Rebound pain after regional anesthesia in the ambulatory patient

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Purpose of review
Regional anesthesia is popular in ambulatory setting allowing safe and fast recovery. The problem of 'rebound pain', that is very severe pain when peripheral nerve block (PNB) wears off represents a clinically relevant problem and a cause of increased healthcare resource utilization. This review tries to make the point on a not so rare, unwanted and often neglected side effect of PNB.

Recent findings
The major finding is the lack of large prospective studies. Incidence of rebound pain is unknown but could reach 40% of patients at PNB resolution. To date, pathophysiological mechanisms remain debated: mechanical and chemical (proinflammatory effect of local anesthetics) nerve insult caused by PNB in predisposed patients (with severe preoperative pain, younger patients). Effective preventive strategies also are missing (e.g. role of analgesic adjuvants in PNB). Long-term consequences in term of functional recovery and persistent pain have not been demonstrated. Interview of patients has underlined the need of information and education about PNB and postoperative analgesia.

Summary
Patients' report of excruciating pain and major distress when PNB wears off questions the quality of current anesthesia practice in ambulatory setting. Rebound pain unanswered questions are challenging in the area of perioperative medicine.

Keywords
acute postoperative pain, ambulatory anesthesia, peripheral nerve block, rebound pain

INTRODUCTION

In developed countries, over 50% of all surgical procedures are now performed on an outpatient basis [1]. In this context, regional anesthesia, specifically short-lasting spinal anesthesia and peripheral nerve blocks (PNBs), is of benefit because it allows a good control of early postoperative pain and a fast hospital discharge [2]. Besides, acute postoperative pain remains poorly controlled as 24.5% of hospitalized patients report severe pain within the first 24 h after surgery [3] and 12–13% within the first week after hospital discharge [4]. That questions acute postoperative pain after discharge in ambulatory patients. According to an old survey, 30% of patients endured moderate to severe pain 24 h after ambulatory surgery [5]. Recent studies support previous observations and mention pain and discomfort in 26.7–60% of outpatients within the first week postsurgery [6,7]. Orthopedic procedures stand among the procedures associated with severe postoperative pain [6]. Regional anesthesia is very popular for perioperative pain management in these patients despite short-lasting benefits [8] and the fact that some studies have highlighted the problem of 'rebound pain' phenomenon after loco-regional anesthesia including spinal anesthesia [9] and single-shot PNB [2]. In ambulatory patients, severe pain occurring outside of a controlled healthcare setting represents a clinically relevant problem. Indeed, severe pain at home led to 14.6% of healthcare resource utilization and to a 0.08% hospital readmission in a 2004-survey [5]. In 2016, 16–25% of ambulatory patients sought any form of medical attention (including physician's visit) for

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Curr Opin Anesthesiol 2018, 31:000–000
DOI:10.1097/ACO.0000000000000651

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KEY POINTS

- 'Rebound pain' defined as very severe pain when PNB wears off is a clinically relevant problem and a cause of increased healthcare resource utilization after ambulatory surgery. There is currently a lack of large prospective studies about the phenomenon which incidence remains unknown but could reach 40%.
- Pathophysiological mechanisms remain debated: mechanical and chemical (proinflammatory effect of local anesthetics) nerve insult secondary to PNB in predisposed patients (preoperative pain, younger patients). Long-term consequences in term of functional recovery and persistent pain have not been demonstrated.
- Interviews of patients have underlined the need of information and education about PNB and postoperative analgesia. Preventive and effective strategies need to be assessed (including the use of different adjuvants to local anesthetics in PNBs).
- In the actual context of perioperative medicine, rebound pain represents a challenge as well as an opportunity to improve the quality of anesthesia practice.

pain problems within the first 48 h after wrist fracture surgery [10▪▪]. In the same study, more patients who had a PNB than patients who undergo surgery under general anesthesia reported severe postoperative pain within the first 48 h (41 versus 10%; odd ratio: 5.9; 95% CI, 2.6–13.4%) [10▪▪]. The present work is intended to review a not so rare but still poorly recognized consequence of loco-regional anesthesia, that is the phenomenon of 'rebound pain' which represents a major concern in ambulatory patients.

REGIONAL ANESTHESIA IN AMBULATORY SURGERY: EARLY BENEFITS AND THEN? THE PHENOMENON OF 'REBOUND PAIN'

Orthopedic surgery on the extremities ranks among the most painful surgery often leading to long-lasting pain [7,11]. Regional anesthesia is often considered as the best option by anesthesiologists, surgeons and also patients. Indeed, avoiding general anesthesia generally ensures rapid recovery and faster hospital discharge. PNBs are usually associated with effective analgesia and no need for opioids administration, reducing bothersome side effects such as nausea, vomiting, dizziness and sedation [2]. Also, avoiding perioperative opioids actually stands as a 'must' in the context of 'opioid epidemic' [12]. Beyond these early benefits, few studies have taken into account what happens to the patients when the PNB wears off. Previous studies already pointed out that PNB did not offer long-term benefit after ambulatory hand surgery when compared to general anesthesia in term of pain relief, opioids consumption, adverse effects, disability or patient' satisfaction on postoperative days 1, 7 and 14 [8]. Recent meta-analysis further questioned the real benefit of adding a single-shot PNB to general anesthesia in various ambulatory orthopedic procedures. After shoulder surgery, interscalene block only reduces postoperative pain at rest and during mobilization up to 8 h and not later [13]. In arthroscopic knee surgery, femoral nerve block and adductor canal block only provide modest analgesic benefits and negligible oral morphine sparing effect during the first 24 h [14]. Finally, fascia iliaca block added to intraarticular infiltration does not improve postoperative pain control after hip arthroplasty but may result in quadriceps weakness and increased risk of fall [15].

Besides no evident added benefit on early postoperative pain control, clinical reports even have warned the clinicians about a risk of very severe pain at PNB resolution in some patients, a phenomenon also called 'rebound pain'. In clinical practice, it was often the surgeons who have attracted the anesthesiologists' attention on the pain problem, which occurs when anesthetic block wears off [16▪]. Most of the time, rebound pain presents during the first night, that is when patients are at home, outside a healthcare setting what constitutes a significant problem to manage their pain. Rebound pain has been studied after distal radius fracture fixation under brachial plexus block [16▪], after ankle fracture surgery under popliteal block [17▪▪,18], after various shoulder procedures where a single shot interscalene block was applied [13,19] and after femoral PNB administered for anterior cruciate ligament reconstruction [20] (Table 1).

By definition 'rebound pain' is mechanical–surgical pain caused by unopposed nociceptive inputs that are brutally uncovered after PNB resolution. The phenomenon is reported as 'a poorly described entity, commonly defined as a dramatic increase in pain once regional anesthesia has dissipated' [16▪]. Definition and characteristics found from current reports should allow to design further clinical trials. In a recent study questioning patient's experience after PNB in ankle fracture surgery by the means of semistructured interviews [17▪▪], most patients reported excruciating pain at night, with burning characteristics and duration of more or less 2 h. Other patients mentioned unpleasant dull ache pain when PNB wore off [17▪▪]. As surgery was usually performed during daytime, most of PNBs wore off during night but rebound pain was also mentioned

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Table 1. Definition and characteristics of rebound pain

The quantifiable difference in pain scores when the block is working versus the increase in acute pain that is encountered during the first hours after the effects of PNB (either single shot or continuous infusion of local anesthetics) resolve
Calculation of rebound pain score: the lowest pain score during the first 12 h before the PNB wears off is subtracted from the highest pain score during the first 12 h after the PNB wears off
Occurs during the first 12–24 h after PNB (either single-shot or continuous infusion of local anesthetic) wears off
Very severe pain (median pain score >7 on a scale from 0 to 10)
Pain is mainly described as burning and in some cases as dull aching pain
Both resting pain and evoked-pain is reported
Pain duration is around 2 h
Pain does not respond to intravenous opioids administration

Data from Williams *et al.* [20,27] and from Henningsen *et al.* [17▪▪]. PNB, peripheral nerve block.

occurring during daytime. Patients also underlined that severe rebound pain was not relieved by intravenous opioids (while patient-controlled analgesia with morphine was available) [17▪▪].

DEALING WITH 'REBOUND PAIN' AFTER PERIPHERAL NERVE BLOCK

Because experimental and clinical studies are scarce in the literature, the mechanisms underlying the phenomenon remain poorly understood. In one of first experimental report [21], the authors have stressed important questions: Can rebound pain after PNB also occur in the absence of surgical trauma? Is rebound pain only attributable to a barrage of previously blocked nociceptive inputs? Which is the role of perioperative inflammation in the phenomenon expression? What is the role of peripheral nociceptors i.e. peripheral inflammation in rebound pain and transient hyperalgesia? Can rebound pain and hyperalgesia be prevented? Until today, these questions remain unanswered. From a scientific point of view, rebound pain mechanisms may either be 'procedure specific' and/or 'patient specific'.

Experimental observations

Kolarczyk and Williams have tried to reproduce rebound pain in rats receiving a sciatic nerve block with ropivacaine [21]. A 3-h after injection, a transient thermal hyperalgesic response to heat stimulus was present in the setting of resolved mechanical sensory block what argues for some sensory modality specific (C-nociceptive fibers) related phenomenon. In neuropathic pain, ongoing burning pain (a characteristic of rebound pain according to patients) is caused by abnormal spontaneous C-fibers activity and hyperexcitability of nociceptors [22]. Furthermore, despite transient heat hyperalgesia, no detectable changes in later sensory thresholds (at 12–14 days postsciatic PNB) and no evidence of nerve lesion were found in the animals [21].

A different group of researchers who made a secondary subanalysis of previously published studies using similar model of ropivacaine sciatic PNB in rats reported very transient (30 min duration) heat hyperalgesia at 240 min post-PNB which value did not reach statistical significance [23]. Clinical relevance of the aforementioned experimental observations is difficult. In animals, PNB were performed without any surgery associated. The later authors also controlled for the possible impact of repeated exposure to heat during animal testing, but it was not significantly correlated with transient hyperalgesia [23]. More recently, bupivacaine-induced rebound pain was also observed in a mouse sciatic PNB model where the animals demonstrated significant thermal hyperalgesia from 5 h until 24 h postinjection [24].

Procedure (surgery and anesthesia) specific hypothesis

Although rebound pain can occur after both upper and lower limbs surgery, the intensity of rebound pain seems to be higher after shoulder surgery than complex knee surgery [20]. Consequently, the site and the type of surgery might influence rebound pain what deserves further studies. Moreover, the type of PNB used for anesthesia, for example axillary versus more distal PNB has not been objectively assessed. Despite the use of ultrasounds, nerve damage from needle insertion as well as injectate pressure trauma could potentially induce some perineural inflammation [23]. In the meta-analysis about single-shot interscalene PNB for shoulder surgery [13], rebound pain was present at block resolution regardless of local anesthetic type, volume or concentration used (all PNBs with adjuvant other than epinephrine were excluded from the analysis). Here, it is interesting to point out that local anesthetics may demonstrate intrinsic proinflammatory properties which combined to injury-related PNB could underly 'neuropathic-like pain' and transient hyperalgesia post-PNB. In a human model of third molar extraction, local bupivacaine, in contrast to local lidocaine, stimulates cyclooxygenase-2 gene expression and local release of proinflammatory prostaglandins E2 that results in higher pain after

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the local anesthetic effect dissipates [25]. Finally, PNB duration which relies on either the use of adjuvants [26] or the use of a continuous perineural infusion might influence rebound pain severity. Among the adjuvants, perineural clonidine (50–100 μg) does not affect rebound pain while buprenorphine seem to reduce rebound pain intensity at dose more than 300 μg [27]. Perineural dexamethasone benefit is unclear and appears to be dose-related with less dexamethasone (2 mg or less) being paradoxically associated with less rebound pain [27]. In clinical practice, both perineural and systemic dexamethasone prolong PNB by a mechanism of action which remains unclear [28]. In an experimental animal model, perineural but not systemic dexamethasone added to clinical concentration of bupivacaine not only prolonged sensory and motor block but prevented transient bupivacaine-induced neurotoxicity and rebound thermal hyperalgesia [24]. Perineural dexamethasone antineurotoxic properties might explain study findings. In agreement, according to its local anti-inflammatory properties [29], perineural dexmedetomidine certainly should be considered in future studies.

One clinical trial has assessed the duration of PNB (continuous infusion versus single-shot femoral nerve block) on rebound pain in patients undergoing anterior cruciate ligament repair, a very painful procedure [20]. Increased PNB duration (up to 33 h) reduced the severity of rebound pain but only at a clinically insignificant degree: 0.03 units on a pain scale from 0 to 10 per hour of block duration.

Patient specific hypothesis

As rebound pain results from mechanical–surgical pain from unopposed nociceptive input that is uncovered when PNB wears off, the phenomenon could be patient-related like the risk to present severe acute postoperative pain. It is worth noting that, whether the incidence of severe postoperative pain after discharge following inpatient surgery is 12–13% [4], the incidence of rebound pain, that is severe pain after discharge in outpatients who received a PNB remains unknown but might reach 40% (versus 10% in ambulatory patients who received general anesthesia alone) [10▪▪]. Presence and severity of preoperative pain at surgery site or elsewhere, younger age and female gender are prominent risk factors to develop severe acute postoperative pain, including for ambulatory patients [3,6]. Preoperative pain score during mobilization correlates to PNB rebound pain severity (association but not causation) [27] what is not really surprising because the intensity of preoperative pain can predict the severity of both acute [3,6] and chronic postsurgical pain [30]. Some patients have a heightened pain susceptibility in relation to individual psycho-physical factors [30]. Besides, rebound pain intensity and incidence tend to be reduced in older patients. Preliminary report mentioned severe pain (i.e. score >7/10) from 16 to 24 h after primary ankle fracture surgery under combined ropivacaine sciatic and saphenal PNBs in 67% of young patients (20–60 years old) versus only 9% of elderly patients (>60 years old) [31]. The pathophysiology of aging at levels of both peripheral and central nervous system might explain that observation [32]. Furthermore, the words chosen to express pain should also taken into account, young peoples using more frequently terms as 'hot, burning, sore, radiating pain' [33]. Finally, nor diabetes mellitus nor obesity, two pro-inflammatory medical conditions, did not increase the intensity of rebound pain [27].

LESSONS OF 'REBOUND PAIN': CRITICAL APPRAISAL OF PERIPHERAL NERVE BLOCKS PROPOSED TO AMBULATORY PATIENTS

Existence of rebound pain, that is patients' report of excruciating pain and major distress when PNB wears off questions the 'quality of current practice' particularly in ambulatory setting. In the past, few anesthesiologists were involved in postoperative cares what is now different with the development of perioperative medicine. However, because of economic pressure, the time allowed for explanations regarding PNB benefits versus harms is usually short. All the papers regarding rebound pain after PNB however highlight the importance of patient's education to either prevent or minimize its occurrence [16▪,17▪▪]. Patient's education should be done hand by hand with surgeons. Patients should be encouraged to take oral multimodal analgesics on a regular schedule and certainly before the PNB will wear off. More, some authors suggested that patients should be advised to compare rebound pain intensity to their preoperative pain rather than to the 'almost zero pain score' when PNB was working [27]. That way of thinking might reduce patient's anxiety and catastrophizing, thereby might help to better cope with pain.

Existence of rebound pain also challenges 'the role of PNBs in preventive analgesia' if one considers that severe acute postoperative pain is a major risk factor to develop persistent postsurgical pain [34]. Nevertheless, according to the few published studies, the phenomenon did not seem to influence patient's later outcome, in term of both function [16▪,19] and pain [10▪▪,13]. Similarly, transient

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thermal hyperalgesia found in experimental setting did not affect animals' behavioral recovery as both sensory thresholds and motor function returned to pre-PNB level at 24 h [23] and at 12 days [21].

CONCLUSION

Rebound pain, although often ignored, should be considered as an unwanted side effect of PNB, particularly in ambulatory setting where pain at home is more challenging to control. A major observation is the lack of large prospective study about the phenomenon. Rebound pain in some patient populations when PNB wears off is an opportunity to question its pathophysiology and also to improve daily practice. Besides patient's education about PNB's effects on sensations [17▪▪] and preventive analgesics intake, further studies should try to answer questions regarding prevalence, impact of type of surgery and type of PNB used (less or more distal PNB), preventive role of analgesic adjuvants added in PNB and endogenous patient's risk factors. Despite economic pressure and the well known early benefits of PNBs, rebound pain unanswered questions are one more challenge in the area of perioperative medicine.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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