgium (Chairperson Professor J.M. Maloteaux, ref 2019/05JUL/303). The study was registered before the first patient enrolment at www. Clinicaltrials.gov (NCT04890418) and Eudract (No: 2019-001079-35).

Recruitment

Patients between 18 and 80 yr of age scheduled for elective ambulatory upper limb surgery (elbow and under) under an axillary plexus block were prospectively enrolled between January 2019 and March 2021. Patients were recruited during preoperative surgical or anesthesia visit. All subjects participating in the study provided full written informed consent forms.

Exclusion criteria included patient refusal, contraindications to the use of ketamine or to the use of regular postoperative analgesics such as NSAIDs and paracetamol, pregnant or suspected pregnant women, patients with diabetes mellitus and vascular disease, and patients unable to understand the perioperative questionnaires (language problem or cognitive impairment).

Preoperative assessment

The preoperative assessment (at Day 0) investigated preoperative pain at rest, with movement, and pain during the previous night at the operative site using a numeric rating scale (NRS) from 0 to 10 (where 0 = no pain and 10 = worst possible pain), as well as the regular use of preoperative medications including analgesic drugs. The patients completed the Central Sensitization Inventory (CSI, 40 questions) to assess key somatic and emotional complaints associated with central sensitization [17]. The French version of CSI was used. As reported in the literature, a cut-off value of 40 (on the scale from 0 to 100) was used to discriminate patients with a positive CSI before surgery [17]. The Pain Catastrophizing Scale (PCS), which assesses negative thinking related to pain (i.e. rumination, magnification, and helplessness), was also completed [18]. The presence of a neuropathic component of pain at the

operative site was assessed using the Douleur Neuropathique 4 (DN4) questionnaire [19].

Moreover, the presence of a preoperative mechanical temporal summation (TS), considered a clinical correlate of the wind-up phenomenon [20] (i.e., increased reactivity of the endogenous excitatory processes), was evaluated on the volar side of both the operated and contralateral arms. The level of pinprick pain intensity on an NRS score from 0 to 10 was recorded after a single stimulus and then after the last application of a train of 10 mechanical stimuli. The difference between the two NRS scores was calculated as the mechanical TS. The mechanical TS was evoked by application of a 281 g von Frey filament (Stoelting, Woodale, CA, USA) at a frequency of 1 Hz within an area of 1 cm in diameter on the volar forearm [21].

Study intervention

Randomization and double-blinding were performed by the clinical research unit of the Pharmacy Department of Cliniques Universitaires Saint-Luc. Patients were randomized into two groups to receive (by slow i.v. injection) either ketamine 0.3 $mg \cdot kg^{-1}$ diluted in 10 ml saline or an equivalent volume of saline 0.9%, after completion of the axillary plexus block, before tourniquet placement and surgical incision. To prevent psychomimetic side-effects related to ketamine, all patients also received midazolam 2 mg i.v. before the axillary plexus block.

Intraoperative and postoperative treatments

Axillary PNB was performed under real-time ultrasound guidance by an anesthetist trained in the technique. All patients also received optimal perioperative multimodal analgesia including intraoperative ketorolac (0.5 $mg \cdot kg^{-1}$ i.v.) and paracetamol 1 g. If necessary (NRS >3/10), postoperative tramadol 2 $mg \cdot kg^{-1}$ was administered in the recovery room. Pain-free patients were discharged from hospital with a standard analgesic regimen: NSAIDs (ibuprofen 400 mg/6 h), paracetamol 3 g/24 h, and tramadol if required as rescue analgesic.

The success of axillary plexus sensory block was assessed using a cold test (ether test) in the different nerve territories before incision. If the block was incomplete, the anesthesiologist in charge administered local infiltration under ultrasound guidance. If this was still insufficient, the patient was converted to general anesthesia.

Outcome measurements

Duration of surgery, tourniquet time, intraoperative and postoperative surgical complications were noted. The duration of the axillary block was recorded, and the different phases of its resolution were measured as follows (according to the patient's report on his/her pain diary): time of block completion (H1, day and time), first occurrence of paresthesia reported by the patient (H2, day and time after block), and onset of pain at the surgical site (H3, day and time after block). At the time the axillary block totally wore off, patients were instructed to record the pain intensity (NRS 0–10) in the diary provided before hospital discharge.

Subjects were contacted by phone on Days 1, 4, and 30 after surgery by a research nurse. Postoperative pain intensity was assessed as daily average and maximal pain (NRS 0–10), and as nocturnal pain intensity (NRS 0–10). On Day 30 after surgery, patients also completed the short form of the Brief Pain Inventory (BPI) to evaluate the impact of pain on daily quality of life (sleep, mood, analgesic intake) [22].

Finally, the presence of a neuropathic component in early postoperative pain on Days 4 and 30 was assessed using the DN4 questionnaire [23].

Statistical analysis

Statistical analysis was performed with SigmaStat 3.5 (Systat Software GmbH, Erkrath Germany). Results were expressed as proportions, mean (standard deviation [SD]) or median value (interquartile range) as specified. According to a Kolmogorove-Smirnov normality test, parametric data between the groups were compared using the unpaired Student *t*-test and non-parametric data with the Manne-Whitney rank-sum test. Categorical data were compared using the chi^2 test and Fisher exact test using a two-tailed probability. For correlation analysis, the Pearson correlation test or Spearman rank order correlation test was used. A value of $P<0.05$ was considered significant. The univariate logistic regression model was used to assess the association between RP when the axillary plexus block wore off (dependent variable) and potential risk factors (non-dependent variables). For the univariate regression, preoperative variables found in the analysis between the RPþ group and the Rpe group with a P value <0.1 were included: bone

surgery, severe pain (NRS >7/10) for maximal pain or night pain, positive PCS (>14/52) or high PCS (>26/52), positive CSI score (>40/100).

The sample size was calculated based on the incidence of RP. The presence of RP was defined as pain intensity score >7 (NRS, 0-10) reported by the patient after axillary plexus block resolution.

Different definitions of RP are proposed in the current literature [6]. We adopted the definition published in a recent large cohort study, namely NRS >7/10 [11].

A retrospective analysis of preliminary data revealed an incidence of 30% RP. Based on this, we calculated that a total of 104 subjects were required to detect a 20% reduction in the incidence of RP from a baseline incidence of 30%, using a two-sided $\alpha = 0.05$ with 80% power. We included a total of 110 subjects, taking into account possible dropouts.

Results

A total of 135 patients were assessed for study eligibility, of which 110 met the inclusion criteria and were enrolled in the study (Consolidated Standards of Reporting Trials (Fig 1.5). The data of 109 subjects who completed the study were analyzed. No axillary plexus block had to be converted to general anesthesia (three subjects reported some discomfort at the surgical incision, and the block was completed with a local infiltration in the nerve territory as previously explained). No subject needed tramadol administration in the recovery room.

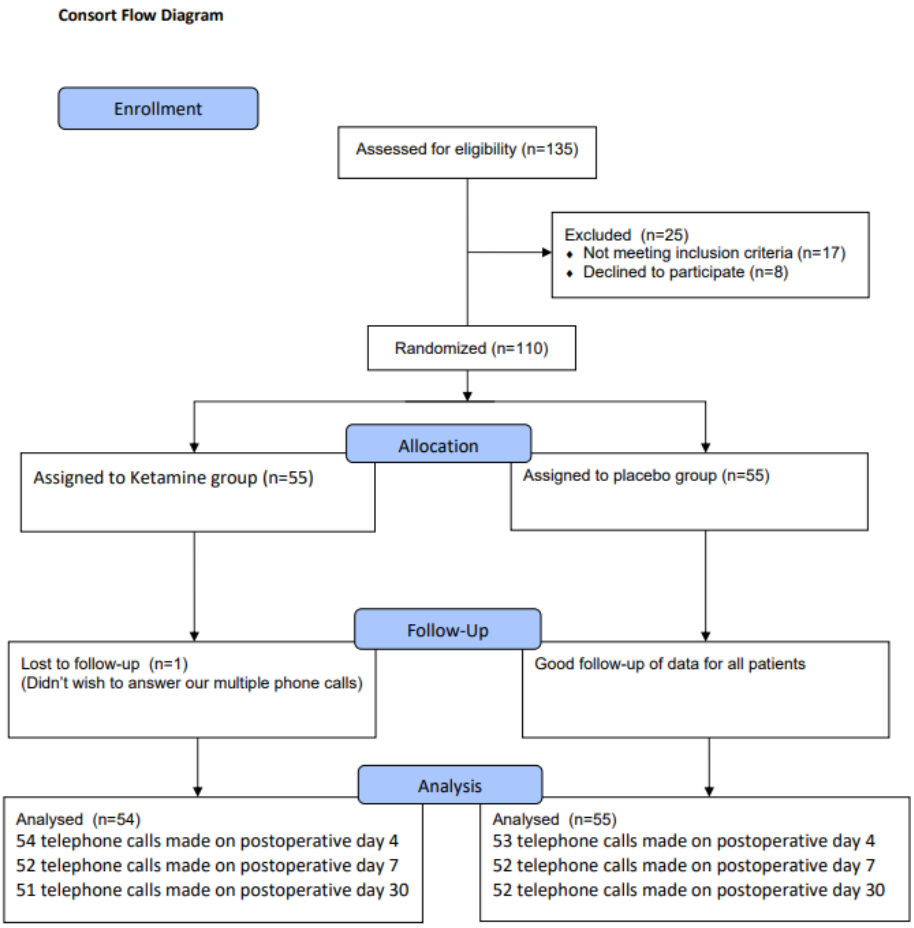

Figure 1.5 – ***Flow Diagram: Prospective study. Final sample size 109 patients***

Evaluation of the effect of intraoperative ketamine treatment

Among 109 subjects who completed the study, 54 received ketamine and 55 received saline (placebo group) (Table 1.1). Demographic data were similar between the two groups (Table 1.1). Preoperative pain scores and results of psychophysical tests (CSI, PCS, TS) did not differ (Table 1.1). The duration of the axillary plexus block was slightly longer in the placebo group but without clinical relevance. The median value of the pain intensity noted by the subject after the block resolution did not differ between the two groups of treatment (p = 0.203). Using the RP definition of NRS score >7 out of 10 when the analgesic effects of the axillary block wore off, 44 patients presented with RP (44/109, 40.4%). Among these subjects, 18 (18/54, 33%) had received an intraoperative dose of ketamine (Table 1.1).

	Ketamine group (*n*=54)	Placebo group (*n*=55)	P value
Male/female ratio (*n*)	27/28	25/29	0.848
Age (yr)	51 (16)	52 (18)	0.687
BMI (kg m^{-2})	26 (6)	24 (6.5)	0.055
Bone surgery (*n*)	20 (37%)	21 (39%)	0.845
Tourniquet duration (min)	27 (17)	26 (17)	0.917
PCS total (0–52)	11 (2.25–23.0)	12 (3.0–23.0)	0.794
Rumination sub-score	4 (0.25–8.0)	4 (0.25–9.75)	0.765
Magnification sub-score	2 (0–4.0)	2 (0–4.0)	0.838
Helplessness sub-score	6 (0–12.5)	5 (1.0–9.75)	0.854
CSI score (0–100)	21 (11.25–33.5)	18.5 (12.0–27.0)	0.806
TS ipsilateral forearm (0–10)	0 (0–1)	0 (0–1)	0.138
TS contralateral forearm (0–10)	0 (0–1)	0 (0–1)	0.279
Preoperative pain			
Average pain (NRS 0–10)	3 (0–5)	2 (0–4)	0.199
Maximal pain (NRS 0–10)	7 (4–8)	4.5 (2–8)	0.185
Night pain (NRS 0–10)	1 (0–5)	0 (0–3)	0.233
Pain when block wear off			
Intensity (NRS 0–10)	6 (4–8)	4.5 (2–8)	0.203
Incidence RP (*n*)	18 (33%)	26 (47%)	0.438
Axillary block duration			
Total duration (min)	520 (347–720)	630 (510–790)	0.043
H1–H2 duration (min)	345 (215–465)	400 (309–538)	0.044
H2–H3 duration (min)	135 (90–300)	180 (120–300)	0.266

Values are expressed as mean (standard deviation) or median (inter-quartile range). H1-H2: time interval between the time of the end of the block (H1, day and time) and the beginning of the onset of the paresthesia reported by the patient (H2, day and time after the block).H2-H3: time interval between of time of beginning of the occurrence of paresthesia reported by the patient (H2, day and time after block) and finally the onset of pain at surgery site (H3,

day and time after block). CSI, Central Sensitization Inventory; PCS, Pain Catastrophizing Scale; RP, Rebound Pain.

Table 1.1 – ***Intraoperative ketamine: comparison between subjects who received ketamine treatment and subjects who did not.***

In the placebo group, 26 patients (26/55, 47%) presented with RB at the resolution of the block (p=0.438). The postoperative evolution of the two groups of treatment was similar regarding postoperative pain scores (average daily pain, average maximal pain, and night pain) recorded at Days 1, 4, 7, and 30 (all P values >0.05). Finally, analysis of BPI items (at Day 30) and DN4 scores (preoperative, Day 4, and Day 30) did not reveal differences between the groups of treatment (all P values >0.05).

Evaluation of Rebound Pain characteristics and risk factors

The characteristics of the 109 subjects are presented in Table 1.2. The incidence of RP in this population was 40.4% (44/109) using the definition of severe pain (NRS >7/10) at the block resolution. Axillary plexus block was successfully performed in all subjects, but three subjects required supplementary local infiltration (among these three patients, one presented with RP). A significant increase in the incidence of RP was found in the context of bone surgery (61% vs 23%, p=0.03). Subjects with RP presented significantly higher pain catastrophizing score (global score and all sub-scores). In contrast, the psychophysical measures of central sensitization such as CSI score and TS assessment did not differ between patients with and without RP. Preoperative DN4 also was not different.

	RP+ group (*n*=44)	RP− group (*n*=65)
Male/female ratio (*n*)	16/28	36/29
Age (yr)	53 (18)	51 (17)
BMI (kg m^{-2})	26 (6.5)	26 (5)
Bone surgery (*n*)	27 (61%)	15 (23%)
Tourniquet duration (min)	29 (17)	25 (17)
PCS total (0–52)	16.5 (7–31.5)	7 (2.0–17.0)
Rumination sub-score	5.0 (1.0–11.5)	3.0 (0–7)
Magnification sub-score	3.0 (0.5–6)	2.0 (0–3)
Helplessness sub-score	8.0 (3.0–15.5)	3.0 (0–7)
CSI score (0–100)	21 (12.5–28)	18 (11–26.5)
TS ipsilateral forearm (0–10)	0 (0–1)	0 (0–1)
TS contralateral forearm (0–10)	0 (0–1)	0 (0–1)
Preoperative pain		
Average pain (NRS 0–10)	4.0 (2.5–5.5)	1.0 (0–3.0)
Maximal pain (NRS 0–10)	8.0 (6.5–8.0)	4.0 (0.5–7.0)
Night pain (NRS 0–10)	3.0 (0–5.5)	0 (0–2.0)
DN4 score (0–10)	3.0 (1–4.25)	2.0 (0.25–4)
Rebound pain		
Intensity (NRS 0–10)	8.5 (7.25–9.75)	3.25 (1–5)
Intraoperative ketamine (n)	25 (57%)	29 (45%)
Axillary block duration		
Total duration (min)	570 (382–748)	612 (465–750)
H1–H2 duration (min)	357 (222–500)	370 (282–535)
H2–H3 duration (min)	142 (60–277)	180 (120–330)

Values are expressed as mean (so) or median (IQR). H1-H2: time interval between the time of the end of the block (H1, day and time and the beginning of the onset of the paresthesia reported by the subject (H2, day and time after the block). H2-H3: time interval between of time of beginning of the occurrence of paresthesia reported by the subject (H2, day and time after block) and finally the onset of pain at surgery site (H3, day and time after block). CSI, Central Sensitization Inventory; DN4, Douleur Neuropathique 4 questionnaire; IQR, interquartile range; NRS, numeric rating scale; PCS, Pain Catastrophizing Scale; sp, standard deviation; TS, temporal summation.

Table 1.2 – ***Demographic data: comparison between subjects with Rebound Pain (RP+) and subjects without Rebound Pain (RP)***

Importantly, subjects in the RP group reported significantly higher preoperative pain at the surgical site, for average pain, maximal pain, and night pain (Table 1.2). Whether the total duration of the axillary block did not differ, the duration of paresthesia felt by the patient during the block alleviation (H2-H3 interval) was shorter in subjects with RP (p=0.031). Regarding the postoperative evolution, the pain trajectories in patients with RP were significantly higher (i.e. worse pain resolution) for daily maximal pain (Fig. 1.6), daily average pain, and night pain (Fig. 1.7) until Day 30. At Day 30, average daily pain was still rated higher in the RP group (p=0.042).

However, the impact of pain on the quality of life as assessed by sleep, mood, and life enjoyment did not differ between the two groups. In the RP group, 14% of the patients mentioned regular intake of analgesics (including weak opioids, n1⁄46/44) vs 3% (n=2/65) in patients without RP (p=0.059). We note that preoperative opioid intake was significantly higher, that is 20% (9/44) in the RP group vs 6% (4/65) in patients without RP (p=0.034). Finally, at Day 30, but not preoperatively nor at Day 2, the DN4 score was higher in patients with RP (median value=2; interquartile range [IQR], 1-3) than in patients without RP (median value1⁄41; IQR, 0e2) (p=0.021) although the incidence of positive DN4 scores did not differ between the groups (29% in the RPþ group vs 22% in the Rpe group, p=0.484).

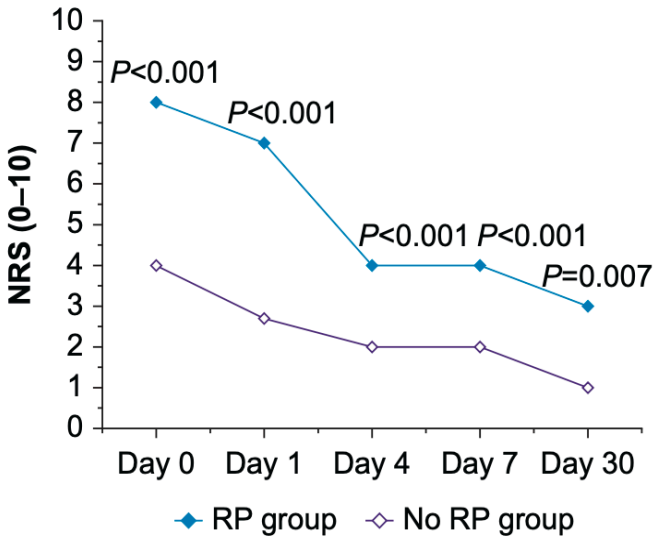

Figure 1.6 – ***Postoperative evolution of maximal pain between subjects with Rebound Pain (RP+) and subjects without Rebound Pain (RP-). NRS, numeric rating scale.***

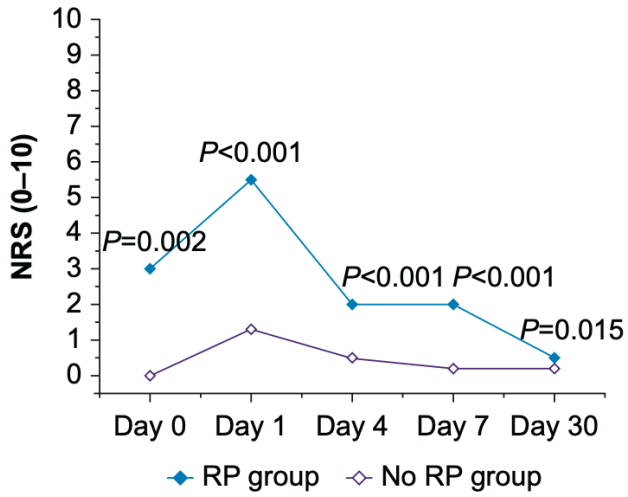

Figure 1.7 ***- Postoperative evolution of night pain between subjects with Rebound Pain (RP+) and subjects without Rebound Pain (RP-). NRS, numeric rating scale.***

We found positive correlations between RP intensity and the score of several preoperative psychophysical tests (Table 1.3) and the 24 h postoperative maximal NRS score questioned at Day 1 (0.729; p=0.0000). Finally, analysis of preoperative CSI revealed the presence of a positive CSI (defined as a value of at least 40/100) in 9% of subjects with RP (4/44) vs 9% in subjects without RP (6/65) (n.s.). Regarding pain catastrophizing, 50% of subjects with RP (22/44) presented with a score >14 (median value of the full group) vs 31% (20/65) in the no RP group (p=0.047). High catastrophizers (i.e., patients in the third percentile, PCS score >26 on the scale from 0 to 52) accounted for 34% (15/44) of the subjects with RP vs 11% (7/65) of subjects without RP (p=0.004). The use of multiple logistic regression model highlighted the following risk factors to develop RP after upper limb surgery under axillary plexus block: bone surgery, presence of severe preoperative maximal pain, and high catastrophizing (Table 1.4).

	Preoperative maximal pain	Preoperative average pain	Preoperative night pain	Preoperative DN4 score
RP intensity	0.467* P=0.0000	0.392* P=0.0000	0.313* P=0.002	0.108 P=0.293
	PCS total score	**PCS sub-score helplessness**	**CSI total**	**TS score on operated arm**
RP intensity	0.250* P=0.009	0.294* P=0.002	0.003 P=0.974	0.188 P=0.052

CSI, Central Sensitization Inventory ; DN4, Douleur Neuropathique 4 questionnaire ; PCS, Pain Catastrophizing Scale ; RP, Rebound Pain ; TS, temporal summation. Asterisks highlight statistically significant results (P value <0.05).

Table 1.3 - ***Pearson's correlations found between the intensity of Rebound Pain reported by the patients when the analgesic effect of the block wears off and different preoperative psychophysical tests.***

Risk factor	Odds ratio	5% Conf. lower	95% Conf. upper	P value
Female sex	0.538	0.201	1.442	0.218
Bone surgery	5.246	1.883	14.619	0.002*
Severe preoperative maximal pain (NRS >7/10)	4.203	1.512	11.683	0.006*
Severe preoperative night pain (NRS >7/10)	0.471	0.102	2.170	0.334
Positive preoperative PCS score (>14/52)	1.021	0.278	3.758	0.975
High preoperative PCS score (>26/52)	4.808	1.036	22.306	0.045*
Positive preoperative CSI score (>40/100)	1.401	0.265	7.399	0.691

CSI, Central Sensitization Inventory; NRS, numeric rating scale;PCS. Pain Catastrophizing Scale, Asterisks highlight statistically significant results (P value <0.05).

Table 1.4 - ***Risk factors associated with the development of severe pain (NRS >7/10), that is RP when axillary plexus block wears off in the context of ambulatory upper arm surgery.***

Discussion

To our knowledge, this is one of the rare prospective randomized studies to specifically address the phenomenon of RP including possible mechanism and preventive treatment in ambulatory patients.

Our results did not show any benefit of a single anti-hyperalgesic dose of ketamine (0.3 $mg \cdot kg^{-1}$), as the incidence of RP did not differ between ketamine and placebo groups (47% vs 33% in ketamine vs placebo), nor did the intensity of RP. Several explanations are possible. First, the failure of single ketamine bolus doses to reduce postoperative pain has been questioned [14]. However, the present setting, that is ambulatory surgery performed in awake patients, precluded the administration of higher or repeated doses of ketamine. Second, multimodal analgesia might have blunted the benefit of ketamine (<0.5 $mg \cdot kg^{-1}$). In studies about low doses of ketamine (0.2–1.0 $mg \cdot kg^{-1}$) to supplement loco-regional analgesia, general anesthesia was often provided [15,16]. In such context, low doses of ketamine showed a postoperative opioid sparing effect but inconstant reduction on pain scores. Interestingly, one study assessed the effect of ketamine 10 mg i.v administered in awake patients under spinal anesthesia during Caesarean delivery [24]. All patients received perioperative multimodal analgesic regimen and the incidence of breakthrough pain during the first 24 h was not reduced (75% vs 74% in ketamine and placebo groups, respectively) [24]. Third, the lack of ketamine effect might be related to the fact that underlying central sensitization does not play a major role in RP development. Our assessment of endogenous pain processes by CSI questionnaire and mechanical TS only concerned the pro-nociceptive systems. The CSI global

score was similar in patients with and without RP, and the preoperative incidence of positive CSI (score >40) did not differ. Mechanical TS measured on the forearm also did not differ between both groups. Finally, in a large retrospective study also reported no effect of intraoperative ketamine on RP incidence (40%) [11].

The secondary aim of the present study was to better characterize the phenomenon of RP. Despite the use of procedure-specific multimodal analgesia [7], RP incidence reached 40% (n=44/109), similar to that reported in patients undergoing wrist fracture fixation under PNB both in a prospective study [25],(50% in the placebo group) and a retrospective study [9] (41% in the PNB group vs 10% in the general anesthesia group) .Thus, better understanding of mechanisms and predictive risk factors (in other words, 'patient-specific' management) is mandatory. Our results support bone surgery of the upper limb, in contrast to soft tissues surgery, as a major risk factor of RP (odds ratio [OR]=5.2) in agreement with a previous retrospective study (OR=1.8) [11]. Female sex and younger age have been identified as risk factors for poor postoperative pain control [26] and risk factors of RP. [11]. In our study, although female sex almost reached statistical significance (p=0.05), age did not probably in relation with exclusion criteria we used, that is diabetes mellitus and vascular diseases, which are more frequent in older patients. We also found preoperative pain intensity to be strongly correlated to RP intensity in agreement with a large retrospective study showing that higher baseline preoperative movement pain scores influenced RP scores [4].

Catastrophizing, an exaggerated negative mental attitude during actual or anticipated pain experience, may predict postoperative pain [27]. Although

catastrophizing has been suspected to be associated to RP, no previous study has specifically explored the relationship [2,6]. Using a validated PCS questionnaire, we found that preoperative PCS was higher in patients with RP, the helplessness sub-score being particularly correlated with RP intensity.

Finally, subjects with RP reported higher sub-acute pain at Day 30 although it did not affect their quality of life. Psychological profile, that is high catastrophizing, certainly accounts for the higher pain scores reported in subjects with RP. Interestingly, subjects with RP scored higher for DN4 at Day 30. The DN4 questionnaire validity in acute and sub-acute post-operative pain remains debated as the score was only validated in established chronic pain [28]. We hypothesized that neuropathic-like characteristics more likely reflect an exacerbated perioperative inflammatory reaction. Dexamethasone seems able to prevent RP both in experimental conditions [29] and clinical studies [11,25]. Beyond the modulation of perioperative inflammation, dexamethasone significantly prolongs the duration of PNB [25], a mechanism supposed to reduce the risk of RP [3,6]. We did not find a significant difference in total axillary block duration between patients with and without RP, in agreement with a retrospective study [4], but the duration of paresthesia was shorter in patients with RP.

Strengths and limitations of the study

The present study is one of the largest prospective studies (n=109) conducted to date about RP after PNB in ambulatory patients. The study tried to better understand the phenomenon by assessing some mechanisms, that is underlying central sensitized state and the potential anti-hyperalgesic effect of ketamine as a preventive strategy. The methods currently used to measure

central sensitization are probably not sensitive and specific enough to detect mechanisms related to outcomes including the response to specific treatments [30]. For example, CSI has been more strongly associated with psychological factors than psychophysical test results in patients with osteoarthritis [31]. The present study is also one of the very few studies to objectively measure the role of psychological factors such as catastrophizing, which is often suspected to promote RP phenomenon.

The study also has several limitations. RP was defined as NRS reported by the patient when the PNB wore off. Several definitions of RP phenomenon exist, including the one that proposes to substitute 'recall pain' (when the PNB wore off) by the highest pain score during the first 24 h [11]. We have compared recall pain with NRS reported by patients during the Day 1 phone call. Both the intensity (0.729; p=0.000) and incidence of severe pain (NRS >7/10) (0.474; p=0.000) were strongly correlated between recall pain and Day 1 maximal pain. In other words, the definition of RP we used may be acceptable. Among other limitations, we limited postoperative follow up to 30 days and the impact of RP on chronic postsurgical pain (at 3 months and later) was not measured. Finally, the dose of ketamine used was low and not repeated. Nevertheless, in awake patients, the psychomimetic side-effects of ketamine precluded a different use. Finally, as aforementioned, the psychophysical tests used to assess underlying central sensitization in patients may be questioned as well the use of the DN4 questionnaire in an acute postoperative setting.

In conclusion, this prospective randomized study showed no benefit of a single pre-emptive anti-hyperalgesic dose of ketamine to prevent occurrence

or to reduce intensity of RP in ambulatory patients undergoing upper limb surgery. Psychophysical tests (CSI, TS) did not demonstrate the involvement of central sensitization as risk factor for RP in contrast with the experience of preoperative pain intensity and pain catastrophizing. Because RP occurrence still remains frequent despite the use of adequate procedure-specific postoperative analgesia, future studies should focus on patient-specific postoperative pain management.

Key messages (PRPK):

- **Rebound Pain occurrence**: a frequently observed phenomenon
- **Ketamine**: no preventive effect with a single anti-hyperalgesic dose
- **Factors associated with RP**: type of surgery, high pain catastrophizing, and high preoperative pain

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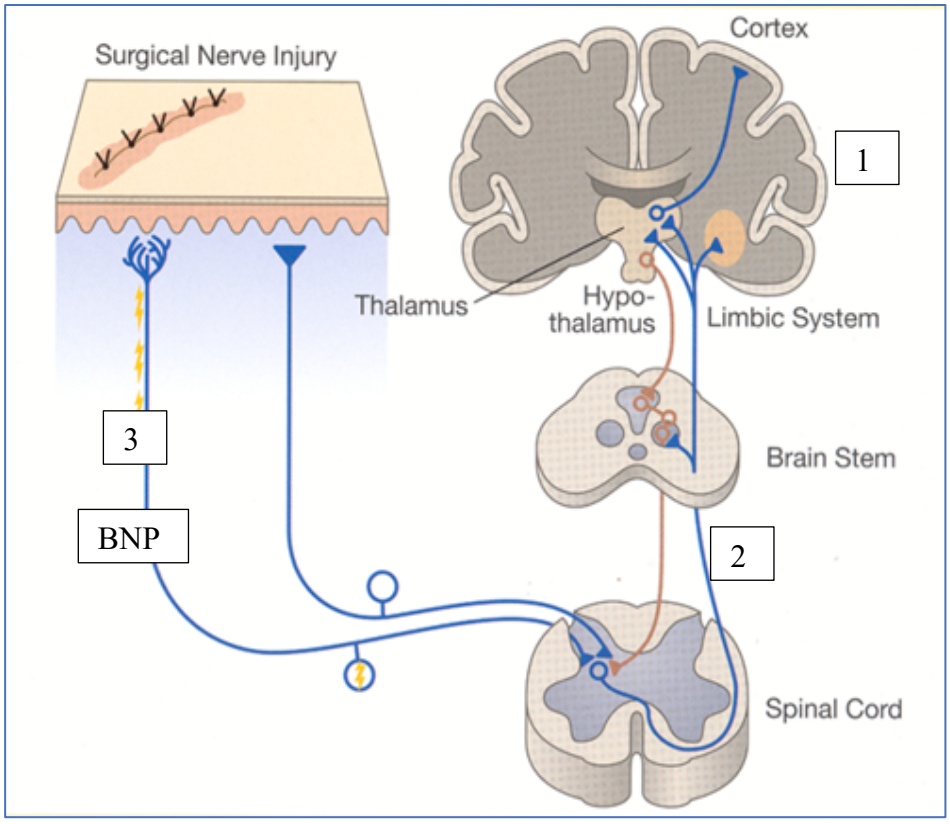
PART III – TOWARDS A MECHANISTIC UNDERSTANDING OF REBOUND PAIN

The development of RP appears to result from a complex interaction of several pathophysiological mechanisms, which may act independently or in combination depending on the patient. In this thesis, three principal pathways were explored (Fig. 3.1).



1. ***Central sensitization***
2. ***Cognitive and emotional factor***
3. ***Peripheral inflammatory response***

Figure 3.1 – ***Hypothesized mechanisms of action involved in the Rebound Pain phenomenon***

3.1. Central Hyperexcitability Hypothesis

The first potential mechanism involves central sensitization. This concept, well described in postoperative and chronic pain [1,2], refers to increased excitability of central nociceptive pathways, leading to hyperalgesia and sometimes allodynia. Clinically, some patients report, at the time of block resolution, pain of disproportionate intensity that progresses rapidly and diffusely, raising the hypothesis of central facilitation as a contributor to RP.

Experimental studies have shown that markers of central sensitization, such as CREB (cAMP Response Element-Binding protein) phosphorylation in dorsal horn neurons and glial activation are associated with hyperalgesia following peripheral injury or inflammation. By analogy, similar mechanisms may contribute to pain recrudescence during the resolution of a peripheral nerve block [3,4]. In certain rat models of nerve block, block resolution has been associated with exacerbated thermal and mechanical hypersensitivity, partially mediated by NMDA (N-Methyl-D-Aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptors [5].

To investigate this hypothesis in our first clinical study PRPK (Prevention of Rebound Pain with Ketamine), we combined a preoperative evaluation of endogenous pain modulation with intraoperative administration of an NMDA receptor antagonist. *The Central Sensitization Inventory* (CSI), validated as a screening tool for central sensitization across different pain conditions [6], together with mechanical temporal summation (a dynamic marker of central facilitation) were used to identify patients with a preoperative high-risk profile.

In our cohort, neither CSI scores (including the proportion of pathological scores > 40) nor mechanical temporal summation measured on the forearm differed significantly between patients with and without RP, suggesting no evidence of a pre-existing central sensitization state before surgery.

The role of NMDA receptors, central to synaptic plasticity in pain and postoperative hyperalgesia [7], was further tested using temporal summation assessments and intraoperative administration of ketamine (0.3 mg/kg), an NMDA antagonist with documented antihyperalgesic properties in certain high-pain surgeries [8] (Fig. 3.2).

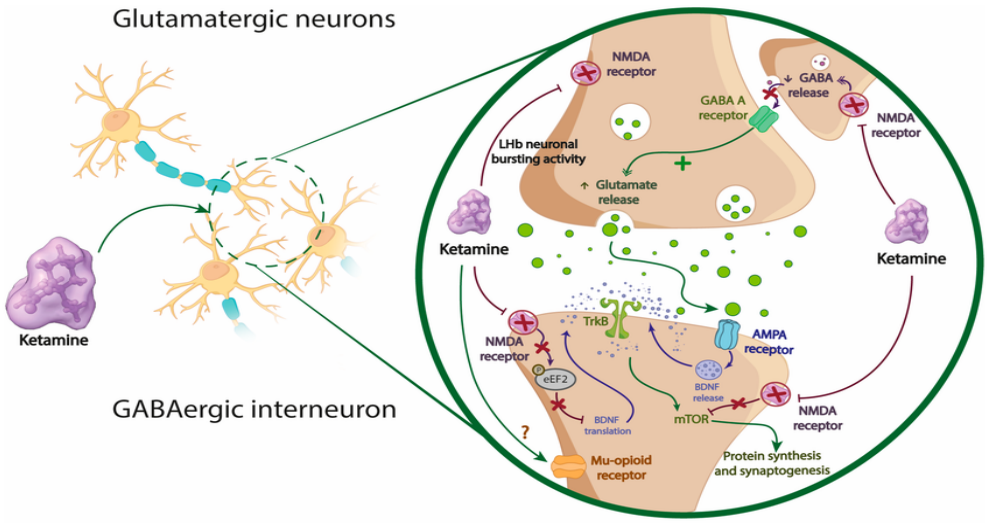


Figure 3.2 - ***Schematic illustration of ketamine's action on post-synaptic NMDA receptors in glutamatergic neurons***

Results, consistent with animal data showing that NMDA blockade may attenuate but rarely abolish hyperalgesia following nerve recovery [9], did

not demonstrate a significant reduction in either the incidence or intensity of RP. At least at the doses we used (low doses because patients were awake).

These findings, aligned with other recent studies [10], suggest that in the context of single peripheral nerve blocks for ambulatory orthopaedic surgery, central sensitization and NMDA-dependent mechanisms are unlikely to be the primary determinants of RP. More promising avenues include the dynamics of local inflammation, pharmacokinetic.

3.2. Cognitive and Emotional Hypothesis

A second area of investigation in this thesis concerns the potential role of cognitive and emotional factors in the onset of RP.

Preoperative anxiety, and particularly catastrophizing, are among the most frequently reported determinants of postoperative pain intensity [11,12]. This association is not specific to orthopaedic surgery: multiple studies have shown that preoperative anxiety is an independent predictor of postoperative pain, analgesic consumption, and functional recovery [13,14].

In the field of regional anesthesia, high levels of preoperative anxiety, assessed using validated tools such as the *Amsterdam Preoperative Anxiety and Information Scale* (APAIS), have been correlated with higher pain scores after block resolution and with lower patient satisfaction [15–17].

In orthopaedic surgery specifically, several studies have confirmed that high scores on the *Pain Catastrophizing Scale* (PCS) are associated with more intense and persistent pain, regardless of surgical or anesthetic parameters [18,19]. Beyond its general effect on postoperative pain, a high PCS appears

to increase both the risk and severity of RP, likely by heightening attentional focus on nociceptive signals during the abrupt offset of the block.

This influence is explained by the fact that catastrophizing is not limited to a subjective cognitive appraisal but is accompanied by measurable activation of brain circuits involved in descending pain modulation, particularly the prefrontal cortex, amygdala, and insula [20] (Fig. 3.3). This neurofunctional profile fosters hypervigilance, negative anticipation, and amplification of pain perception, which may contribute to the occurrence of more intense and earlier RP.

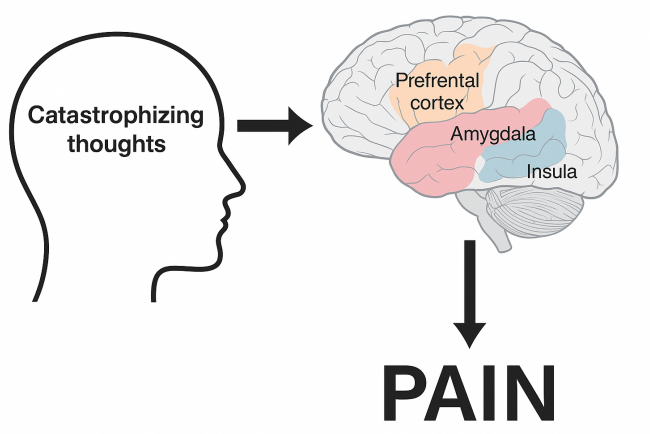


Figure 3.3 – ***Brain Regions Involved in Catastrophizing***

In addition, both experimental and clinical data point to a link between catastrophizing and an amplification of physiological stress responses, including heightened inflammatory reactivity. In surgical patients, high preoperative catastrophizing scores have been associated with increased

plasma concentrations of interleukin-6 (IL-6) and other pro-inflammatory mediators [21,22] (Fig. 3.4). This interaction between cognitive dysregulation and inflammatory activation may contribute to the earlier onset and greater severity of RP in some patients by creating a biological environment favourable to transient post-block hyperalgesia. (Fig. 3.4)

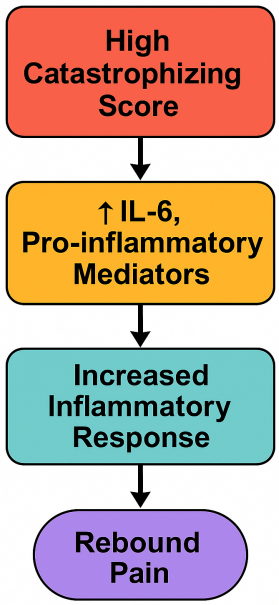


Figure 3.4 – ***Schematic representation of the hypothesized interaction between catastrophizing and inflammatory pathways contributing to the development of Rebound Pain*** [21] [22] [24]

3.3. Inflammatory Hypothesis

Among the mechanisms proposed in the literature, the inflammatory hypothesis currently stands out as one of the most robust explanations for the occurrence of RP [23,24]. The partial preventive efficacy of dexamethasone, discussed in detail in the following section, further supports the idea that an inflammatory component, most likely local, plays a decisive role at the time of peripheral nerve block resolution.

Clinically, RP is often described by patients as localised pain, near the surgical site, accompanied by burning sensations and pronounced hyperalgesia. This distribution and sensory profile suggest an exacerbation of the local inflammatory response [10,23].

Several pathophysiological mechanisms could underlie this amplification. Experimental studies have shown that certain local anesthetics, such as bupivacaine and ropivacaine, induce the release of pro-inflammatory mediators, particularly prostaglandin E_2, interleukin-1β, and TNF-α, which contribute to the sensitization of peripheral nociceptor endings [25,26]. Other factors have also been considered, such as tissue trauma related to needle insertion or the pressure exerted during injection, both of which may promote a local inflammatory reaction [23].

Furthermore, resolution of the peripheral sympathetic block leads to vasodilatation and increased tissue vascularisation, which may facilitate plasma extravasation, leukocyte recruitment, and mast cell activation, thereby reinforcing the inflammatory response [27]. Distinguishing between “true”

inflammation and vascular changes secondary to the block, however, remains challenging, particularly in clinical settings.

Another unresolved question concerns the influence of the site and type of block on the inflammatory dynamics. Could a proximal block with mixed components (sensory and motor) elicit a different local response compared with a more distal block, which is predominantly sensory? Some data from orthopedic anesthesia suggest that the location and extent of the block may not only modulate the analgesic efficacy but also influence local tissue responses, possibly related to the density of neural structures [28]. However, the currently available comparative data are insufficient to determine whether the intensity of the inflammatory reaction truly varies according to block type.

The limitations of the current literature and the remaining uncertainties regarding the impact of block type on local inflammatory responses led to the design of the CBFR (Comparison of Blocks for Forefoot Surgery and Rebound Pain) study. This study specifically aimed to explore the influence of block type on inflammatory dynamics and the occurrence of Rebound Pain. The results of this study will be presented in detail in the fourth part of this work.

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PART IV – STRATEGIES FOR PREVENTING REBOUND PAIN

A detailed understanding of the clinical features of RP, particularly its risk factors together with greater insight into its pathophysiological mechanisms, is essential for the development of effective preventive strategies. Findings from recent studies [1,2] now provide a more solid framework to guide therapeutic considerations.

In the context of ambulatory surgery, where patients experience RP outside direct medical supervision, prevention becomes a priority [3]. While some interventions, particularly pharmacological ones, have suggested a beneficial effect in recent literature (most notably intravenous or perineural dexamethasone [4,5]) results remain heterogeneous and not always easily applicable to routine clinical practice.

The diversity of anesthetic practices, the absence of a consensus definition of RP, and the limited number of rigorous comparative studies continue to hinder the development of standardised recommendations [6,7]. Within this context, two complementary preventive approaches appear relevant: first, non-pharmacological strategies based on patient education and autonomy [8], and second, pharmacological measures designed to prolong or modulate regional anesthesia and thereby reduce the risk of RP, including the use of adjuvants with a preventive role [9,10].

4.1. Non-pharmacological approaches

Preoperative patient education on the potential occurrence of RP and the importance of anticipatory analgesic intake is a major preventive tool. As Murphy and O'Donnell emphasise [11], this phenomenon may occur regardless of the type, volume, or concentration of local anesthetic used, highlighting the importance of factors beyond the anesthetic agent alone. Several studies have shown that when patients are informed beforehand about the transient yet potentially intense nature of post-block pain, they adhere more closely to prescribed analgesic regimens and are less likely to resort to excessive opioid use [8,12].

Managing patient expectations is central. Postoperative pain is among the main concerns before surgery, yet the impact of regional anesthesia on these expectations remains poorly understood. Neuroscience research has demonstrated that positive expectations about treatment effectiveness can modulate brain networks involved in pain, leading to a genuine reduction in pain perception through activation of endogenous opioid and dopaminergic systems [13]. Conversely, when initial expectations, often heightened by the prospect of prolonged analgesia with peripheral nerve blocks, are not met, patients may perceive greater pain intensity [14].

Clear, realistic information on the expected duration of the block and on signs signalling its regression is therefore essential. Structured educational initiatives, such as preoperative sessions or consultations with the anesthetist, improve adherence to regional anesthesia techniques and support acceptance of multimodal strategies [11]. Supplementing oral explanations with written

or multimedia resources can also enhance patient understanding, optimise anticipatory analgesic intake, and reduce perioperative anxiety.

The systematic implementation of anticipatory analgesic cover, combined with clear communication and structured information, helps not only to reduce RP intensity but also to improve overall patient experience. Nonetheless, these measures, although effective in most cases, may fall short when RP reaches very high intensities, underlining the need for a comprehensive preventive approach combining both non-pharmacological and pharmacological strategies.

4.2 Pharmacological approaches

In RP prevention, the quality and anticipation of postoperative analgesia are central. Implementing an anticipatory multimodal analgesic protocol remains essential to limit pain surges as the peripheral nerve block resolves [11,15]. Early initiation (i.e., before complete regression of the block) of a regimen combining paracetamol, non-steroidal anti-inflammatory drugs or COX-2 selective inhibitors, and, where required, a short-acting opioid, aims to maintain stable analgesia at the time of nerve conduction recovery [2]. However, it should be noted that despite adequate preventive information and education, some patients remain reluctant to initiate analgesic treatment in the absence of pain. This reluctance, combined with the potential side effects of opioids (somnolence, dizziness, nausea), can be a practical limitation, particularly in ambulatory settings [11].

In major orthopaedic surgery, the addition of adjuvants such as gabapentin or pregabalin may also help reduce postoperative hyperalgesia [8,16]. This

approach not only decreases discomfort but also reduces the risk of misinterpreting insufficient analgesic cover as true RP [17,18].

In addition, several local anesthetic adjuvants have been studied preoperatively for their potential to limit RP, including dexmedetomidine, clonidine, buprenorphine, midazolam, and adrenaline [9]. Dexmedetomidine has been shown to delay the re-emergence of postoperative pain, though its effect on overall RP intensity remains uncertain [19]. Clonidine also prolongs analgesia, but its specific role in RP is less clearly established [20].

With buprenorphine, some studies suggest that high doses (>300 μg) may reduce RP incidence, whereas more commonly used doses do not provide significant benefit [21]. Midazolam and adrenaline extend anesthetic duration, but there is no strong evidence to confirm their specific effectiveness against RP [10]. Similarly, extended-release formulations of local anesthetics, such as liposomal bupivacaine, have yet to demonstrate formal benefit [15].

Ketamine, a non-competitive NMDA receptor antagonist, combines anti-hyperalgesic properties with local anesthetic effects (Fig. 4.1). Administered perineurally, it has shown potential in preventing RP, particularly through prolongation of analgesia and reduced opioid consumption, without significantly altering the duration of sensory or motor block [22].

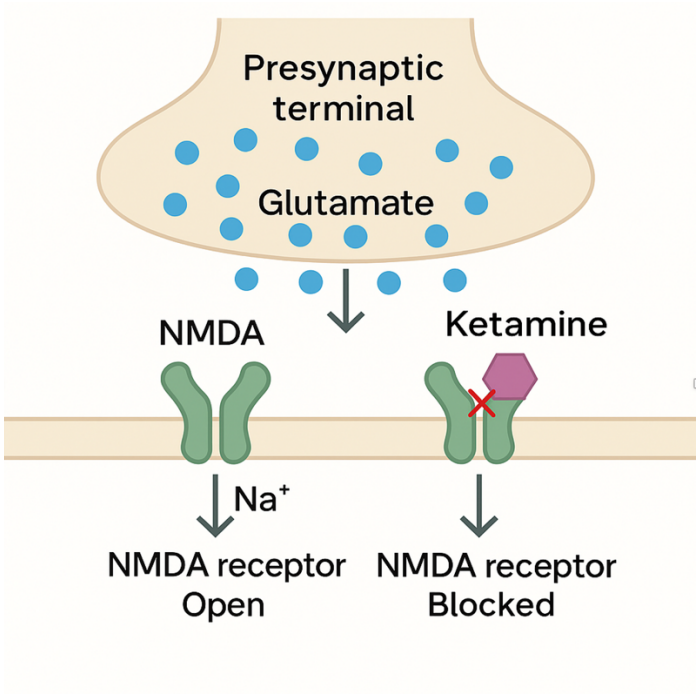

Figure 4.1 - ***Illustration Noncompetitive action of Ketamine on NMDA receptor***

By contrast, intravenous administration, evaluated in several studies, has yielded more mixed results. In the PRPK trial, a low-dose infusion (0.3 $mg \cdot kg^{-1}$) did not significantly reduce RP incidence [p = 0.438], despite a strong pharmacological rationale [23].

Some evidence suggests that higher doses might be more effective, but their use is limited by the risk of adverse effects such as hallucinations and dysphoria [24].

Esketamine, the S (+) enantiomer of ketamine, is characterised by a stronger affinity for NMDA receptors and generally better tolerability. Preliminary

observations indicate a potential role in reducing RP, but large-scale controlled trials are still required to confirm these findings [25].

Thus, the analysis of the previously discussed adjuvants highlights an absence of preventive efficacy, or at best a clinically questionable effect, thereby justifying the exploration of alternative pharmacological approaches. In contrast, dexamethasone appears to have emerged as a particularly promising candidate, leading us to further investigate its specific effects, notably through the RETRODEXA study examining the hypothesis of a dose–response relationship.

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4.3. Focus on dexamethasone: The RETRODEXA (Retrospective analysis of the impact of intravenous dexamethasone dosing on the occurrence of Rebound Pain) study

"Effect of intravenous dexamethasone dose on the occurrence of Rebound Pain after axillary plexus block in ambulatory surgery."

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Background: Rebound Pain (RP) remains a challenge in ambulatory surgery, characterized by severe pain upon resolution of a peripheral nerve block (PNB). Intravenous (IV) administration of Dexamethasone (DEXA) potentiates PNB analgesic effect and reduces RP incidence although preventive effective dose remains undetermined. This retrospective analysis evaluates preventive effect of IV DEXA on RP in outpatients undergoing upper limb surgery under axillary block.

Methods: was divided into high (HD >0.1 $mg \cdot kg^{-1}$) or low (LD <0.1 $mg \cdot kg^{-1}$) doses. RP was defined as severe pain (NRS ≥7/10) within 24 hours of PNB resolution. DEXA HD and LD patients were matched with control patients without DEXA (n=55) from a previous randomized controlled study.

Results: Records of 118 DEXA patients were analyzed (DEXA dose ranged from 0.05 to 0.12 $mg \cdot kg^{-1}$). Intraoperative IV DEXA was associated to a significant reduction of the pain felt when PNB wore off as well as to a significant reduction of RP incidence (n=27/118, 23% versus 47% in controls, p=0.002) with no effect related to the dose administered (p=0.053).

Conclusions: Our results support the administration of intraoperative DEXA as a preventive measure to reduce the occurrence of RP.

Introduction

Regional anesthesia offers several advantages in ambulatory setting, including high-quality perioperative analgesia and faster discharge from the hospital.

Peripheral nerve blocks (PNBs) using different techniques [1] are extensively used in orthopedic limb surgeries as they ease the surgical procedure and they improve patient satisfaction [2], particularly in terms of long-lasting postoperative analgesia without systemic drug side effects [1]. However, following PNB resolution, a rapid increase in pain intensity commonly referred to as “Rebound Pain” may occur. The phenomenon is observed within the first 24 to 48 h of the PNB dissipation. Occurring outside of health care setting, it is actually considered as a clinically relevant problem [3,4]. Further, RP is the most frequent factor of dissatisfaction reported by the patients following PNB. The RP phenomenon is frequent as it may affect nearly 40% to 50% of orthopedic patients operated under PNB [2,5,6].

For the aforementioned reasons, the prevention of RP occurrence has become a priority, particularly in ambulatory surgery setting. Several risk factors have been found to be associated with the phenomenon such as younger age, female gender, high catastrophizing mind set, bone surgery and the absence of perioperative administration of dexamethasone [5,6]. Dexamethasone (DEXA), a synthetic corticosteroid, is widely used in anesthesia practice for its well-known perioperative analgesic and antiemetic properties [7]. Moreover, DEXA also serves as an adjuvant to PNB to increase the block duration and the analgesic related effect [8]. PNB prolongation has been

observed after the administration of DEXA by either the perineural or intravenous (IV) route [9]. The literature suggests that 4 mg of DEXA may be the optimal perineural dose to potentiate PNB, whereas the optimal intravenous dose is likely higher but still remains undetermined [10]. However, the intravenous administration should be preferred because perineural use may cause delayed neurotoxicity and the perineural route is still off-label [9]. Several studies have reported a reduction of RP incidence after PNB dissipation when perioperative DEXA was administered by either the perineural [11,12] or intravenous route [5,13]. To date, the dose-related preventive effect of intravenous DEXA on RP has not been evaluated.

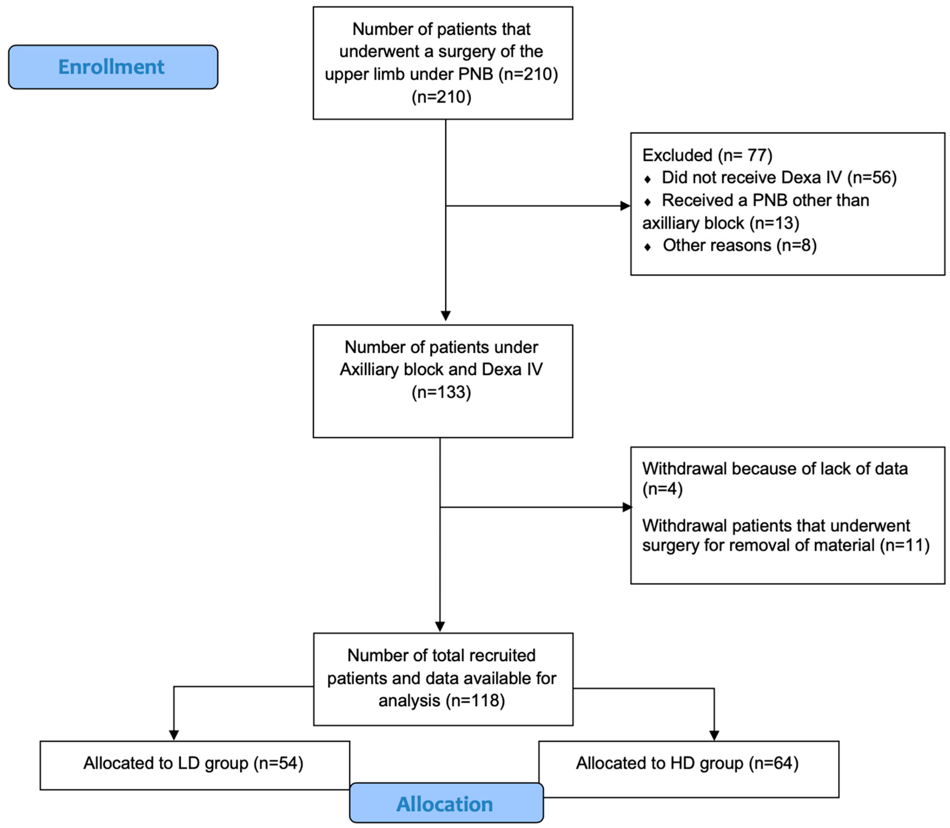
The main objective of this retrospective study was to assess the occurrence of RP when perioperative IV DEXA was administered at analgesic (dose higher than 0.1 $mg \cdot kg^{-1}$) [14] and/or antiemetic doses [7,15] (i.e., doses ranging between 4 and 10 mg) in ambulatory patients undergoing upper limb orthopedic surgery under axillary plexus block. The secondary objective was to evaluate a potential dose-related preventive effect of IV DEXA on the development of RP.

Materials and Methods

This single-center retrospective cohort study was conducted at the Cliniques Universitaires Saint-Luc (Brussels, Belgium). It is a retrospective analysis of data collected prospectively in the context of Quality Reporting in the Out-Patients Unit. The data were collected over a period of 1 year, between January 2021 and February 2022, from patients' files and perioperative questionnaire-based sources.

Recruitment

Ambulatory adult patients (18 to 80 years old) who underwent elective upper limb surgery (elbow and below) under axillary plexus block between January 2021 and February 2022 were included (Fig.4.2). Only patients who had complete perioperative data records were considered. Eligible patients had received an intravenous DEXA dose left to the discretion of the anesthesiologist in charge. Intraoperative IV DEXA was administered either as an antiemetic or as an analgesic adjuvant to the PNB, i.e., IV doses ranging from 4 to 10 mg. All the patients underwent axillary PNB under real-time ultrasound guidance by a trained anesthesiologist. The control group was composed of patients included in a previous prospective study on Rebound Pain, who had not received DEXA [6]. All the patients, in the control group and those included between January 2021 and February 2022, received the same type of PNB, i.e., an axillary plexus block. Each axillary plexus was performed using a 50:50 mixture of ropivacaine (0.5%) and mepivacaine (1%). The reuse of prospective data did not require the consent of the patients concerned for the retrospective analysis by the ethics committee.



PNB: Peripheral Nerve. Block; Dexa IV: Intravenous Dexamethasone; LD: Low dose; HD: High dose. All the patients benefited from the same perioperative analgesic protocol using multimodal analgesia. Patients who had contra-indication to the analgesics used in the perioperative multimodal analgesic protocol (i.e., paracetamol or non-steroidal analgesic use) were not included in the analysis. Patients who received IV DEXA were matched with patients of the control group regarding age, sex and type of surgery (bone or soft tissues surgery) (Table 4.1).

Figure 4.2 - ***Flow Diagram retrospective study. Final sample size 118 patients***

Data Collection

To improve the management of postoperative pain by better focusing on patients at risk of developing severe acute postoperative pain when back home, a set of preoperative questionnaires is commonly proposed to all ambulatory patients including those undergoing regional anesthesia for

ambulatory orthopedic surgery. All the questionnaires are completed on a voluntary basis.

All the patients included in the study had complete perioperative records. Preoperative data collected on day 0 included preoperative pain at rest, pain on movement and pain overnight at the surgical site, using a numerical rating scale (NRS) from 0 to 10 (where 0 = no pain and 10 = worst pain). Preoperative medications, including pain relievers, were also noted. Patients also completed a pre-operative questionnaire that had been developed in 2019 as part of a previous prospective study [6]. The anesthesia team continued to use this questionnaire in their practice to help prevent severe acute postoperative pain at home, mainly related to a Rebound Pain phenomenon.

Patients were therefore asked to answer a series of preoperative questions such as the French version of the Pain Catastrophizing Scale (PCS) questionnaire, which assess negative thoughts related to pain (i.e., rumination, amplification and helplessness) on a scale from 0 to 52 [14]. Patients were classified as high catastrophizers if they scored higher than the 75th percentile.

The French version of the Central Sensitization Inventory (CSI) was used to measure the main somatic and emotional complaints associated with central sensitization. A validated short-form was used as CSI-9 (i.e., 9 questions derived from the original 40 questions, with a cut-off value of 20 on a 0–36 scale) to distinguish patients presenting with a preoperative positive central sensitization [16]. Finally, the presence of a neuropathic component in the preoperative pain at the surgical site was assessed using the “Douleur

Neuropathique 4" (DN4) questionnaire (cutoff value of 4 on a 10-point score) [17].

Before the surgical incision, the effectiveness of the sensory blockade of the axillary plexus was evaluated by a cold test (ether test) in the different territories. Only patients who presented with fully effective axillary PNB were considered for inclusion in the study (Fig.4.2). For various reasons (surgeon's request, patient comfort, PNB failure …), 8 patients who received general anesthesia during the procedure in addition to the axillary plexus were excluded. All the patients were operated upon by two orthopedic surgeons (O.B. and X.L). A standardized optimal perioperative multimodal analgesic treatment was applied to all the patients, including intraoperative administration of paracetamol (1 g) and intraoperative ketorolac (0.5 $mg \cdot kg^{-1}$). In the recovery room, when the postoperative pain score (NRS) was >3/10, intravenous tramadol ($2mg \cdot kg^{-1}$) was administered. Patients were discharged with written recommendations for the use of standard postoperative oral analgesics, i.e., ibuprofen 400 mg/6 h, paracetamol 3 g/24 h and, if necessary, tramadol as a rescue analgesic (1–2 $mg \cdot kg^{-1}$; Maximum 400 mg/day). The patients were also asked to note in a pain diary the time when the axillary block wears off, as well as the intensity of the pain felt (NRS, 0–10) at that time and the analgesics intake. All the patients were contacted by phone call on day 1 at 24 h after surgery (regular telephone call for quality audit purpose) by a hospital nurse. Postoperative pain intensity was questioned, including average and maximal pain on a NRS scale from 0 to 10. The definition of RP was the same we used in our previous study [6], i.e., the same used in the control group. RP was defined as severe pain with a

NRS score ≥ 7/10 within the first 24 h after the termination of the axillary plexus block.

Power Analysis

The sample size was calculated based on the incidence of Rebound Pain. The presence of RP was defined as pain intensity score > 7 (NRS, 0 to 10) reported by the patient after axillary plexus block resolution [6]. Based on values of RP incidence after peripheral nerve block resolution approaching 45% to 50% [5,6] and assuming that the incidence of RP with intravenous DEXA administration would be reduced by half and thereby would approach 25% [18], a minimum of 46 patients was needed in each group to have an alpha value of 0.05 and a power of 0.8.

Data Analysis

For analysis of retrospective data, the intravenous DEXA dose was separated into high (HD; >0.1 $mg \cdot kg^{-1}$) or low (LD; <0.1 $mg \cdot kg^{-1}$) doses. DEXA HD and LD patients were compared to control patients (n = 55) included in a previous randomized controlled trial [6] regarding demographics (age, gender parity and BMI) to ensure adequate matching.

Statistical analysis was performed with SigmaStat 3.5 (Systat Software GmbH, Erkrath, Germany). Results were expressed as proportions, mean ± standard deviation or median value (interquartile range) as specified. According to a Kolmogorov–Smirnov normality test, parametric data between the groups were compared by an unpaired Student *t*-test and

nonparametric data by Mann–Whitney and Kruskal–Wallis Rank Sum tests. Categorical data were compared using the chi-squared test and Fisher exact test using a two-tailed probability. A p-value less than 0.05 was considered to be significant. A backward stepwise regression model ($p < 0.05$ significant) was also be used to test the predictive value of intravenous DEXA prevention on the development of RP.

Results

Between January 2021 and January 2022, 210 patients underwent elective upper limb surgery under axillary plexus block, and intraoperative IV DEXA administration was noticed in 133 of these patients. A total of 118 patients were included in the retrospective analysis (Fig.4.2). As reported in Table 1, these patients were comparable regarding age, sex and type of surgery to the control group where patients did not receive intraoperative DEXA (patients included in a previous prospective randomized study on RP, n = 55) [6]. Intraoperative administration of IV DEXA was associated with a significant reduction of the pain felt when PNB wore off as well as to a significant reduction of RP incidence (23% versus 47%, $p = 0.002$) (Table 4.1). The total duration of PNB however was not influenced by IV DEXA administration at the doses used. The DEXA doses ranged from 0.05 to 0.12 $mg \cdot kg^{-1}$.

Thereafter, for statistical analysis, patients who received IV DEXA were divided into a high-dose DEXA group (DEXA HD, dose > 0.1 $mg \cdot kg^{-1}$, n = 64) and a low-dose DEXA group (DEXA LD, dose < 0.1 $mg \cdot kg^{-1}$, n = 54) as described in Table 4.2. By comparison with the control group (i.e., no DEXA

administration), intraoperative DEXA reduced the occurrence of RP. We observed a dose-related trend which, however, was not significant. Similarly, a DEXA dose-related trend to less pain felt when PNB wore off was noticed by the patients, but it was not statistically significant either.

	Control group (n=55)	DEXA group (n=118)	P value
Age (years)	52 ± 18	45 ± 16	0.428
Sex ratio (female/male) (n)	29/26	78/40	0.298
BMI[2] (kg/m2)	25 (21 – 29)	26 (22 – 29)	0.266
Bone surgery (n)	21 (39%)	64 (40%)	0.854
Tourniquet duration (min)	22 (14 – 38)	21 (12 – 33)	0.742
Preoperative			
Catastrophizing (0-52)	12 (3 – 23)	11 (3 – 22)	0.774
Central sensitization (0-36)	9.0 (6 – 12)	8.5 (4 – 15)	0.449
Preoperative pain			
Average pain (NRS 0-10)	2.0 (0 – 4)	2.0 (0 – 5)	0.403
Maximal pain (NRS 0-10)	4.5 (1 – 8)	5.0 (0 – 7)	0.510
Night pain (NRS 0-10)	0 (0 – 3)	0 (0 – 4.5)	0.764
DN4[3] value (0-10)	3.0 (1 – 4)	2.0 (1 – 4)	0.622
PNB[4] duration			
Total duration (min)	630 (506-795)	640 (410 – 905)	0.892
Pain when PNB wears off (NRS[5] 0-10)	4.5 (2 – 8)	3.3 (1 – 6) *	0.030
Incidence of rebound pain (NRS ≥7/10) (n)	26 (47%)	27 (23%) *	0.002

*[1] Dexamethasone; [2] Body Mass Index; [3] Douleur Neuropathique en 4 Questions; [4] Peripheral Nerve Block; [5] Numerical Rating Scale; * $p < 0.05$.*

Table 4.1 - ***Comparison between control group and DEXA' group****.*

	Control group (n=55)	DEXA LD (n=54)	DEXA HD (n=64)	P value
DEXA dose (mg/kg)	----	0.06 (0.05-0.07)	0.10 (0.10-0.12)	<0.001
PNB duration				
H1-H2[5] (min)	400 (309-541)	292 (195-540)	332 (223-577)	0.092
H2-H3[6] (min)	180 (120-307)	240 (165-300)	205 (79-405)	0.331
Total duration (min)	630 (506-795)	583 (445-825)	661 (402-960)	0.650
Preoperative pain at day 1				
Average pain (NRS[7] 0-10)	25 (1 – 55)	2.0 (1 – 4)	2.0 (0 – 5)	0.408
Maximal pain (NRS 0-10)	4.0 (2-7)	6.0 (2 – 8)	5.0 (1 – 8)	0.564
Pain when PNB wears off (NRS 0-10)	4.5 (2 – 8)	4.0 (1 – 7)	3.0 (1 - 6)	0.053
Incidence of rebound pain (NRS >7/10) (n)	26 (47%)	14 (26%) *	13 (20%) *	0.029

** p < 0.05 with control group: [1] Dexamethasone; [2] Low Dose; [3] High Dose; [4] Peripheral Nerve Block; [5] Time interval between the end of the block (H1) and the onset of paresthesia reported by the subject (H2); [6] Time interval between the onset of paresthesia (H2) and the onset of pain at the surgical site (H3); [7] Numerical Rating Scale.*

Table 4.2 - ***Effect of intraoperative DEXA[1] administration (LD[2] & HD[3]) on PNB outcomes***

At the DEXA doses used, no significant impact on the duration of the axillary block was observed. Postoperative pain scores assessed at 24 h after surgery were not affected by the dose of intraoperative DEXA.

The characteristics of patients who had received IV DEXA and presented with and without RP phenomenon are presented in Table 4.3. The main differences were higher BMI, higher average preoperative pain score at the surgical site, higher catastrophizing score and higher incidence of patients defined as "high catastrophizers" (score > 23/52, i.e., >75th percentile). Bone surgery also was more frequent in RP patients. The dose of IV DEXA did not differ between patients with and without Rebound Pain.

	Rebound Pain (n=27)	No Rebound Pain (n=91)	P value
Age (years)	45 ± 16	51 ± 18	0.073
Sex female (n)	20 (74%)	48 (53%)	0.075
BMI[2] (kg/m2)	28 ± 6*	25 ± 5.5	0.026
Bone surgery (n)	17 (65%) *	31 (34%)	0.013
Tourniquet duration (min)	34 ± 26	24 ± 17	0.121
Preoperative			
Catastrophizing (0-52)	20 (4 – 37) *	9 (2 – 21)	0.017
High catastrophizers (n)	11 (42%) *	14 (16%)	0.007
Central sensitization (0-36)	8.5 (2 – 17)	8.5 (4 – 15)	0.787
Central sensitization positive (n)	4 (16%)	12 (14%)	0.757
Preoperative pain			
Average pain (NRS[3] 0-10)	4.5 (2 – 6) *	2.0 (0 – 4)	0.009
Maximal pain (NRS 0-10)	7.3 (1 – 9)	4.5 (0 – 7)	0.065
Night pain (NRS 0-10)	1 (0 – 6)	0 (0 – 3.8)	0.222
DN4[4] value (0-10)	3.0 (2 – 4.5)	2.0 (1 – 4)	0.135
PNB[5] duration			
Total duration (min)	630 (506-795)	640 (410 – 905)	0.892
Pain when PNB wears off (NRS[5] 0-10)	8.0 (7 – 8.9) *	2.0 (1 – 4)	< 0.001
DEXA dose (mg/kg)	0.08 (0.06 – 0.10)	0.09 (0.06 – 0.10)	0.650

[1] Dexamethasone; [2] Body Mass Index; [3] Numerical Rating Score; [4] Douleur Neuropathique 4 questions; s Peripheral Nerve Block. * $p < 0.05$ with control group

Table 4.3 - **Characteristics of patients with and without Rebound Pain among patients who received intraoperative DEXA [1] (n = 118).**

Discussion

The present results support the intraoperative use of intravenous DEXA (dose 0.05–0.12 mg·kg^{-1}) for the prevention of Rebound Pain after upper limb surgery under axillary plexus block. Regardless the dose of IV DEXA administered, our study showed a significant decrease in RP occurrence (23% vs. 47%; p = 0.002). This finding is in agreement with previous reports [5,13]. However, at the doses we used, a dose-dependent effect of DEXA on the occurrence of RP could not be found.

Several studies have assessed the use of perineural DEXA to increase the duration of sensory nerve block, mostly the interscalene plexus block, and to improve postoperative analgesia after upper limb procedures. These studies have shown a dose-dependent effect with a ceiling effect for doses higher than 4 mg [19,20]. Because the Rebound Pain phenomenon has increased as a subject of interest, some studies have recently evaluated the preventive effect of perineural DEXA. After shoulder surgery, perineural DEXA 5 mg reduced RP occurrence from 83% to 37% [11], and perineural DEXA 8 mg decreased RP from 48.8% to 11% [12]. Despite the effectiveness of perineural DEXA, that route of administration is still considered off-label due to potential neurotoxicity [9].

Intravenous DEXA also potentiates PNB and increases the duration of the sensory block. Equipotent doses between perineural and IV routes have been questioned. From published meta-analyses, perineural DEXA seems more effective to prolong PNB analgesia, but no greater difference is observed

between both routes when DEXA doses of 8 mg and higher are used [21]. Regarding lower doses of IV DEXA, Desmet and colleagues found a dose-dependent effect on PNB duration after shoulder surgery but only a significant effect for doses higher than 2.5 mg DEXA (i.e., 0.03 mg·kg^{-1}) [22]. Studies assessing the preventive effect of IV DEXA on RP incidence are still scarce. First, a large retrospective cohort study [5] which included different types of blocks in both upper and lower limbs procedures reported a beneficial effect for an average DEXA dose of 6 mg (range: 4–20 mg). Second, a prospective randomized study including 51 adult patients scheduled for hand surgery found a reduction of RP within the first postoperative 36 h from 50% in the placebo group to 9% in the 16 mg (i.e., around 0.23 mg·kg^{-1}) IV DEXA group [13]. To the best of our knowledge, the present study is the first to assess a dose-related preventive effect of low IV DEXA doses on RP after axillary PNB in ambulatory patients.

According to the aforementioned findings, a dose-related preventive effect of IV DEXA on RP might be questioned. However, if we compare the incidence of RP in our DEXA-LD (<0.1 mg·kg^{-1}) with that of RP in Holmberg's study (0.23 mg·kg^{-1}), the difference is not statistically significant (14/54 [26%] vs. 2/23 [9%], p = 0.13, Fisher exact two-tailed). Similarly, if we compare RP incidence in our DEXA-HD group (20%) with that in Holmberg's study (9%), there is no statistically significant difference (p = 0.33) [13]. A ceiling effect in DEXA RP preventive effect should also be taken into account. Based on the fact that perineural and intravenous DEXA doses > 8 mg are equipotent to prolong PNB duration and analgesic effect [21], no significant difference in RP incidence could be found regarding IV DEXA-HD in our patients (0.10–0.12 mg·kg^{-1}: 13/64 = 20%) versus IV DEXA 16 mg (0.23 mg·kg^{-1}:

2/23 = 9%) [13] versus perineural DEXA 8 mg (7/63 = 11%) [12]. These results further question the mechanisms underlying the DEXA preventive effect on RP.

Prolonged nerve block, hence, a smoother recovery of nociceptive sensations, has been proposed as a mechanism to reduce RP [13]. At the doses used in our patients, we did not observe an increase in the duration of PNB what is in opposition with previous studies. In example, IV DEXA 16 mg significantly prolonged the axillary block analgesia [13], and Desmet reported a time extension to the first analgesic request after PNB at an IV DEXA dose as low as 0.03 $mg \cdot kg^{-1}$ [22]. In contrast to the aforementioned studies, our study was retrospective and powered to assess the Rebound Pain incidence and not the PNB duration. It is worth noting that the sensory block duration may not affect the RP phenomenon as previously underlined [5].

Two studies in healthy volunteers [23,24] using a moderate dose of IV DEXA (4 mg) did not observe a prolongation of nerve block duration but pointed out the fact that benefits observed in patients probably rely on the anti-inflammatory effect of IV DEXA [25]. A previous meta-analysis about intravenous DEXA has suggested that only doses higher than 0.1 $mg \cdot kg^{-1}$ demonstrate analgesic effects which are not dose-related [15]. Our results show a reduction of both pains felt when PNB wears off and RP incidence at IV DEXA doses is lower than 0.1 $mg \cdot kg^{-1}$, independent of the axillary block duration. The individual sensitivity to the anti-inflammatory effect of glucocorticoids is variable as observed for the response to other analgesics with anti-inflammatory properties. Among the risk factors of RP, bone

surgery and high catastrophizing score are well known [5,6]. Both risk factors interact with inflammatory processes that may be involved in RP.

Bone surgery leads to the local release of pro-inflammatory cytokines, such as interleukin 6 (IL-6), which activate and sensitize sensory nerves, leading to an amplified pain signal [26]. More, these pro-inflammatory mechanisms may be exacerbated in some patients, enhancing postoperative pain and hyperalgesia [27]. For example, a higher level of catastrophizing is associated with greater reactivity of inflammatory mediators (e.g., IL-6) [28] which suggests that cognitive and emotional responses during the experience of pain may shape the pro-inflammatory responses of the immune system to noxious stimulation. The involvement of inflammatory mechanisms in RP may explain the predisposition to RP in patients with a high catastrophization score. Therefore, by reducing the inflammatory cascade, DEXA may help to reduce hyperalgesia when the PNB wears off.

There are some limitations of this study. First, its retrospective nature involving a single center. Additionally, data regarding DEXA administration and data regarding the control group were collected in different cohorts. Second, the follow-up of DEXA patients was limited to the first 24 h, which could have contributed to the loss of additional data. In the literature, late RP, i.e., at 36 and even 48 h, is reported. Finally, the doses of IV DEXA used were left to the discretion of the anesthesiologists in charge of the patients, which may have led to possible distribution bias due to common practices and habits.

It is worth noting that no adverse effects in relation to the administration of DEXA were found in the patients' files. The relatively low doses of DEXA used in our study may actually have contributed to the absence of glycemic disorders in the patients [29]. Similarly, we did not record any cases of perineal irritation in the patients included in our study which is probably due to a slow administration of DEXA (a common practice within our team of anesthetists) [30].

In conclusion, our results support the administration of intraoperative IV DEXA as a preventive measure to reduce the occurrence of RP.

To our knowledge, this study is the first dedicated to investigating the dose-dependent effect of intraoperative DEXA (low doses used to prevent PONV and to improve postoperative analgesia) in the prevention of RP. We found a preventive effect on RP including at very low doses (<0.1 $mg \cdot kg^{-1}$) and independent of the PNB duration. A comparison with the existing literature may be in favor of an IV DEXA ceiling effect on RP prevention which contrasts with the IV DEXA dose-related effect on sensory block duration. Further prospective studies should confirm the present findings and investigate the mechanisms underlying the IV DEXA preventive effect on Rebound Pain.

Key messages (RETRODEXA)

- **Intravenous dexamethasone**: reduced RP occurrence regardless of dose
- **Dose effect**: no significant difference between analyzed doses
- **Residual RP**: persistence of RP cases despite intravenous dexamethasone administration

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4.4. Additional analysis

The results of the RETRODEXA study show that a non-negligible proportion of patients (around 23%) still develop RP despite dexamethasone administration, suggesting the existence of less responsive phenotypes. In this context, and given the already established role of pain catastrophizing as a risk factor for RP, we conducted a complementary analysis of this cohort to assess the impact of this psychological parameter on dexamethasone efficacy.

Among the 228 patients who underwent upper-limb surgery under axillary plexus block, the effect of dexamethasone was analysed according to the level of preoperative catastrophizing, classified as low pain catastrophizers (LPC) or high pain catastrophizers (HPC, catastrophizing score >75th percentile). Results showed that RP was significantly more frequent among high catastrophizers (53% vs 23%, $p < 0.001$) (Table 4.4). A low dose of dexamethasone reduced both block-offset pain and RP incidence only in the LPC group but was associated with a reduction in mean day-one pain in both groups.

	HPC DEXA n=28	HPC no DEXA n=30	LPC DEXA n=90	LPC no DEXA n=80
Pain catastrophizing score (0-52)	30 (24-38)	29 (24-37)	6 (1-15)	7 (1-14)
Pain at block end (NRS 0-10)	4 (1-7)	7 (4.5-9)	3 (1-5)	5 (2.5-8)*
RP (NRS ≥7/10) (n)	11 (39%)	20 (67%)	15 (17%)	24 (30%)*
Day1 average pain (NRS 0-10)	1 (0-5)	4 (2-7)*	0 (0-2)	3 (1-5)*
Day1 maximal pain (NRS 0-10)	4 (1-7)	5 (3-7)	3 (1-5)	4 (2-7)*

*p value <0.05 between DEXA and no DEXA in same group

Table 4.4 - **Comparative analysis of dexamethasone effect according to catastrophizing status: low (LPC) versus high (HPC, score > 75th percentile)**

This analysis, presented at the ESRA 2023 congress (*Effect of Intravenous Dexamethasone on Rebound Pain after Axillary Plexus Block in High versus Low Pain Responders*), suggests that the response to dexamethasone may be modulated by individual factors, particularly psychological ones. These findings underscore the need to better identify the determinants influencing dexamethasone efficacy in preventing Rebound Pain. Accordingly, the subsequent VEDR study was specifically designed within this framework to generate prospective data and provide robust clinical evidence for optimising preventive strategies and tailoring protocols to individual patient profiles.

*4.5. Focus on dexamethasone: The VEDR (*Variation in the Efficacy of Dexamethasone for the Prevention of Rebound Pain) study

"Factors associated with a reduction in the preventive effect of intravenous dexamethasone on Rebound Pain after axillary brachial plexus block"

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Background: Rebound Pain after regional anesthesia remains a significant clinical problem. Intravenous dexamethasone is commonly used as an adjuvant to prevent Rebound Pain although its effectiveness varies among patients. We aimed to identify phenotypic and biological factors influencing glucocorticoid sensitivity contributing to dexamethasone resistance in the prevention of Rebound Pain.

Methods: Patients undergoing ambulatory upper limb surgery with an axillary brachial plexus block were enrolled prospectively to receive dexamethasone (0.1 mg kg− 1 i.v.) before surgery. Preoperative factors analyzed encompassed clinical aspects (central sensitivity, anxiety, and pain scores) and biological parameters (salivary cortisol, annexin-A1, and blood inflammatory markers). Postoperative outcomes comprised Rebound Pain incidence (numerical rating scale >7 within the first 24 h) and persistent pain at 3 months.

Results: Of the 104 patients included, 36 (34.6%) developed Rebound Pain. Preoperative nocturnal awakening pain (odds ratio [OR]=3.09, P=0.03), severe anxiety (OR=3.54, P=0.01), high catastrophizing score (OR=4.14, P=0.01), and low salivary cortisol levels (<1147 $pg \cdot ml^{-1}$ (OR=3.33, P=0.02) were associated with an increased risk of Rebound Pain. Persistent pain at 3 months (27%) was associated with the presence of postoperative Rebound Pain (P=0.04).

Conclusions: Preoperative nocturnal pain, severe anxiety, high catastrophizing, and low salivary cortisol levels are factors that might reduce the efficacy of dexamethasone in preventing Rebound Pain. These findings support the development of personalized preventive strategies.

Introduction

Nearly half of patients undergoing surgery with regional anesthesia, particularly with peripheral nerve blocks (PNBs), experience Rebound Pain (RP), defined as a sudden and intense pain surge occurring 12–24 h after block resolution [1]. With the growing use of regional techniques in ambulatory settings, RP prevention has become both a clinical and socioeconomic priority, given its association with patient dissatisfaction, increased suffering, and unplanned healthcare utilization [2,3]. Known risk factors include female sex, younger age, bone surgery, and the absence of perioperative dexamethasone [1].

Dexamethasone, a long-acting glucocorticoid, is widely used in anesthesia for its analgesic, antiemetic, and anti-inflammatory properties. It prolongs the duration of PNB-induced analgesia, delays the first analgesic request, and enhances block duration [4,5]. Intravenous dexamethasone currently appears to be the most effective preventive strategy against RP, with efficacy supported by randomized trials and retrospective studies [1,6–9]. A recent systematic review estimated the number needed to treat (NNT) at 2.8 [8]. However, 23–42% of patients still develop RP despite dexamethasone, underlining the existence of interindividual variability in treatment response [6,8,10].

This variability may be explained by differences in glucocorticoid sensitivity. Chronic stress, for instance, promotes glucocorticoid resistance by altering hypothalamic–pituitary–adrenal (HPA) axis regulation, sometimes resulting

in hypocortisolism [11–16]. Chronic inflammatory conditions, such as rheumatoid arthritis, can similarly reduce glucocorticoid sensitivity and limit the anti-inflammatory efficacy of glucocorticoids [17,18].

Annexin-A1, formerly known as lipocortin, plays a key role in mediating the anti-inflammatory actions of glucocorticoids. It contributes to feedback inhibition of ACTH release at the pituitary level, modulates the innate immune response, and amplifies glucocorticoid anti-inflammatory effects [18,21]. Importantly, annexin-A1 is also measurable in saliva, where its secretion correlates with free cortisol, thus providing a non-invasive biomarker of glucocorticoid sensitivity [19,20].

In this context, and in line with the principles of personalized and stratified medicine, this prospective study seeks to identify individual predictors of dexamethasone effectiveness in RP prevention after axillary plexus block, focusing on both clinical parameters (preoperative anxiety and pain intensity) and biological markers (salivary cortisol and annexin-A1).

Methods

This was a single-center prospective study conducted at Cliniques Universitaires St. Luc (Brussels, Belgium) adhering to the ethical principles of the Helsinki Declaration. The protocol was approved by the local ethical committee (ref. 2022/28SEP/ 358) and was registered on ClinicalTrials.gov before patient recruitment (NCT05763433).

Recruitment

Outpatients aged 18-75 yr undergoing elective upper limb surgery (at or distal to the elbow) under single-shot axillary brachial plexus block were included between April 2023 and April 2024 (Supplementary material). Patients provided written informed consent during the preoperative visit.

Exclusion criteria were patient refusal, contraindications to intraoperative dexamethasone administration or postoperative analgesic use (nonsteroidal anti-inflammatory drugs [NSAIDs], paracetamol), pregnancy, diabetes mellitus, chronic corticosteroid intake, and inability to complete questionnaires. A qualified anesthetist performed ultrasound-guided blocks, injecting mepivacaine 0.5% (4-5 $mg \cdot kg^{-1}$). Dexamethasone (0.1 $mg \cdot kg^{-1}$ i.v.; maximum 10 mg) was administered after the block and before surgical incision. The need for surgical supplementation of the axillary brachial plexus block or administration of systemic drugs such as sedatives, anxiolytics, or hypnotics was considered an exclusion criterion.

Data collection

On the day of surgery, baseline pain was assessed using a numeric rating scale (NRS; 0 = no pain, 10 = worst pain imaginable). Patients were also questioned about recurrent preoperative nocturnal pain in the limb scheduled for surgery, as well as regular medication intake, including analgesics.

Psychological and sensory assessments included the French version of the Pain Catastrophizing Scale (PCS; 13 items, total score 0–52), used to evaluate

negative pain-related thoughts. A PCS score >18 (above the 75th percentile) was considered indicative of high catastrophizing [22]. Preoperative anxiety was measured using the validated French version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS; 6–30), which explores anxiety (four items, with scores >11 indicating severe anxiety) and information-seeking behaviour (two items, with scores >8 reflecting high anxiety linked to information need) [23] (Fig 4.3).

Original items	French items
1. I am worried about anaesthesia	Je suis inquiet à propos de mon anesthésie
2. The anaesthesia is constantly on my mind	Je pense continuellement à mon anesthésie
3. I would like to know as much as possible about anaesthesia	Je désire savoir tout ce qui est possible à propos de mon anesthésie
4. I am worried about the procedure	Je suis inquiet(e) à propos de mon opération
5. The procedure is constantly on my mind	Je pense continuellement à mon opération
6. I would like to know as much as possible about the procedure	Je désire savoir tout ce qui est possible à propos de mon opération

*From Maurice-Szamburski A, Loundou A, Capdevila X, Bruder N, Auquier P. Validation of the French version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS). Health Quality Life Outcomes 2013; **11**: 166.*

*Figure 4.3 - **The Amsterdam Preoperative Anxiety and Information Scale (APAIS)***

Central sensitization was evaluated with the CSI-9 (short version of the Central Sensitization Inventory), a 9-item questionnaire (0–36 scale), with a score >20 indicating central sensitization [24]. Neuropathic pain features were assessed using the Douleur Neuropathique 4 (DN4) questionnaire, with a cut-off score ≥4/10 [25].

In addition, a preoperative venous blood sample was obtained to measure high-sensitivity C-reactive protein (hs-CRP) and the neutrophil-to-lymphocyte ratio (NLR) as systemic inflammatory markers.

The quality of the axillary brachial plexus block was confirmed before incision by cold testing across sensory territories. All surgical procedures were performed by the same two orthopaedic surgeons (OB and XL) under axillary brachial plexus block alone.

Postoperative care

Postoperative pain management was standardized. In the recovery room, all patients received an oral dose of ibuprofen and paracetamol. If the postoperative pain score (NRS) exceeded 4/10, the patient received 2 $mg \cdot kg^{-1}$ of tramadol i.v. Patients were given instructions for managing pain after discharge: 400 mg ibuprofen every 6 h, up to 3 g of paracetamol per day, and oral tramadol as needed.

All patients were contacted by phone at 1, 4, and 30 days and at 3 months after surgery by a research nurse. During each call, postoperative pain intensity was assessed, including average and maximum daily pain and nocturnal pain intensity (NRS, 0-10). Rebound Pain was defined as initial mild pain <4/10 when the patient left the recovery room, progressing to severe pain >7/10 (NRS, 0-10) occurring within the first hours after resolution of the axillary brachial plexus block, typically 12 to 24 h after the procedure. The Rebound Pain threshold was based on two recent prospective studies focusing

on Rebound Pain in upper limb surgeries under axillary brachial plexus block [7,26].

Preoperative saliva analysis of annexin-A1 and cortisol

For each patient, whole saliva was collected between 08:00 and 11:00 using a standard Salivette tube (Sarstedt, Lower Saxony, Germany) following the manufacturer's instructions. After collection, the saliva sample was centrifuged and stored at − 80◦C until analysis.

Annexin-A1 and cortisol levels were measured in saliva samples using the InvitrogenTM Human ANXA-1 ELISA Kit and the Human Cortisol ELISA Kit (Thermo Fisher Scientific, Waltham, MA, USA). The analyses were performed according to the manufacturer's protocols without modification. Enzyme-linked immunosorbent assay (ELISA) data were analyzed using a microplate reader (absorbance at 450 nm) and curve-fitting software to generate standard curves for annexin-A1 and cortisol.

Given the variability in salivary cortisol thresholds reported in the literature based on laboratory standards and detection methods, we selected a normal range of 1150-4160 $pg \cdot ml^{-1}$ (25th-75th percentile). For annexin-A1, in the absence of precise data in the literature, the analysis focused on trends and correlations without arbitrary thresholds, to optimize statistical sensitivity.

Statistical analyses and power analysis

Statistical analysis was performed using IBM SPSS Statistics (version 29.0.1.0; Armonk, NY, USA), and results are presented as proportions and means (SD). Parametric data were compared using the Student *t*-test, whereas nonparametric data were analyzed using the Mann-Whitney test. Categorical variables were assessed using $\chi 2$ test or Fisher's exact test. A *P*-value <0.05 was considered statistically significant. A univariate logistic regression model was used to assess the association between Rebound Pain and preoperative risk factors, with inclusion criteria of a $P<0.1$ in $\chi 2$ or Mann-Whitney tests.

Considering an observed proportion of 23% of patients experiencing Rebound Pain, we estimated a medium effect size for logistic regression with five predictive variables.6 To achieve a significance level of 0.05 and a power of 0.80, a minimum of 91 participants was required for inclusion in the study.

Results

Of the 138 eligible patients scheduled for upper limb surgery under peripheral nerve block, data from 104 participants were analyzed (Fig.4.4). Participant characteristics are reported in Table 4.5.

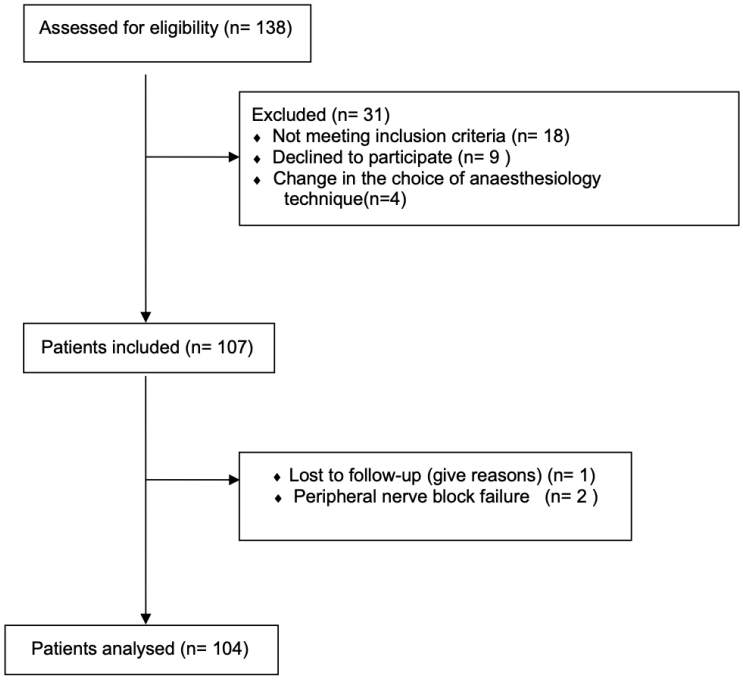

Figure 4.4 - ***Flow Diagram, Prospective study. Final sample size 104 patients***

	n=104
Sex (female) (*n*)	59 (56.7%)
Age (yr)	49.6 (20-74)
Rebound pain (*n*)	36 (34.6%)
Bone surgery	62 (59.6%)
CSI-9 score (0–36)	20.5 (7)
Preoperative APAIS score (6–30)	12.6 (6.1)
PCS score (0–52)	13.2 (11.6)
Preoperative NTAP* (*n*)	13 (12.5%)
BMI score (kg m^{-2})	25.5 (4.4)
Preoperative hs-CRP (mg L^{-1})	5.5 (23.7)
Preoperative NLR score	2.3 (1.0)
Salivary annexin-A1 (ng ml^{-1})	71.4 (45.4–108.2)
Salivary cortisol (pg ml^{-1})	2270 (1150–4160)

Bone surgery: including fractures and trapeziectomies, excluding any soft tissue surgery, cyst excision, and tendon interventions. The absolute difference in salivary annexin-A1 levels between the Rebound Pain+ and Rebound Pain- groups was 29.5 ng ml 1 (-41.3% of the overall mean). APAIS, Amsterdam Preoperative Anxiety and Information Scale; GSI-9, Central Sensitization Inventory, nine items; hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PCS, Pain Catastrophizing Scale; preoperative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment.
NTAP: Night-time awakening pain.

Table 4.5 - ***Participant characteristics. Results are expressed as mean (standard deviation) unless otherwise indicated (median [25th-75th percentile]).***

Thirty-six participants (34.6%) developed Rebound Pain. Preoperative night-time awakening pain (*P*=0.01), severe anxiety (*P*=0.02), and low salivary cortisol levels (<1150 pg·ml⁻¹, *P*=0.02) were associated with the occurrence of Rebound Pain (Table 2). No significant relationship was found with hs-CRP levels or the NLR ratio. Among participants with low salivary cortisol (<1150 pg·ml⁻¹), nine (64%) developed Rebound Pain, whereas five (36%) did not (*P*=0.02) (Table 4.6).

Preoperative factor	Rebound pain+ with factor (%)	Rebound pain+ without factor (%)	χ^2 value	P-value
Sex (female)	38.9	28. 8	1.15	0.28
Bone surgery	38.7	28.5	1.14	0.28
Positive central sensitisationCSI-9 score ≥20	38.4	30.7	0.68	0.40
Severe preoperative anxietyAPAIS score	50	27.1	5.50	0.02*
High catastrophising scorePCS score >18	54.1	29.1	3.62	0.06
BMI >30 kg m^{-2}	33.3	34.8	0.16	0.90
hs-CRP >3 (mg L^{-1})	42.8	31.5	1.10	0.20
NLR score >2.5	25	38.1	1.50	0.20
Preoperative NTAP	53.5	27.6	6.08	0.01*
Salivary cortisol <1147 (pg ml^{-1})	52	29	6.10	0.02*
Salivary cortisol >4160 (pg ml^{-1})	40.7	32.4	0.61	0.42
DN4 score >4	36.8	34.5	0.37	0.80

Bone surgery: including fractures and trapeziectomies, excluding any soft tissue surgery, cyst excision, and tendon interventions. Severe preoperative anxiety is an anxiety score >10, an information need score >8, or both on the APAIS. APAIS, Amsterdam Preoperative Anxiety and Information Scale; CSI-9, Central Sensitization Inventory, nine items; DN4, Douleur Neuro-pathique 4 (neuropathic pain score); hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PCS, Pain Catastrophizing Scale; preoperative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment.

**P<0.05.*

Table 4.6 - ***Impact of preoperative factors on Rebound Pain (Rebound Pain+): rates with and without the presence of the preoperative factor.***

The Mann-Whitney test revealed no statistically significant correlation between preoperative annexin-A1 levels and Rebound Pain occurrence (P=0.06). The boxplots (Fig. 4.5 and 4.6) show a lower median and reduced dispersion of annexin-A1 and cortisol levels in the Rebound Pain+ group compared with the Rebound Pain− group. Factors showing a significant relationship with Rebound Pain occurrence (P<0.05) were included in the regression analysis (Table 4.7).

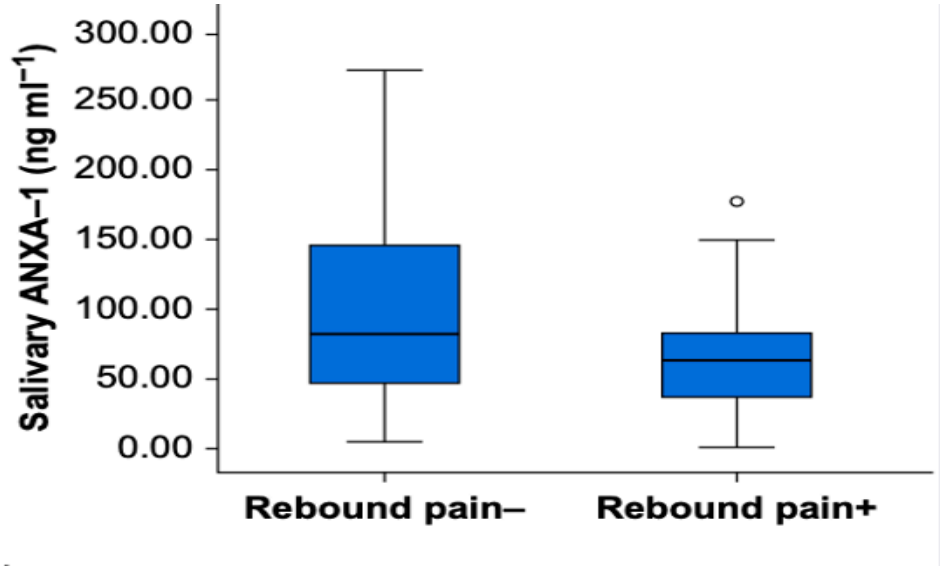

Figure 4.5 - ***Distribution of preoperative salivary annexin-A1 concentrations in patients with (+) and without (-) Rebound Pain***.

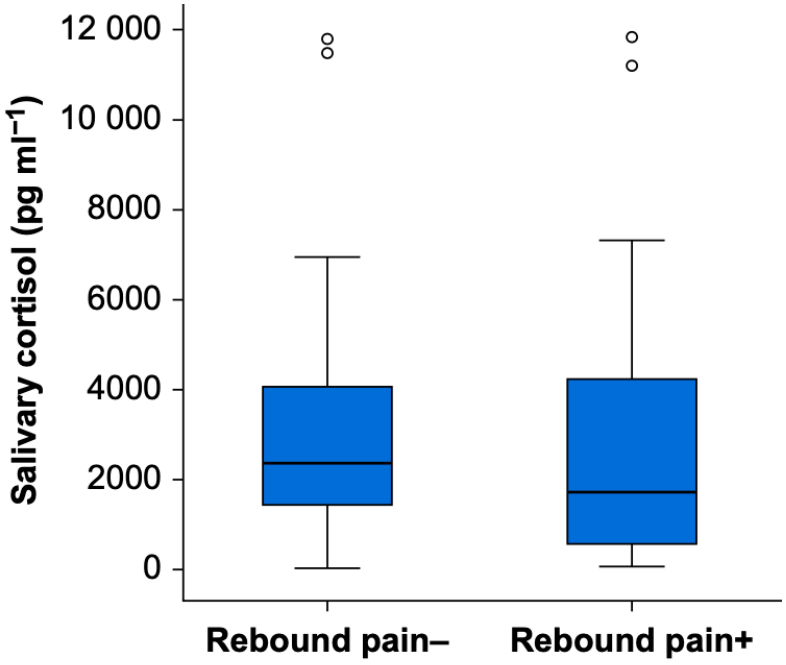

Figure 4.6 - ***Distribution of preoperative salivary cortisol concentrations in patients with (+) and without (-) Rebound Pain***.

	B	OR	95% CI	P-value
Preoperative NTAP	1.106	3.02	1.23–7.41	0.02*
High catastrophisers (PCS score >18)	0.829	2.29	0.90–5.82	0.08
Severe preoperative anxiety	1.335	2.68	1.14–6.31	0.02*
Low salivary cortisol (<1150 pg ml^{-1})	1.09	2.97	1.19–7.41	0.02*
Salivary annexin-A1 concentration (ng ml^{-1})	−0.01	0.99	0.98–0.99	0.03*

*Severe preoperative anxiety is an anxiety score >10, an information need score>8, or both on the Amsterdam Preoperative Anxiety and Information Scale. The regression coefficient for annexin-A1 levels was negative in univariate analysis. Linear regression analysis reveals a significant interaction between salivary annexin-A1 and cortisol (B=0.06, P<0.001), with no excessive collinearity (variance inflation factor=1.00). B, Logistic regression coefficient; CI, confidence interval; OR, odds ratio; pre-operative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment; PCS, Pain Catastrophizing Scale. *P<0.05.*

Table 4.7 - ***Univariate logistic regression analysis of Rebound Pain occurrence based on preoperative factors.***

Multivariable analysis identified severe anxiety (odds ratio [OR]=3.54, *P*=0.01), night-time awakening pain (OR=3.09, *P*=0.03), low salivary cortisol (OR=3.33, *P*=0.02), and high catastrophizing score (OR=4.14, *P*=0.01) as significant predictors of Rebound Pain (Table 4.8).

Finally, at 3 months post-surgery, 28 participants (27%) reported chronic pain (NRS >4/10). Among them, 14 belonged to the Rebound Pain+ group (14/36,

38.9%), whereas 14 (14/68, 20.6%) were from the Rebound Pain group (*P*=0.04).

	Adjusted B	Adjusted OR	95% CI	P-value
Preoperative NTAP	1.13	3.09	1.13–7.65	0.03*
High catastrophisers (PCS score >18)	1.42	4.14	1.32–12.99	0.01*
Severe preoperative anxiety	1.26	3.54	1.31–9.55	0.01*
Salivary cortisol (<1150 pg ml^{-1})	1.20	3.33	1.17–9.50	0.02*
Salivary annexin-A1 concentration (ng ml^{-1})	−0.01	0.99	0.98–0.99	0.02*

Severe preoperative anxiety is an anxiety score > 10, an information need score >8, or both on the Amsterdam Preoperative Anxiety and Information Scale. The regression coefficient for annexin-A1 levels was negative in multivariate analysis. Linear regression analysis reveals a significant interaction between salivary annexin-A1 and cortisol (B 0.06. P<0.001). with no excessive collinearity (variance inflation factor=1.00). B, logistic regression coefficient; CI, confidence interval; OR, odds ratio; preoperative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment; PCS, Pain Catastrophizing Scale.
**P<0.05.*

Table 4.8 - ***Significant risk factors associated with the occurrence of Rebound Pain by multivariate logistic regression.***

Discussion

Although all participants in our study received intraoperative dexamethasone (0.1 $mg \cdot kg^{-1}$ i.v.), 35% still exhibited Rebound Pain when their axillary brachial plexus block resolved. Three significant risk factors emerged from the screening of preoperative clinical parameters: high anxiety scores, high catastrophizing score, and nocturnal awakening pain. Additionally, participants with low salivary cortisol and annexin-A1 levels were more likely to experience Rebound Pain when their block resolved despite dexamethasone administration.

Our findings are of clinical interest for two principal reasons. Firstly, the results highlight the lack of preventive effect of dexamethasone against Rebound Pain in some patients, with the phenotypes identified here. Secondly, our findings contribute to a better understanding of Rebound Pain mechanisms, which remain poorly understood.

Preoperative anxiety levels were assessed in our patients using two tools: the APAIS (evaluating acute preoperative anxiety) and the PCS (measuring anxiety related to pain perception). High scores on the PCS and the APAIS questionnaire were predictive of reduced dexamethasone efficacy in preventing Rebound Pain. Thus, high levels of preoperative anxiety, including pain perception-related anxiety, that is, catastrophizing, might be a reliable indicator of reduced glucocorticoid responsiveness. These conditions, often underestimated or overlooked, ideally require time and sometimes specialized follow-up (psychologist, psychiatrist, etc.) for optimal therapeutic management. APAIS was a particularly relevant choice for the questionnaire used to measure preoperative anxiety, not only because of its simplicity and easy clinical use, but also because it specifically evaluates preoperative anxiety related to stress in a surgical context. Other anxiety scales, such as the State–Trait Anxiety Inventory (STAI) score, have been validated in various clinical contexts [27]. The STAI provides a comprehensive assessment of anxiety, encompassing both current emotional responses and chronic vulnerability to anxiety. However, use of STAI requires more time for completion and interpretation, posing challenges in the clinical setting [27].

Salivary cortisol measurements were included to assess the impact of factors such as chronic stress or chronic pro-inflammatory conditions on glucocorticoid resistance [16,28,29]. Although stress typically elevates cortisol levels, recent research has identified a paradoxical effect where chronic stress (e.g. in post-traumatic stress disorder or burnout) leads to reduced cortisol secretion (i.e., hypocortisolism) owing to the hypothalamic–pituitary–adrenal axis dysregulation. Univariate and multivariate analyses showed an association between low salivary cortisol levels (<1150 $pg \cdot ml^{-1}$) and increased Rebound Pain risk despite dexamethasone administration.

Persistent pro-inflammatory conditions can induce glucocorticoid resistance through several mechanisms such as reduced histone deacetylase-2 expression and elevated macrophage migration inhibitory factor levels [17]. In our study, we assessed pro-inflammatory status both clinically and biologically. Classical markers such as hs-CRP and the NLR score showed no significant correlation with dexamethasone response, which might be explained by the lack of specificity of systemic markers to reflect the complexity of perioperative inflammation, particularly the localized inflammatory reaction at the surgical site [30,31]. Similarly, obesity, associated with low-grade chronic inflammation, did not appear to be a risk factor for reduced dexamethasone preventive effect in our patients, which is consistent with a similar study that failed to demonstrate reduced glucocorticoid sensitivity in obese patients [32]. In contrast, preoperative nocturnal awakening pain, caused by localized inflammation at the future surgical site, was associated with reduced treatment efficacy. Nocturnal pain, potentially related to night-time cortisol decline, could reactivate inflammatory processes, worsening pain and disrupting sleep [33].

Fowkes and colleagues [19] reported a positive correlation between salivary cortisol and annexin-A1 levels. In our study, low annexin-A1 and cortisol levels were associated with reduced dexamethasone efficacy in preventing Rebound Pain. Annexin-A1 is a key marker of glucocorticoid sensitivity, acting as a mediator of anti-inflammatory effects by reducing neutrophil migration [19,34,35]. Low cortisol levels have been linked to downregulation of dexamethasone sensitivity in leucocytes, that is, reduced inhibition of pro-inflammatory cytokine release [13]. Because annexin-A1 is a marker of glucocorticoid sensitivity, low levels might reduce the efficacy of both endogenous and exogenously administered glucocorticoid [19]. In individuals with low annexin-A1 levels, increased neutrophil infiltration associated with enhanced release of pro-inflammatory mediators at the surgical site could exacerbate local inflammation, increasing the risk of Rebound Pain despite dexamethasone administration.

Among the mechanisms underlying the Rebound Pain phenomenon, an exacerbated local inflammatory reaction at the surgical site, facilitated by vasodilation induced by the peripheral nerve block, has been proposed [2,36]. I.V. dexamethasone administration reduces the incidence of Rebound Pain (15% vs 44%) and is also associated with decreased postoperative release of pro-inflammatory cytokines (interleukin [IL]-1β, IL-6, and tumor necrosis factor-α [TNF-α]) [37]. Although both i.v. and perineural dexamethasone reduce Rebound Pain, i.v. dexamethasone appears to be more effective [8,9]. In a study comparing the preventive effect of 5 mg dexamethasone administered intravenously or perineurally during interscalene plexus block, the duration of analgesia and the onset of Rebound Pain were longer in the perineural group, whereas the incidence of Rebound Pain was lower in the

i.v. dexamethasone group (20% vs 44%) [38]. These findings suggest a more potent anti-inflammatory effect of i.v. dexamethasone compared with that of perineural dexamethasone, which is likely attributable to secondary systemic drug absorption. Accordingly, in the large retrospective study of Barry and colleagues [1], duration of sensory block was not associated with the incidence or severity of Rebound Pain.

Finally, our results suggest an association between postoperative Rebound Pain and the persistence of pain at 3 months after surgery. Although the study was not designed to explore the relationship between Rebound Pain and chronic postsurgical pain, the findings underline the link between acute postoperative pain intensity and a potential progression to chronic pain [39]. Therefore, optimizing Rebound Pain prevention could help reduce the risk of chronic postoperative pain, particularly in the setting of orthopaedic procedures where more than half of patients report long-lasting pain beyond 3 months [40].

In personalized medicine, identifying predictive factors of therapeutic effectiveness can guide clinical management. At-risk patients could benefit from enhanced monitoring, improved education on analgesia, and customized analgesic strategies. Increasing the dexamethasone dose could also be considered for patients with specific preoperative risk factors. Although our results suggest that low cortisol levels reduce dexamethasone efficacy, a higher dose might paradoxically benefit high-risk patients. Indeed, one study reported a lower incidence of Rebound Pain (9%) in a similar setting with a dexamethasone dose of 16 mg, twice the dose used in our study (34.6% Rebound Pain) [7]. Given the potential side-effects of glucocorticoids (e.g.

hyperglycemia, infection risks), targeting patients who could benefit from higher doses would be appropriate [5]. Future studies should assess the potential benefits of higher dexamethasone doses to prevent Rebound Pain in patients with high preoperative anxiety, high catastrophizing, and severe nocturnal pain.

Strengths and limitations

This study is the first to explore the variability in dexamethasone efficacy for Rebound Pain prevention. Several methodological limitations must be acknowledged. Saliva samples were collected in the morning without standardized timing, which could introduce bias due to diurnal cortisol variation. Additionally, we assessed baseline cortisol levels using a single measurement, without repeated measures or stress assessments, and we did not perform stress or ACTH challenge. Our results suggest that annexin-A1 could be a useful biomarker for predicting the effectiveness of dexamethasone in preventing Rebound Pain. However, saliva analysis requires specialized expertise and infrastructure, limiting its regular clinical use. Moreover, we did not assess blood pro-inflammatory cytokine release in patients with or without Rebound Pain, nor did we correlate it with salivary annexin-A1 levels. Finally, the absence of a control group without dexamethasone administration could limit our findings on dexamethasone efficacy in subgroup analysis.

Conclusion

This study highlights the variability in the efficacy of iv. dexamethasone in preventing Rebound Pain. Limited efficacy was related to specific individual preoperative factors such as severe anxiety, high catastrophizing, nocturnal pain, and reduced salivary cortisol levels. These results also support the hypothesis that the extent of the local inflammation caused by surgical trauma and exacerbated by peripheral nerve block is a major mechanism underlying the Rebound Pain phenomenon.

In line with these observations, and in order to further explore the hypothesis of a local inflammatory process involved in the development of RP, a fourth study was initiated: the CBFR study (not yet published to date).

Key messages (VEDR)

- Predictors **of poor DEXA response identified**
- Enables stratification **of DEXA non-responders**
- Supports **an inflammatory component in RP mechanisms**

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4.6. The CBFR (Comparison of Blocks for Forefoot Surgery and Rebound Pain) study

"*Rebound Pain occurrence in patients undergoing forefoot bone surgery under popliteal sciatic nerve block or distal sensory ankle block.*"

The CBFR study, currently in the process of publication, has already been presented in abstract form at the ESAIC 2025 and SFAR 2025 congresses.

Introduction

A growing body of evidence has identified multiple factors that influence the occurrence of Rebound Pain (RP), including individual patient characteristics such as sex, age, pain catastrophizing, and preoperative anxiety, as well as pharmacological parameters such as the use of adjuvant drugs [1,2].

Beyond these factors, the literature also highlights variability in the incidence of RP depending on the surgical site and the nerve territory involved. Several studies have reported a higher frequency of RP following upper-limb regional anesthesia compared with lower-limb blocks, suggesting a potential role for block density and the speed of sensory recovery in the dynamics of the phenomenon [3,4].

Recent advances in regional anesthesia have broadened the choice of peripheral nerve blocks, which can be tailored to patients' preferences and surgical requirements. For forefoot surgery, the anesthesiologist may choose either a popliteal sciatic block (sensory-motor) or an ankle block (purely sensory), depending on the analgesic and anesthetic objectives as well as the patient's profile [5]. However, there are still few prospective comparative data regarding the impact of block location (proximal versus distal) when performed as a single-injection (one-shot) on the incidence of RP.

Dingemans et al. compared continuous popliteal sciatic block with a single-shot block for ankle fracture surgery, reporting improved postoperative analgesia and reduced analgesic consumption in the continuous infusion group [6]. These findings suggest that the abrupt cessation of analgesia typical of single-shot blocks may promote RP, whereas a more gradual offset,

as observed with continuous infusions, might attenuate its incidence. Nevertheless, these observations do not allow direct conclusions regarding proximal versus distal blocks performed as single-shot.

Other studies have focused more specifically on the duration of analgesia depending on the type of block performed [3,7]. For example, Schipper et al. showed that a single-injection popliteal sciatic block provided longer-lasting analgesia and reduced the need for immediate opioids compared with an ankle block, which could indirectly influence RP intensity [7].

Based on these findings, the Rebound Pain experienced upon resolution of a distal block may partly depend on the type of fibers affected: mixed blocks, such as the popliteal sciatic, produce deeper anesthesia with delayed sensory recovery, potentially modulating the pain perception at block offset [1,3]. In contrast, purely sensory blocks, such as the ankle block, have a shorter duration of action and expose patients to earlier Rebound Pain.

Finally, it is also conceivable that part of the variability observed in RP incidence may be related to differences in local inflammatory response depending on the site or type of block. This modulation could result from complex mechanisms involving vasodilation, tissue perfusion, and the recruitment of inflammatory mediators, themselves partially influenced by the sympathetic effects associated with each block [8,9].

Methods

This prospective, randomised, single-centre study was conducted within the Department of Anesthesia at Cliniques universitaires Saint-Luc (UCLouvain), involving patients hospitalised for forefoot surgery requiring osseous intervention. All procedures were performed under regional anesthesia using a PNB combined with general anesthesia. The study was approved by the hospital-faculty ethics committee of UCLouvain (reference 2022/22SEP/352, chaired by Professor Jean-Marie Maloteaux) and registered with the Belgian competent authority under number B4032022000083. All participants provided written informed consent after confirming their understanding of the study's objectives and procedures.

Eligible patients were aged between 18 and 75 years, scheduled for forefoot bone surgery, and suitable for both PNB and general anesthesia. Exclusion criteria included contraindications to either anesthetic technique, recent dexamethasone treatment, cognitive or speech disorders precluding completion of preoperative questionnaires, as well as diabetes, vasculopathy, or contraindications to NSAIDs or paracetamol.

Prior to anesthetic management, patients were assessed for medical and medication history, baseline pain at rest and during mobilisation (day and night), and any ongoing analgesic treatment. Psychological and pain-related assessments were performed using validated questionnaires: APAIS for anxiety, the *Central Sensitization Inventory* (CSI) for central sensitization, DN4 for neuropathic pain, and the *Pain Catastrophizing Scale* (PCS) for catastrophizing. In parallel, baseline inflammatory markers were measured,

including high-sensitivity C-reactive protein (hs-CRP) and the neutrophil-to-lymphocyte ratio (NLR).

Repeated measurements were performed near the surgical site (Fig. 3.5), of skin temperature (Fig. 3.6) and tissue oxygen saturation using an INVOS® sensor (Fig. 3.7) with reproducible positioning ensured by skin marking (Fig. 3.5). The same measurements were also carried out on the contralateral limb, at an anatomically equivalent site serving as a control. To ensure data reliability, each recording was preceded by a standardized period of immobility and rest, with the exposed limb kept in ambient air for approximately 15 minutes. Measurements were taken before and after the nerve block, upon awakening, and again on postoperative day 1.

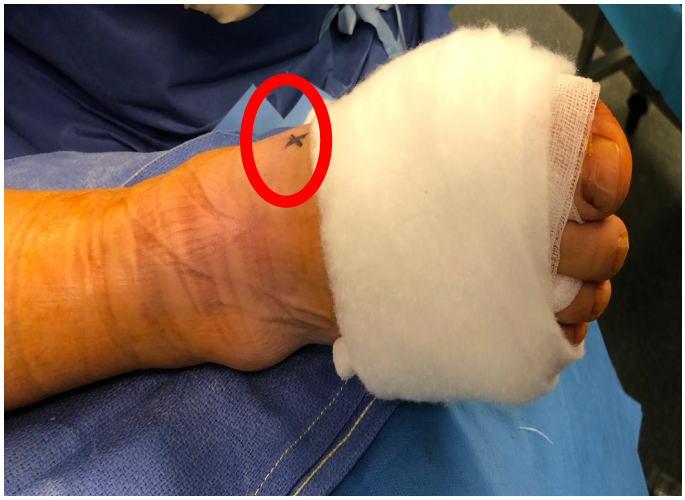


Figure 3.5 ***- Photograph of an operated foot, with a cross marking the site of repeated measurements of skin temperature and transcutaneous oximetry (INVOS technology)***

Figure 3.6 - ***Device for measuring skin temperature (Fora IR42)***

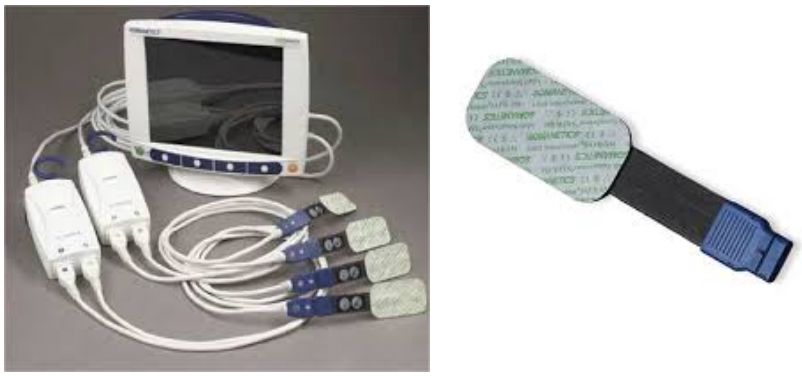


Figure 3.7 ***- INVOS monitoring device and electrode.***

Patients were randomly allocated to one of the two groups using SPSS software (version 29). Each patient received either a popliteal sciatic nerve block or an ankle block (covering the tibial, deep and superficial peroneal, and saphenous nerves). All blocks were performed by an anesthetist trained in ultrasound guidance (Sonosite® S-Nerve), using a Stimuplex® Ultra 360® needle (B. Braun®). Ropivacaine 0.5% was injected, combined with adrenaline and 75 µg of clonidine. The injection volume ranged from 15–20

ml for ankle blocks and 20–30 ml for popliteal blocks, with a maximum dose of 4 mg·kg^{-1}, capped at 300 mg. Block success was confirmed by loss of cold sensation.

Once block efficacy was established, general anesthesia was induced according to a standardised protocol applied to all patients. Postoperative analgesia, both on the ward and at discharge, was also standardised, consisting systematically of paracetamol and non-steroidal anti-inflammatory drugs, with tramadol available as rescue within the first 24 hours. Postoperative follow-up (NRS and DN2 scores) was carried out by telephone interviews conducted by the investigative team on days 4, 30, and at 3 months, in line with protocol.

Power calculation

The minimum required sample size was estimated at 41 patients per group, with an α risk of 0.05 and statistical power of 80%. This calculation was based on an expected RP incidence of approximately 55% after ankle block, with the hypothesis of a 30% reduction after popliteal block [2].

Statistical analysis

The incidence of RP was compared using a Chi-square test. The influence of inflammatory parameters (skin temperature and tissue oximetry) on RP occurrence, according to block type and time course, was analysed using a linear mixed-effects model.

Results

Among the 154 patients undergoing forefoot surgery, 89 were included (Fig. 3.8). Baseline characteristics are presented in Table 3.1. The overall incidence of RP was 41.5% (37/89), with no significant difference observed between the two block techniques (p = 0.54) (Fig. 3.9).

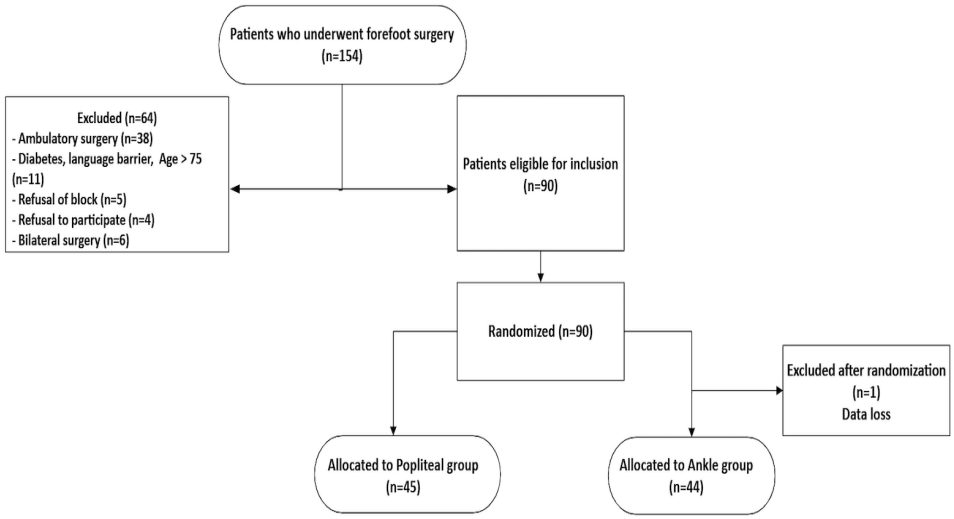
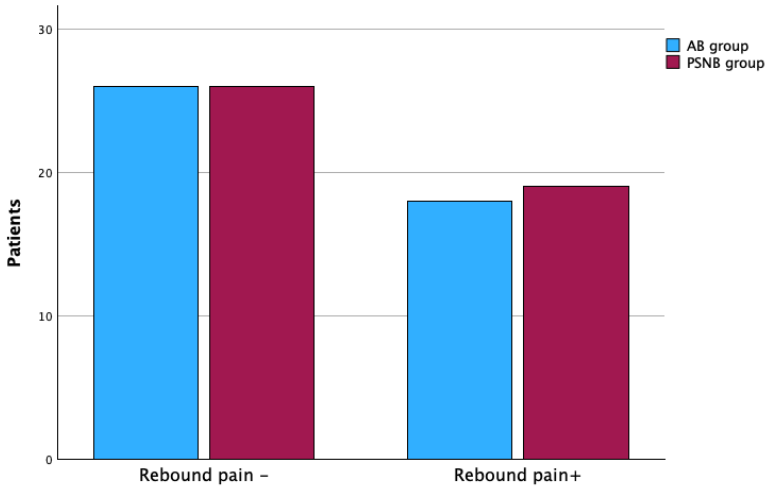


Figure 3.8 ***- Flow diagram prospective study. Final sample size 89 patient***

	PNSB group	AB Group	p-value
Female sex (n)	35	34	0.6
Age (years)	53 .8 ± 12.9	54.1 ± 14.1	0.8
BMI (kg/m²)	27.8 ± 4.7	27.3 ± 5.4	0.7
Preoperative NRS pain score (0–10)	3.6 ± 2.4	3.2 ± 2.3	0.4
Preoperative PCS score (0–52)	17.7 ± 14.8	17.6 ± 14.8	0.9

PSNB: Popliteal sciatic nerve block; AB: Ankle block, P-value: Indicates statistical significance (results are considered statistically significant if $p < 0.05$). *Mann–Whitney test / Chi-squared test, PCS: Pain Catastrophizing Scale.*

Table 3.1 - ***Descriptive Characteristics of the Study Population (n = 89 patients)***



p value =0.54

Figure 3.9 - ***Incidence of Rebound Pain in Patients Undergoing Popliteal Sciatic Nerve Block (PSNB) and Ankle Block (AB).***

The analysis restricted to the operated limb revealed a significant association between the increase in skin temperature and the measurement time ($p < 0.01$), as well as between the increase in temperature and the occurrence of Rebound Pain ($p < 0.01$). In contrast, for tissue oximetry values (INVOS®), only the evolution over time was significant, with a progressive elevation of the values ($p < 0.01$) (Table 3.2).

Consistently, the analyses performed on the contralateral (control) limb demonstrated a significant increase in both skin temperature and INVOS® values over time ($p < 0.01$), with a trend toward significance also observed for temperature across time ($p = 0.05$) (Table 3.2).

Dependant variable	**Explanatory Factor**	**Operated limb F value-(DDL)**	**p-value**	**Contralateral limb F value-(DDL)**	**p-value**
Temperature	4 time points	90.1(266)	0.01*	2.6 (266)	0.05
	Occurrence RP (yes /no)	6.8 (87)	0.01*	1.9 (87)	0.16
	Type of block (PSNB vs AB)	0.12 (87)	0.9	0.3 (87)	0.6
INVOS values	4 time points	87.7 (266)	0.01*	14.5 (266)	0.01*
	Occurrence RP (yes /no)	0.06 (87)	0.7	0.3 (87)	0.58
	Type of block (PSNB vs AB)	9.1 (87)	0.3	1.9 (87)	0.16

- RP: Rebound Pain
- PSNB: Popliteal sciatic nerve block.
- AB: Ankle block
- F value: The calculated F statistics used to assess the significance of each explanatory variable
- DDL (Denominator): Represents the denominator degrees of freedom used in the calculation of the F statistic.
- p-value: Indicates the statistical significance of the F value for each explanatory factor.
- The asterisk highlights a statistically significant result (p-value < 0.05). -4 time points: t1 = Pre-block time, t2 = post-block time, t3 = Recovery room time, t4 = Day
- RP: Rebound Pain; PSNB: Popliteal sciatic nerve block; AB: Ankle block

Table 3.2 - **Results of the Linear Mixed Model Analysis: Variations in Temperature and INVOS Values Measured on the Operated Limb and the Contralateral Limb, According to Time Points, Rebound Pain Occurrence, and Type of Nerve Block.**

Based on this, a complementary analysis (Table 3.3) was conducted to integrate the "side" factor (operated vs. contralateral limb) and to explore its interactions with time. This analysis confirmed a significant "side × time" interaction for both skin temperature ($p < 0.01$) and INVOS® values ($p < 0.01$). These findings suggest that the temporal evolution of these parameters differs between the operated and the contralateral limb, most likely reflecting the local reaction to surgical trauma. In contrast, no meaningful interaction could be explored with Rebound Pain occurrence or type of nerve block on the contralateral limb, as these variables are specific to the operated side.

Dependant variable	**Explanatory Factor**	**Main effect**	**Interaction with side (Operated vs. contralateral) (p-value)**
Temperature	4 time points	<0.01	<0.01
	Occurrence RP (yes /no)	<0.01 NS *	–
	Type of block (PSNB vs AB)	NS *	–
INVOS values	4 time points	<0.01	<0.01
	Occurrence RP (yes /no)	NS *	–
	Type of block (PSNB vs AB)	NS *	<0.01

- The asterisk highlights: operated side only

- NS: non-significant result (Significant p-values are reported for $p < 0.05$)

Table 3.3 - ***Results of Linear Mixed Model: Influence of Time, Rebound Pain, and Block Type on Temperature and INVOS, with Operated vs. Contralateral Comparison***

Discussion

To our knowledge, this study is the first prospective investigation specifically comparing the incidence of RP according to block type, by contrasting a proximal block (popliteal sciatic) with a distal block (ankle), both performed as single-injection (one-shot) techniques. The absence of a significant difference in RP occurrence between the two patient groups does not allow us to conclude that block location exerts a decisive influence on the genesis of this phenomenon. These findings are consistent with several reports in the literature, which have not consistently demonstrated a clear correlation between block site or extent and the intensity of RP.

Barry et al., in a large multicenter retrospective study involving nearly 1,000 patients, reported an overall RP incidence of approximately 50%. Although incidence variations were noted depending on the type of peripheral block performed, this parameter was not identified as an independent risk factor, suggesting instead that other variables, such as individual patient characteristics or pharmacological parameters, play a more prominent role [1]. Similarly, Ilfeld et al., through several clinical trials, demonstrated that prolonging analgesia with a catheter did not fully prevent RP, reinforcing the concept that its mechanism extends beyond the simple question of block site [3].

Nonetheless, certain data suggest that peripheral nerve blocks may, under specific conditions, influence RP dynamics, particularly through local inflammatory pathways. Among the mechanisms proposed is sympathetic block–induced vasodilation, which may enhance tissue hypervascularisation

and promote leukocyte recruitment, thereby facilitating the accumulation of pro-inflammatory mediators such as prostaglandins, cytokines, and chemokines [8,9]. These processes could contribute to exacerbated peripheral sensitization, acting as potential triggers or amplifiers of RP.

This mechanistic hypothesis is indirectly supported by fundamental research in pain physiology, which has highlighted the central role of inflammatory responses and oxidative stress in nociceptive hyperexcitability [1,2]. In particular, during post-ischemic reperfusion, neutrophil recruitment, increased production of reactive oxygen species, and cytokine release have been documented [10,11]. While not specific to peripheral nerve blocks, these findings provide a plausible mechanistic framework: profound muscle relaxation induced by certain blocks may reduce vascular tone and slow venous return, thereby favoring transient hypoperfusion followed by reperfusion-associated inflammation.

Within this context, one might theoretically assume that proximal blocks, due to their motor component, could be more likely to induce ischemia–reperfusion episodes and subsequent localized inflammatory exacerbation than purely sensory distal blocks. However, our results do not support this hypothesis, suggesting instead that other, yet insufficiently elucidated mechanisms are likely to contribute to the genesis of RP (Fig. 3.9).

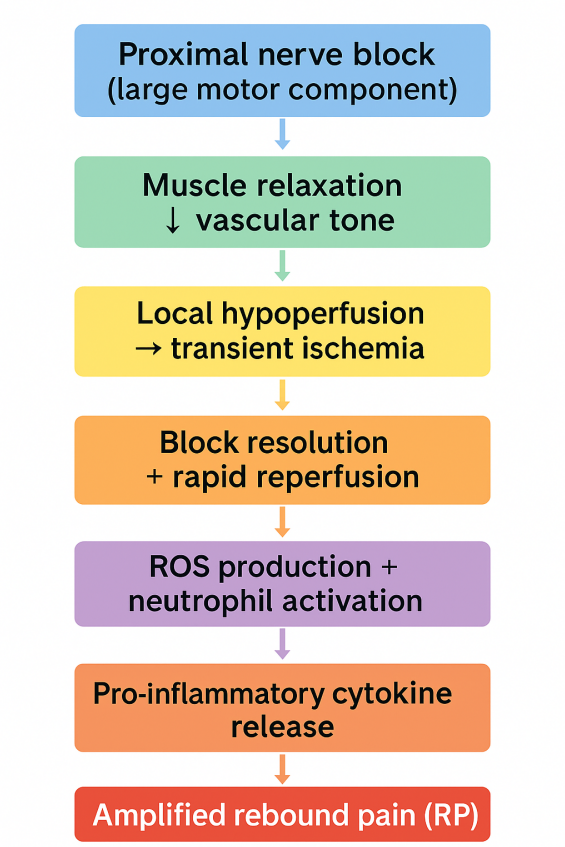


Figure 3.9 - ***Hypothesized Mechanism: Proximal Nerve Block, Transient Ischemia, and Rebound Pain***

An alternative hypothesis, compatible with our observations, suggests that the RP phenomenon may rather reflect a compartmentalised vasoconstrictive dysregulation. Indeed, the over-representation of RP following bone surgery [1,2] points to the involvement of specific mechanisms related to the physiological properties of this tissue, recognised as one of the most

algogenic in the body due to its rich nociceptive innervation and the substantial presence of sympathetic nerve fibres with vasoconstrictive function [12,13].

Resolution of the PNB may constitute an abrupt transition phase, combining the re-emergence of nociceptive afferent input with restoration of sympathetic tone. Such reactivation could induce transient periosteal vasoconstriction, altering the microcirculatory balance within inflamed tissue and lowering the activation threshold of nociceptive fibres, notably through a sympathetic–nociceptive coupling mechanism [14]. In recently injured bone tissue, this disturbance may be followed by secondary amplification of the local inflammatory response [15–17], providing a coherent pathophysiological framework to explain the frequency and intensity of rebound pain observed after certain bone surgeries, without implying overt tissue hypoxia.

However, the absence of a significant correlation between tissue oximetry measurements (INVOS®) and the occurrence of RP may also reflect the limitations of this technique. Although near-infrared spectroscopy (NIRS) has demonstrated its usefulness for monitoring muscle oxygenation in various settings, notably during tourniquet-induced ischemia–reperfusion in orthopaedic surgery [16,17] or under acute physiological stress [18], its sensitivity appears insufficient to detect more subtle microcirculatory alterations, particularly when they involve deep tissue compartments such as bone or the periosteum.

In conclusion, this study did not demonstrate a significant difference in the incidence of Rebound Pain between popliteal sciatic block and ankle block in

patients undergoing forefoot surgery. However, the observed association between Rebound Pain and postoperative thermal changes suggests a potential contribution of inflammatory and microcirculatory processes to its pathophysiology. These findings support the hypothesis that mechanisms other than block location alone may be involved in the development of Rebound Pain. Further prospective studies are warranted to better characterise these mechanisms and to identify reliable, clinically applicable biomarkers for risk stratification and prevention.

Key messages (CBFR)

- **Block type:** no effect on RP occurrence or on markers of local inflammatory exacerbation
- **Skin temperature:** postoperative increase associated with RP occurrence
- **Findings support** an inflammatory exacerbation mechanism involved in RP

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PART V – DISCUSSION

Given that peripheral nerve blocks are an important part of the current anesthesia and analgesia armamentarium, the aim of this thesis was to explore RP following peripheral nerve block in depth, with a focus on characterising its incidence, management strategies, and underlying pathophysiological mechanisms.

Characterisation of Rebound Pain

The first objective of this work was to characterise RP as a postoperative clinical entity following single-shot regional anaesthesia in ambulatory and short-stay orthopaedic surgery. As previously highlighted, the wide variability in RP incidence reported in the literature primarily reflects both the absence of consensual diagnostic criteria and the intrinsically multifactorial nature of the phenomenon.

Among the various definitions proposed [1–4], we deliberately adopted a pragmatic and clinically discriminant definition, describing RP as pain initially well controlled under regional anaesthesia (NRS <4), followed by a sudden and marked pain exacerbation (NRS >7) occurring within 12 to 24 hours after block resolution, in the absence of primary block failure. This definition integrates two essential dimensions that distinguish RP from expected postoperative pain: a delayed temporal profile and an abrupt rupture from the immediate postoperative period of analgesic comfort. By excluding early block failure and moderate pain fluctuations, this approach allows a more specific identification of clinically meaningful RP episodes.

Although different thresholds were used to define RP in our prospective studies conducted at our centre (PRPK: NRS ≥7; VEDR and CBFR: NRS >7), all consistently showed that RP is a frequent postoperative event, with an incidence ranging from 34.6% to 42.2%, after orthopaedic surgery performed under PNB. Importantly, however, RP did not occur uniformly across patients. Instead, a marked interindividual variability was observed in both its occurrence and intensity, supporting the notion that RP represents a heterogeneous clinical phenomenon rather than a systematic consequence of block resolution.

In line with our first hypothesis, this variability appeared to be partly explained by patient-related factors, particularly psychological determinants. Higher levels of preoperative anxiety and pain catastrophising were associated with an increased likelihood of experiencing RP [1,5,6]. These findings suggest that RP preferentially affects specific patient subgroups characterised by distinct psychological profiles, independently of technical block performance or surgical factors alone. Such observations are consistent with the growing body of literature emphasising the role of affective and cognitive factors in postoperative pain modulation [4].

Taken together, these results support the hypothesis that RP constitutes a frequent and clinically relevant postoperative phenomenon with a heterogeneous expression, influenced by identifiable patient-related characteristics. From a clinical perspective, they underline the importance of a comprehensive and standardised approach to RP assessment, integrating not only pain intensity and temporal patterns but also psychological and contextual parameters. This approach is essential to improve the

identification of patients at increased risk of RP and provides a necessary foundation for exploring the underlying mechanisms of this phenomenon.

Understanding the mechanisms of RP

Combined data from the PRPK, VEDR, RETRODEXA, and CBFR studies support the hypothesis that Rebound Pain (RP) does not merely reflect the passive return of nociceptive afferent input upon resolution of a peripheral nerve block, but rather results from the interaction of several specific and interconnected pathophysiological processes (Fig. 5.1).

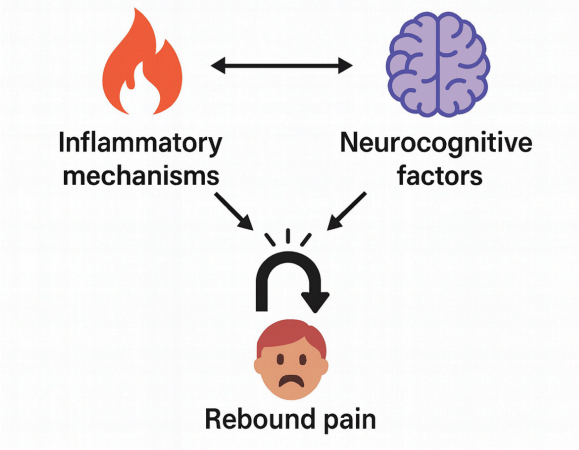

Figure 5.1 - ***Illustration potential Interactions Underlying Rebound Pain***

From a central perspective, our studies did not demonstrate the involvement of central sensitisation in the strict sense. No significant association was observed between RP occurrence and CSI-9 scores used in our studies. Although this tool is clinically validated, it remains relatively limited and

does not comprehensively explore the central mechanisms involved in pain modulation, particularly from a fine pathophysiological standpoint.

In this context, the absence of evidence supporting established central sensitisation does not preclude the existence of an impairment of the central nervous system, likely transient and dynamic, the precise nature of which remains to be defined and will require future investigations with a more specifically mechanistic focus.

Psychological factors, meanwhile, appear to be major modulators of the clinical expression of RP. Profiles characterised by high pain-related anxiety, negative anticipation, hypervigilance, and elevated catastrophising scores were consistently associated with an increased risk and greater severity of RP. Catastrophising, already recognised as an independent predictor of more intense and persistent postoperative pain [5,7], has been associated with altered activation of brain networks involved in the cognitive and emotional modulation of pain, notably the prefrontal cortex, amygdala, and insula [8]. These alterations may amplify conscious pain perception and emotional salience at the time of the abrupt transition from dense regional analgesia to the re-emergence of nociceptive afferent input, thereby contributing to the sudden and intense nature of RP.

At the interface between central mechanisms and psychological determinants, the concept of nociplastic pain provides a relevant interpretative framework for understanding RP [9]. Nociplastic pain refers to pain arising from altered central processing of nociceptive signals, in the absence of sufficient tissue damage to fully account for the intensity of the symptoms. It should therefore not be regarded as a strictly psychological or strictly neurophysiological

entity, but rather as the expression of a dysregulation of central pain modulation mechanisms, within which psychological factors closely interact with neurobiological processes [10]. In this perspective, RP may not reflect a durable process of central sensitisation, but rather a functional and transient alteration of central pain processing, revealed by the abrupt withdrawal of dense regional analgesia.

On the peripheral side, the partial yet reproducible efficacy of intravenous dexamethasone observed in the RETRODEXA study reinforces the hypothesis of an acute inflammatory contribution at the time of nerve block resolution. This effect does not appear to be solely attributable to systemic analgesia but rather suggests the involvement of local inflammatory processes at the surgical site, likely modulating the excitability of nociceptive fibres [3,4].

The preliminary results of the CBFR study are consistent with this perspective. The significant association between postoperative increases in skin temperature and the occurrence of RP may reflect local inflammatory activation accompanied by transient microcirculatory changes [11]. The precise mechanism remains to be determined and may involve dynamic vasoactive processes or transient micro-ischemic phenomena, without allowing a single explanatory model to be established at this stage.

Taken together, these findings suggest that RP arises from the convergence of a transient peripheral inflammatory amplification and a dysregulation of central pain processing, modulated by psychological vulnerability. This integrated model provides a coherent pathophysiological basis for the

development of individualized preventive strategies tailored to patients' risk profiles (Fig. 5.2).

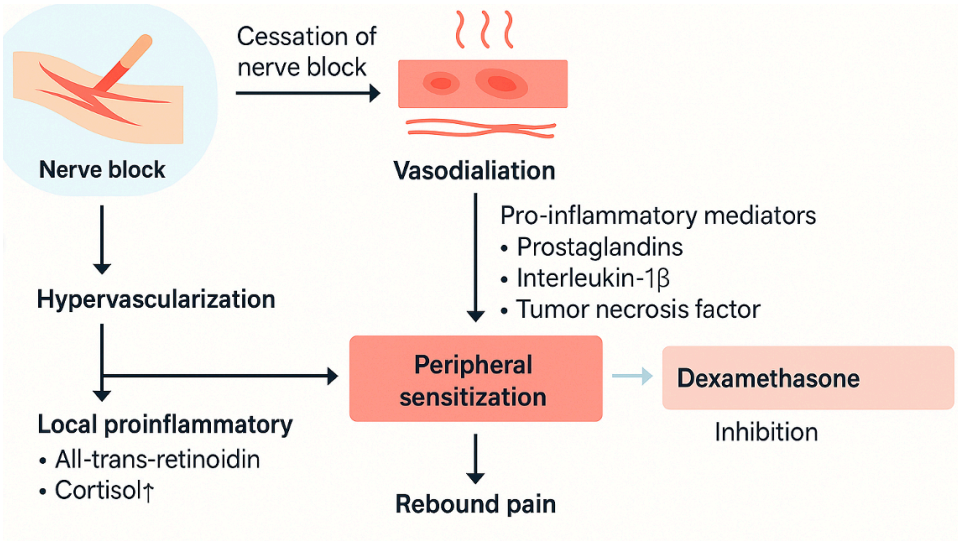

Figure 5.2 - ***Illustration of the hypothesized inflammatory cascade involved in Rebound Pain.***

Preventive strategy for Rebound Pain

In line with our third hypothesis, which postulates that RP may be at least partially prevented or attenuated through targeted perioperative interventions, intravenous dexamethasone currently appears to be the most robust and consistently documented pharmacological strategy to reduce RP incidence, although its effect on RP severity remains limited [12,1]. Supported by several recent publications, dexamethasone seems to exert its analgesic effect primarily by limiting postoperative hyperalgesia. Although the precise mechanisms remain debated, its action likely involves a reduction in nociceptive C-fibre activity, a decrease in the production of pro-inflammatory mediators, and an attenuation of the inflammatory response induced by surgery [13].

The retrospective RETRODEXA study demonstrated a significant reduction in RP incidence, even with low intravenous doses of dexamethasone below 0.1 $mg \cdot kg^{-1}$, without formal evidence of a strict dose–response relationship. Nevertheless, the presence of a statistical trend suggests that such a relationship may exist and warrants further investigation in adequately powered prospective studies. These findings support the role of dexamethasone as a cornerstone of pharmacological prevention, while highlighting the need to refine dosing strategies.

However, the results of the VEDR study temper this apparent efficacy by revealing substantial interindividual variability in corticosteroid response. Specific patient profiles, particularly those characterised by marked preoperative anxiety, high pain catastrophising scores, persistent nocturnal

pain, or low preoperative salivary cortisol levels, appear to derive less benefit from dexamethasone. These observations are consistent with previous reports emphasising the influence of psychological and biological factors on postoperative pain modulation [5,6]. Taken together, these data argue against a uniform preventive strategy and instead support the development of more individualised perioperative approaches.

Such individualisation should not detract from the importance of preventive measures applicable to all patients undergoing regional anaesthesia. Preoperative patient education remains a fundamental component of RP prevention, particularly in ambulatory and short-stay surgical settings where postoperative medical supervision is inherently limited [2,3]. Information focused on the expected timing of block resolution, the potential occurrence of RP, its presumed mechanisms, and the need for anticipatory multimodal analgesia is therefore essential, particularly in ambulatory and short-stay surgical settings where postoperative medical supervision is inherently limited [4,14].

Personalised approach to Rebound Pain management

For patients identified as being at increased risk of Rebound Pain, such as those undergoing bone surgery, presenting with significant pre-existing pain, elevated anxiety levels, or other vulnerability profiles, the implementation of an individualised perioperative strategy appears particularly relevant. Such an approach should begin with a targeted preoperative assessment using validated tools, including measures of anxiety, pain catastrophising, and baseline pain intensity, in order to better characterise individual risk profiles.

Based on this assessment, adaptation of anaesthetic and analgesic strategies may be warranted. This may include the systematic use of intravenous dexamethasone when not contraindicated, optimisation of anticipatory multimodal analgesia with appropriately tiered non-opioid and opioid-sparing agents, and the judicious use of anti-inflammatory therapies where appropriate [4,14]. Beyond the intraoperative period, enhanced postoperative surveillance may be required for the most vulnerable patients, including structured telephone follow-up after discharge or, in selected cases, reconsideration of eligibility for ambulatory management [15].

The coordinated integration of these clinical, psychological, and biological considerations into perioperative care pathways represents a concrete step towards a personalised approach to regional anaesthesia. By tailoring preventive strategies to individual risk profiles, such an approach has the potential to optimise the benefit–risk balance of regional techniques, improve postoperative pain trajectories, and enhance patient-centred outcomes. (Fig. 5.3).

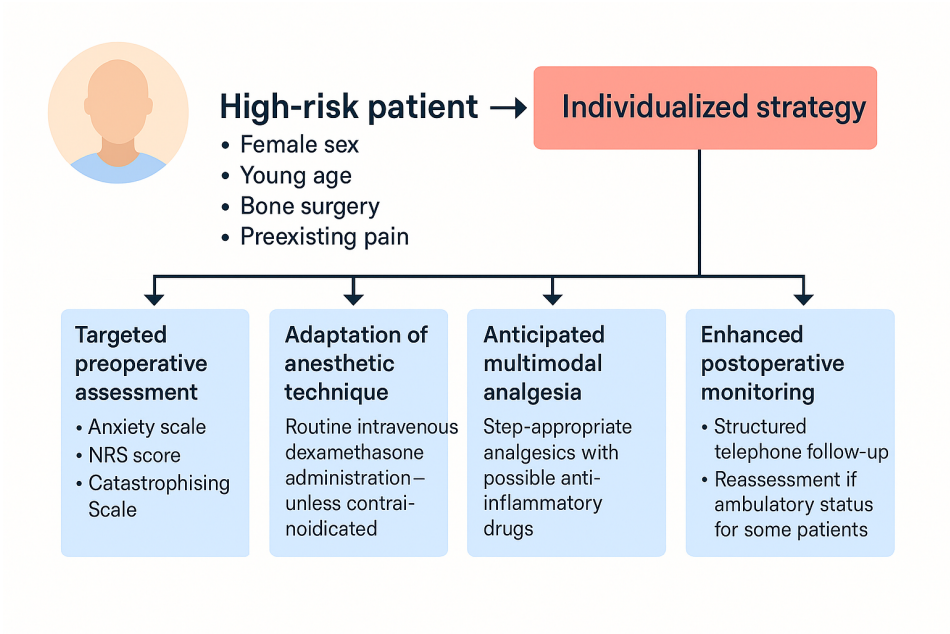

Figure 5.3 - **Overview of individualized preventive strategies for patients at high risk of Rebound Pain**

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PART VI – CONCLUSION AND PERSPECTIVES

The occurrence of RP extends beyond the purely technical parameters of anesthesia and appears to be closely influenced by individual, psychological, biological, and neurocognitive factors, which modulate both its risk of onset and the response to preventive strategies.

Current evidence confirms that Rebound Pain is a frequent and multifactorial phenomenon, reported in approximately 30% to 70% of cases, and remains underestimated, particularly in the setting of ambulatory surgery. It is characterised by an acute, often severe postoperative pain occurring upon resolution of a peripheral nerve block after an initial period of dense analgesia, typically within 12 to 24 hours postoperatively, and differs from conventional postoperative pain by its sudden and transient nature.

In this context, a personalised approach is required, based on a dual framework:

- Firstly, a universal prevention strategy, centred on the systematic provision of information regarding the risk of RP to patients receiving regional anesthesia, along with education on postoperative pain management.
- Secondly, a targeted approach for patients identified as high-risk (e.g. anxiety, catastrophizing, preoperative pain, bone surgery), including, when appropriate, the use of intravenous corticosteroids and reinforced postoperative follow-up.

The main challenge now lies in the individualisation of care pathways, through refinement of predictive tools and integration of psychobiological parameters into preoperative assessment. This evolution towards predictive and personalised medicine opens concrete opportunities to optimise RP prevention, improve patient comfort, and enhance safety in ambulatory surgery.

Future research should focus on developing more specific and dynamic biomarkers of local or systemic inflammation that are applicable in the perioperative setting. The integration of continuous monitoring technologies, such as wearable skin thermosensors, heart rate variability tracking devices reflecting stress responses, and repeated salivary assays of cytokines and cortisol, may help refine the temporal characterisation of critical phases leading to RP [1,2].

Beyond inflammatory markers, the exploration of individual neurophysiological vulnerability represents a promising avenue. Preoperative assessment of descending pain modulation systems may serve as a relevant tool for risk stratification. Techniques such as nociceptive pupillometry performed during calibrated stimuli allow evaluation of autonomic reactivity and may indirectly reflect the efficiency of descending inhibitory mechanisms [3,4]. Similarly, preoperative electroencephalographic activity analysis may help identify at-risk profiles, as specific oscillatory patterns, particularly reduced alpha power, have been associated with increased susceptibility to postoperative pain [5].

Advances in functional imaging and artificial intelligence applied to integrated multimodal data analysis represent a further step towards a truly

personalised approach. By combining psychological, neurophysiological, and biological data, these strategies may contribute to more refined identification of patients at risk of intense pain or unfavourable pain trajectories [6,7].

Furthermore, continuous perineural catheter–based regional anesthesia, as an alternative to single-injection techniques, deserves particular attention in the context of painful orthopedic or ambulatory surgery [8]. By prolonging the duration of the sensory block, this approach may reduce both the incidence and severity of Rebound Pain [9], allowing for a more gradual resolution of postoperative pain and improved adjustment of systemic analgesic therapy, thereby limiting the intense pain peaks frequently observed during the rapid regression of a single-injection block [8]. In a randomized controlled trial involving patients undergoing rotator cuff repair, continuous catheter techniques significantly reduced the incidence of severe pain compared with single-injection blocks, with benefits persisting up to postoperative day seven [10]. However, technical constraints, infection risk, and the complexity of postoperative follow-up, particularly in ambulatory settings, limit its widespread implementation. This strategy may therefore be considered in patients at high risk of Rebound Pain, including women and those undergoing bony procedures or upper limb surgery [11]. Novel administration modalities such as programmed intermittent boluses or delayed infusion initiation are currently under investigation and may further optimize block duration and quality, although additional prospective studies are required to confirm these findings [12–14].

Within the same framework of pharmacological optimization for the prevention of Rebound Pain, systematic reviews and meta-analyses primarily

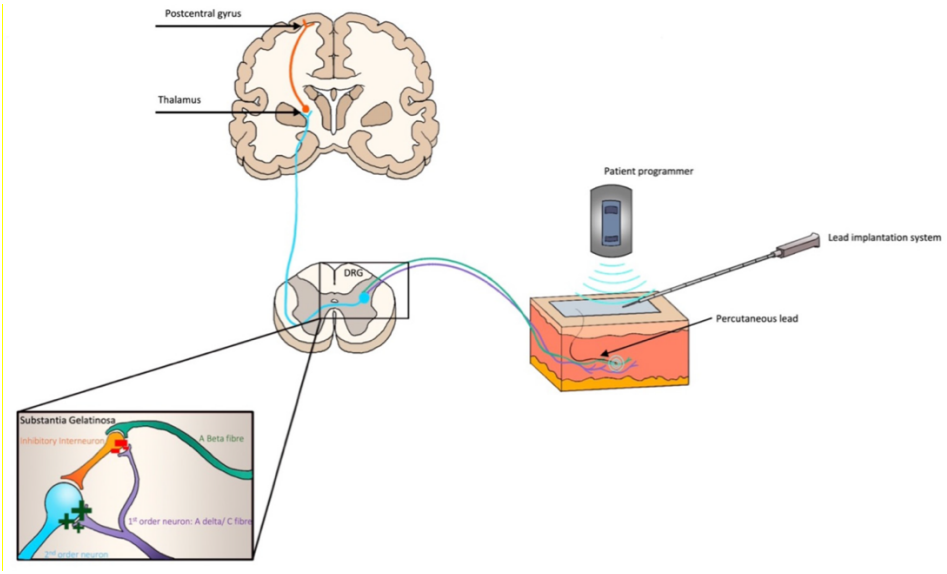
confirm the efficacy of a single dose of dexamethasone in prolonging analgesia and reducing its incidence [15,16]. However, repeated postoperative administration of dexamethasone has been proposed as a complementary strategy aimed at further extending analgesia and limiting pain recurrence. Although this approach has not been specifically evaluated for Rebound Pain, it has demonstrated, in orthopedic and arthroplasty surgery, additional reductions in pain scores and opioid consumption up to 48 hours postoperatively [17,18].

An alternative to repeated administration could be increasing the preventive dose as a single injection in order to enhance the preventive effect on RP during the critical period corresponding to block resolution. The findings reported by Holmberg et al., showing a low incidence of RP with a higher intravenous dose, suggest the possible existence of a dose effect [19].

However, this hypothesis should be interpreted with caution. The randomized trial by Nielsen et al., conducted in high pain responders undergoing total hip arthroplasty, showed that a substantial dose increase improved certain analgesic parameters without demonstrating a marked or universal benefit on postoperative pain [20]. Although not specific to RP, these data temper the assumption that simple dose escalation would be sufficient to optimise its prevention.

Dedicated randomised trials remain necessary to clarify the benefit–risk profile of repeated or increased-dose strategies, particularly with regard to potential metabolic or infectious complications in frail or diabetic patients [21].

Finally, non-pharmacological strategies may also be considered in the prevention of Rebound Pain. Neuromodulation, already established in chronic pain management, is currently being evaluated for acute postoperative pain control [22]. Peripheral nerve stimulation (PNS) involves the percutaneous implantation of electrodes near a target nerve, delivering electrical impulses via an external generator [23,24] (Fig. 6.1). Its analgesic effect primarily relies on activation of Aβ fibres and inhibition of nociceptive transmission at the spinal level ("Gate Theory"), as well as complementary mechanisms such as modulation of inflammatory mediators and reduction of peripheral excitability [25–28].



Peripheral stimulation of Aβ fibres enhances the activity of inhibitory interneurons, thereby reducing the transmission of pain signals from Aδ and/or C fibres to second-order (blue) and third-order (orange) neurons.

Figure 6.1 ***- Neuromodulation via percutaneous peripheral nerve stimulation for acute pain management.*** *[17].*

A pilot randomized trial reported reduced postoperative opioid consumption and prolonged analgesia following orthopedic surgery [29]; however, these findings have not been consistently replicated, likely due to methodological limitations including small sample sizes, technical challenges, and protocol heterogeneity [30]. Moreover, the cost and technical complexity of pPNS currently restrict its use mainly to major, non-ambulatory procedures associated with severe and prolonged postoperative pain [29,30]. Although promising for modulating acute pain and potentially reducing Rebound Pain, its clinical value and cost-effectiveness require confirmation in larger, standardized randomized controlled trials

To be continued…

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