

# Possible Mechanisms of Rebound Pain After Peripheral Nerve Block Subsides and Preventive Therapy Measures

Zeng Xu, Zhang Xianjie\*

Department of Anesthesiology, People's Hospital of Deyang City, Deyang, China

## Email address:

1185697091@qq.com (Zeng Xu), 16177211@qq.com (Zhang Xianjie)

\*Corresponding author

## To cite this article:

Zeng Xu, Zhang Xianjie. Possible Mechanisms of Rebound Pain After Peripheral Nerve Block Subsides and Preventive Therapy Measures. *International Journal of Anesthesia and Clinical Medicine*. Vol. 11, No. 2, 2023, pp. 82-87. doi: 10.11648/j.ijacm.20231102.16

Received: July 17, 2023; Accepted: August 1, 2023; Published: August 10, 2023

**Abstract:** Peripheral nerve block can enhance the analgesic impact for the duration of and after the operation, which is conducive to the early recuperation of useful workouts and bodily features after the operation, and enhance the relief of the patients. With the development and improvement of nerve block positioning technology, nerve block has grown to be greater and greater specific and safe, and has obtained greater and extra interest in the improvement of anaesthesia. However, rebound pain (RP) can also occur after the nerve block subsides. If RP occurs, it may also limit affected person delight in the much less extreme cases, and in the greater extreme cases, it may additionally have an effect on the patients' postoperative recovery, extend the medical institution stay, and make bigger the burden of clinical care. The pathogenesis of RP is nonetheless unclear, and it is now not nicely understood, and RP is frequently overlooked through clinical personnel in medical work. Preventing and treating RP is of top notch magnitude in enhancing postoperative restoration of sufferers present process peripheral nerve block anaesthesia. At present, there is nevertheless a lack of consensus on the prevention and remedy of RP. In latest years, pupils at domestic and overseas have performed a lot of lookup on RP, put ahead various conjectures on its pathogenesis, and supplied many preventive and healing measures, which include drug intervention, nerve stimulation, psychological intervention, etc., which supply greater theoretical groundwork for medical work. In this paper, we generally evaluation the prevention and therapy of RP from the elements of mechanism and intervention methods, and grant reference for the prevention and remedy of RP after nerve block cessation.

**Keywords:** Peripheral Nerve Block, Rebound Pain, Mechanism, Treatment

## 1. Introduction

Due to its benefits of effective analgesia, decreased postoperative opioid dosage, and shorter hospital stays, peripheral nerve blocks (PNBs) are frequently utilized; however, when the nerve block effect wears off, moderate or severe pain may develop. Rebound Pain (RP), which is defined as severe pain (NRS>7) that develops after the effects of a peripheral nerve block have worn off, can cause unintended usage of medical resources in addition to being exceedingly distressing for the patient.

## 2. Status of Research on Rebound Pain

Although the idea of RP following nerve block has been

modified continuously since 2007 till the present, a standardized formal definition has not yet been established. RP is frequently described as an underappreciated and poorly understood phenomenon in contemporary studies. Effective control strategies are still unavailable, and the mechanism by which RP occurs is unknown. The pathophysiology of RP has been the subject of several contemporary ideas, including nociceptive hypersensitivity, insufficient multimodal analgesia, local anesthetic harm, and patient-related reasons. This can be accomplished with continuous PNB, the addition of local anesthetic adjuvants (such dexamethasone), and multimodal analgesia to stop patients from experiencing severe RP after surgery.

### 3. Possible Mechanisms for the Occurrence of Rebound Pain

#### 3.1. Nociceptive Sensitization: Hyperactivity of C-fibers and Overexcitation of Nociceptive Receptors

The two most noticeable symptoms in people with neuropathic pain are nociceptive hypersensitivity (pain felt in response to painless stimuli) and nociceptive sensitization (increased response to painful stimuli). Nociceptive sensitization is a clinical phenomenon marked by decreased pain thresholds and increased sensitivity to injurious stimuli, which produces varying degrees of nociceptive sensitization at, around, and even away from the site of injury. A more potent nociceptive response results as a result. The primary pathophysiological mechanism of RP may involve aberrant spontaneous C-fibre hyperactivity and overactivation of nociceptive receptors in the presence of non-mechanical nerve injury [1]. Nociceptive sensitization can be classified as thermal, cold, or mechanical depending on the technique of detection, with thermal nociceptive sensitization being strongly associated to RP. When Kolarczyk et al. [2] examined the behavioral changes that occurred in rats after receiving a single injection of ropivacaine to block the sciatic nerve, they discovered that significant thermal nociceptive hypersensitivity might develop after the effect of the nerve block had worn off. This finding was later corroborated by Janda et al. [3]. The sciatic nerve was also blocked by An [4] and colleagues using bupivacaine plus dexamethasone (test group) and without dexamethasone (control group), as well as toluidine blue staining and immunohistochemistry.

#### 3.2. Side Effects of Local Anaesthesia: Mechanical Injury

Local anesthetic (LA) procedures may be a significant factor in the development of RP due to mechanical (needle injury, local compression) nerve damage [5]. A nerve block may result in intra-neural injections and local hemorrhages, which can increase intra-neural pressure and, if the capillary occlusion pressure is exceeded, cause nerve ischaemia and focal demyelination. On the one hand, the needle may directly damage the peripheral nerve, which could result in pain [6]. It's unclear whether nerve damage sustained during PNB worsens RP once the nerve block wears off.

#### 3.3. Toxic Reactions to Local Anesthetics

The reversible neurotoxicity of neighborhood anesthetics might also be one of the mechanisms main to RP. The mechanism of action varies between neighborhood anaesthetics, with amide and ester neighborhood anaesthetics main to DNA breakage, endoplasmic reticulum calcium depletion, calcium overload in mitochondria, decreased membrane doable and uncoupling of oxidative phosphorylation, ensuing in decreased ATP synthesis [7]. Studies have proven that bupivacaine reasons a excessive manufacturing of intracellular reactive oxygen species (ROS) and induces mobile autophagy, and that the aggregate of these

intracellular elements motives harm to Schwann cells and apoptosis, macrophage infiltration, injury to myelin sheaths, and hence ache [8]. If large doses of nearby anaesthetic are injected around the goal nerve, this can lead to a neighborhood muscular poisonous response which is dose, awareness and time dependent. In addition, some neighborhood anaesthetics are inherently pro-inflammatory and might also lead to a in addition make bigger in pain. A potential find out about through Gordon et al. on oral surgical treatment sufferers located that bupivacaine upregulated COX-2 expression in oral mucosal epithelial cells, promoted PGE2 manufacturing and improved ache after LA subsided [9]. Other nearby anaesthetic pills related with the improvement of RP after the withdrawal of nerve blocks consist of mepivacaine [10] and ropivacaine [11].

#### 3.4. Inadequate Multi-Modal Analgesia

Multimodal analgesia refers to the aggregate of analgesic modalities and drugs with one-of-a-kind mechanisms to minimize the quantity of single pills used, limit poisonous aspect outcomes and acquire ultimate analgesia via synergistic or superimposed results [12]. The software of multimodal analgesia strategies can limit the quantity of opioids used for the duration of surgery, limit toxicities, enhance analgesic efficacy and shorten the common quantity of days sufferers remain in hospital. However, it might also additionally lead to RP if analgesia is now not enough [12].

#### 3.5. Patient Related Factors

Patient-related risk factors such as age and gender have been suggested to be related with the incidence and severity of RP, and younger, girl sufferers have been proven to have a greater incidence of RP [13]. A find out about by using Sort et al [11] confirmed that the incidence and severity of RP after nerve block used to be decrease in sufferers over 60 years of age in contrast to these between 20-60 years of age, and that the mechanism of prevalence can also be associated to altered nociceptive grasp and deep tissue harm perception. In experiments with younger and older volunteers, Lautenbacher et al [14] observed an make bigger in the threshold of bodily sensation to innocuous stimuli and a limit in the threshold to demanding ache with growing age, and variations in the understanding of deep tissue (muscle) damage versus superficial tissue (skin) damage with recognize to age. Furthermore, as nociceptive sensation consists of each bodily and emotional dimensions, psychological research have proven that sturdy contrasts and abrupt modifications beautify terrible stimuli extra significantly, such as the disappearance of a nerve block [15], it is possibly that sufferers dealt with with PNB will have a assessment bias that impacts the patient's nociceptive sensation score.

#### 3.6. Surgery-Related Factors

Studies have proven [8] a greater incidence of RP in orthopaedic surgery, specially in top limb surgery. Surgical damage reasons ordinary plasticity modifications in peripheral

harm receptors and central neurons [16], and harm to peripheral damage receptor receptors may also set off power ache signals, which in flip may additionally lead to nociceptive hypersensitivity or unusual nociception [17]. Reichling et al [16] recommended that acute inflammatory damage or environmental stress stimuli (such as surgical trauma) set off a extended hypersensitivity of damage receptors to inflammatory cytokines in response to neuronal plasticity in major afferent harm nerve fibres (injury receptors), a phenomenon related with the  $\epsilon$  isoform of protein kinase C and the switching of intracellular signalling pathways that mediate cytokine-induced damage receptor hyperexcitability.

## 4. Preventive and Therapeutic Measures

### 4.1. Drug Control

There are many pills presently used clinically to minimize rebound ache after nerve block, together with glucocorticoids, sedatives, analgesics, calcium channel modulators, etc. These drugs, used as adjuvants to nerve block, no longer solely lengthen the length of analgesia and reduce the incidence of RP, however additionally limit the want for opioids.

#### 4.1.1. Glucocorticoids

Glucocorticoids have a range of features such as anti-inflammatory, anti-allergic and immunomodulatory, and are extensively used in scientific practice. They have been validated in countless research to relieve RP after nerve block, however their mechanism is now not but clear. In a randomised managed find out about [18] investigating whether or not the addition of dexamethasone decreased the incidence of RP after a single nerve block, 132 sufferers scheduled for inside fixation of top limb fractures below brachial plexus nerve block had been randomised into two groups, one given 0.375% ropivacaine + eight mg dexamethasone and the different given 0.375% ropivacaine only. The effects of the find out about showed that dexamethasone as a nerve block adjuvant decreased RP after a single nerve block. Morita et al [19] observed that levobupivacaine compounded with dexamethasone for interosseous groove get entry to brachial plexus nerve blocks each extended block length and decreased RP after arthroscopic rotator cuff repair. Woo et al [20] located that combining dexamethasone with ropivacaine for a single brachial plexus block resulted in a smoother withdrawal of the nerve block and a decrease incidence of RP after block withdrawal. Other glucocorticoids that play a position in decreasing RP consist of betamethasone [21] and others. Glucocorticoids can reason negative consequences such as osteoporosis, expanded blood sugar and cardiovascular disorder all through treatment. These detrimental results are associated to elements such as dose, dosage form, dosing regimen, inappropriate discontinuation, length of cure and age of the patient, the most essential being excessive doses and long-term use and inappropriate discontinuation. Clinical journey and experiments have tested that the blessings of the

usage of glucocorticosteroids in small doses and for brief durations of time outweigh the dangers and can acquire accurate scientific results.

#### 4.1.2. Sedative-Hypnotics and Intravenous Anaesthetics

From the reachable literature, sedative-hypnotics (dexmedetomidine, etc.) and intravenous anesthetics (ketamine, esketamine) [22] are used as adjuvants for PNBs, which may additionally alleviate RP to some extent after the block wears off. Hwang et al [23] discovered that dexmedetomidine blended with PNBs had a sizable potentiating impact in relieving postoperative ache after arthroscopic rotator cuff repair, decreasing VAS rankings at forty eight hours postoperatively and contributing to extended affected person satisfaction, as nicely as lowering serum stages of inflammatory elements such as IL-6 and IL-8 and delaying the onset of RP nodes at forty eight hours postoperatively. In a latest potential medical learn about of ketamine for the prevention of RP in peripheral nerve blocks, a single intravenous antinociceptive dose (0.3 mg/kg) of ketamine was once discovered no longer to decrease the incidence and depth of RP after cessation of peripheral nerve blocks [24]. However, some other potential learn about confirmed that the mixture of ketamine with a neighborhood anaesthetic (ropivacaine) resulted in higher analgesia inside forty eight h and multiplied affected person satisfaction. In addition to this, it has additionally been shown [25] that the perioperative sedation of ketamine can no longer solely decrease the prevalence of postoperative nausea and vomiting to a positive extent, however additionally decrease the consumption of perioperative analgesic drugs, which is conducive to lowering the depth of postoperative pain.

#### 4.1.3. Analgesics

Currently, the effectiveness of analgesics such as nalbuphine, ketorolac and tramadol as nerve blockading adjuvants in stopping and treating RP stays to be investigated. Ketorolac, one of the regularly used analgesics, can be used in mixture with opioids such as fentanyl, sufentanil, oxycodone and diazoxide for postoperative analgesia. Studies have cautioned [26] that perioperative non-use of ketorolac is a excessive chance thing for postoperative RP and that perioperative software of ketorolac can also furnish tremendous ache comfort for most patients, however in addition scientific research are lacking. In addition, Rao et al [27] located that nalbuphine as a nerve block adjuvant ought to extend sensory blockade and may want to furnish some remedy to patients' postoperative pain, as a consequence decreasing the want for emergency postoperative analgesia and successfully lowering the incidence of persistent postoperative pain.

#### 4.1.4. Calcium Channel Modulator

Calcium channel modulators are the first-line pills used in the therapy of neuropathic pain, the predominant frequent pills being gabapentin and pregabalin. Pregabalin is a gamma-aminobutyric acid (GABA) analogue that modulates the voltage-dependent  $\text{Ca}^{2+}$  channels in the central worried

machine thru the blood-brain barrier, thereby affecting  $\text{Ca}^{2+}$  inward glide and presenting high quality manipulate of neurotransmitter transmission, which in flip inhibits central sensitization for analgesic purposes. Pregabalin has been suggested foreign places for postoperative analgesia in orthopaedics [28, 29].

#### **4.2. Transauricular Vagus Nerve Stimulation**

Zhou et al [30] determined that intra-auricular vagus nerve electrical stimulation (taVNS) used to be fine in relieving rebound ache after anterior cruciate ligament reconstruction (ACLR) and decreased the want for extra postoperative analgesia and decreased the incidence of postoperative complications.

#### **4.3. Hyper-Advanced Analgesia**

Hyper-analgesia refers to a kind of analgesic remedy that prevents the transmission and conduction of peripheral damage impulses to the centre. It can attain post-traumatic analgesia and minimize the quantity of analgesic tablets used in the perioperative length by way of decreasing peripheral and central sensitisation brought on with the aid of sign afferents from noxious stimuli, thereby inhibiting adjustments in neuroplasticity. Pre-analgesia performs a key position in lowering intraoperative ache and stopping postoperative ache [31]. Various animal research and medical research have proven that pre-analgesia has giant preventive and inhibitory results on peripheral and central sensitization, which can efficiently relieve postoperative pain, limit the quantity of postoperative opioids and enhance patients' postoperative comfort, in line with the scientific notion of "early intervention". Zhang et al [32] confirmed by using Meta-analysis that the use of over-the-top analgesia in sufferers present process lumbar backbone surgical operation relieved postoperative pain, decreased opioid consumption and did no longer expand complications, as validated by means of a find out about through Wang et al [33].

#### **4.4. Multi-Modal Analgesia**

Multimodal analgesia refers to the synergistic utility of analgesic tablets and analgesic techniques with exclusive mechanisms to obtain the excellent analgesic impact and to minimise the facet outcomes of a single drug or method. Multimodal analgesia can act on specific aims in the ache transmission pathway to acquire a superimposed or synergistic analgesic impact and minimize peripheral and central sensitization, accordingly attaining top of the line analgesia [34]. In addition, some research have proven that the period of motion of regional anaesthesia can be extended the usage of non-stop catheter strategies or supplemented with techniques such as nearby anaesthesia, which ought to additionally theoretically assist to alleviate RP, however similarly research are wanted to affirm this.

#### **4.5. Ultrasound-Guided Puncture**

A present day learn about [5] suggests that one mechanism

for the incidence of RP after surgical procedure may also be mechanical nerve harm brought on in the course of the nerve block operation, such as direct needle damage to the nerve and nerve ischaemia and hypoxia induced by way of neighborhood haematoma compression of the nerve. To keep away from the above, firstly, ultrasound Doppler method can be used to become aware of the nerves round the goal site, the blood vessels in the puncture course and the blood drift sign to stop injury to the nerves and blood vessels; secondly, real-time ultrasound-guided puncture can be used to discover the deflated blood vessels by means of the use of the probe lifting technique to keep away from injury to the blood vessels at some stage in puncture; thirdly, inject the drug slowly, pay interest to the backdrawing earlier than every drug administration and pay shut interest to whether or not the affected person suggests any nerve dissociation; fourthly, if no liquid darkish place of drug diffusion is discovered close to the goal nerve after drug injection, interest must be paid to whether or not there is any neighborhood anesthetic into the blood and the drug injection ought to be stopped right away [34].

#### **4.6. Reduce the Amount of Local Anesthetic and Choose the Lowest Effective Concentration**

The reversible neurotoxicity of nearby anesthetics is one of the viable mechanisms for the prevalence of RP. Although numerous research have proven that nearby anesthetics are neurotoxic to some extent, the extent of their impairment of motor and sensory function, the length of toxicity and whether or not they are reversible continue to be unclear. In order to prevent RP after nerve block due to neurotoxic reactions, we can, on the one hand, reduce the amount of local anaesthetics for a single nerve and, on the other hand, try to avoid using high concentrations of local anaesthetics, such as bupivacaine and ropivacaine, with concentrations generally not exceeding 0.375% and 0.5% respectively. At the same time, during continuous nerve blocks, it is important to use as low a concentration of local anaesthetic as possible and for as short a time as possible.

#### **4.7. Prolong the Nerve Block Time**

Another way of mitigating RP is to lengthen the nerve block so that it covers the interestingly dangerous enter time factors at the web page of surgical or pathological harm [35]. Using Meta-analysis, Williams et al [36] confirmed that the longer the length of the nerve block, the much less in all likelihood it used to be that RP would occur. Fang et al [16] confirmed that sufferers in the ropivacaine plus dexamethasone team ought to have a five-hour longer nerve block and a decrease incidence of RP after the block wore off in contrast to sufferers with ropivacaine only.

#### **4.8. Patient Education**

Pain is a subjective sensation that is no longer clearly a physiological response, however a twin bodily and intellectual sensation. Because the quantification of rebound ache is

decided by using the ache rankings mentioned with the aid of sufferers at extraordinary time factors throughout their postoperative recovery, some sufferers might also ride comparative biases that have an effect on their ache ratings due to psychological elements and insufficient preoperative verbal exchange [34], making preoperative schooling of sufferers important. On the one hand, preoperative schooling can provide sufferers and their households a simple appreciation of the surgical manner and assist to limit patients' anxiety and anxiety; on the different hand, it can additionally provide sufferers a sure grasp of perioperative ache thru preoperative visits and schooling by means of anaesthetists, so that sufferers have a right expectation of postoperative pain.

## 5. Conclusion

The reasons of RP after nerve block regression are complicated and, to our cutting-edge knowledge, the most important motives for the prevalence of RP are that the nerve block did no longer regress at the most efficient time factor and that the transition to a subsequent ache administration routine was once poorly planned. Factors presently recognized to be clinically related with an expanded chance of RP encompass being young, being female, orthopaedic surgical operation (particularly in the top limb), and now not having intravenous dexamethasone in the perioperative period. Currently, there are few medical modalities to mitigate RP and a good deal exploration is wished to locate higher analgesic strategies.

## References

- [1] Dada, O., Gonzalez Zacarias, A., Ongaigui, C., Echeverria-Villalobos, M., Kushelev, M., Bergese, S. D., & Moran, K. (2019). Does Rebound Pain after Peripheral Nerve Block for Orthopedic Surgery Impact Postoperative Analgesia and Opioid Consumption? A Narrative Review. *International journal of environmental research and public health*, 16 (18), 3257. <https://doi.org/10.3390/ijerph16183257>
- [2] Kolarczyk, L. M., & Williams, B. A. (2011). Transient heat hyperalgesia during resolution of ropivacaine sciatic nerve block in the rat. *Regional anesthesia and pain medicine*, 36 (3), 220–224. <https://doi.org/10.1097/AAP.0b013e3182176f5a>
- [3] Janda, A., Lydic, R., Welch, K. B., & Brummett, C. M. (2013). Thermal hyperalgesia after sciatic nerve block in rat is transient and clinically insignificant. *Regional anesthesia and pain medicine*, 38 (2), 151–154. <https://doi.org/10.1097/AAP.0b013e3182813aae>
- [4] An, K., Elkassabany, N. M., & Liu, J. (2015). Dexamethasone as adjuvant to bupivacaine prolongs the duration of thermal antinociception and prevents bupivacaine-induced rebound hyperalgesia via regional mechanism in a mouse sciatic nerve block model. *PLoS one*, 10 (4), e0123459. <https://doi.org/10.1371/journal.pone.0123459>
- [5] Lavand'homme P. (2018). Rebound pain after regional anesthesia in the ambulatory patient. *Current opinion in anaesthesiology*, 31 (6), 679–684. <https://doi.org/10.1097/ACO.0000000000000651>
- [6] Brull, R., Hadzic, A., Reina, M. A., & Barrington, M. J. (2015). Pathophysiology and Etiology of Nerve Injury Following Peripheral Nerve Blockade. *Regional anesthesia and pain medicine*, 40 (5), 479–490. <https://doi.org/10.1097/AAP.0000000000000125>
- [7] Perez-Castro, R., Patel, S., Garavito-Aguilar, Z. V., Rosenberg, A., Recio-Pinto, E., Zhang, J., Blanck, T. J., & Xu, F. (2009). Cytotoxicity of local anesthetics in human neuronal cells. *Anesthesia and analgesia*, 108 (3), 997–1007. <https://doi.org/10.1213/ane.0b013e31819385e1>
- [8] Yang, S., Abrahams, M. S., Hurn, P. D., Grafe, M. R., & Kirsch, J. R. (2011). Local anesthetic Schwann cell toxicity is time and concentration dependent. *Regional anesthesia and pain medicine*, 36 (5), 444–451. <https://doi.org/10.1097/AAP.0b013e318228c835>
- [9] Gordon, S. M., Chuang, B. P., Wang, X. M., Hamza, M. A., Rowan, J. S., Brahim, J. S., & Dionne, R. A. (2008). The differential effects of bupivacaine and lidocaine on prostaglandin E2 release, cyclooxygenase gene expression and pain in a clinical pain model. *Anesthesia and analgesia*, 106 (1). <https://doi.org/10.1213/01.ane.0000296474.79437.23>
- [10] Sellbrant, I., Karlsson, J., Jakobsson, J. G., & Nellgård, B. (2021). Supraclavicular block with Mepivacaine vs Ropivacaine, their impact on postoperative pain: a prospective randomised study. *BMC anesthesiology*, 21 (1), 273. <https://doi.org/10.1186/s12871-021-01499-z>
- [11] Sort, R., Brorson, S., Gögenur, I., Nielsen, J. K., & Møller, A. M. (2019). Rebound pain following peripheral nerve block anaesthesia in acute ankle fracture surgery: An exploratory pilot study. *Acta anaesthesiologica Scandinavica*, 63 (3), 396–402. <https://doi.org/10.1111/aas.13290>
- [12] O'Neill, A., & Lirk, P. (2022). Multimodal Analgesia. *Anesthesiology clinics*, 40 (3), 455–468. <https://doi.org/10.1016/j.anclin.2022.04.002>
- [13] Barry, G. S., Bailey, J. G., Sardinha, J., Brousseau, P., & Uppal, V. (2021). Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. *British journal of anaesthesia*, 126 (4), 862–871. <https://doi.org/10.1016/j.bja.2020.10.035>
- [14] Lautenbacher, S., Kunz, M., Strate, P., Nielsen, J., & Arendt-Nielsen, L. (2005). Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain*, 115 (3), 410–418. <https://doi.org/10.1016/j.pain.2005.03.025>
- [15] Voichok, G., & Novemsky, N. (2021). Asymmetric Hedonic Contrast: Pain Is More Contrast Dependent Than Pleasure. *Psychological science*, 32 (7), 1038–1046. <https://doi.org/10.1177/0956797621991140>
- [16] Reichling, D. B., & Levine, J. D. (2009). Critical role of nociceptor plasticity in chronic pain. *Trends in neurosciences*, 32 (12), 611–618. <https://doi.org/10.1016/j.tins.2009.07.007>
- [17] Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *The journal of pain*, 10 (9), 895–926. <https://doi.org/10.1016/j.jpain.2009.06.012>
- [18] Fang, J., Shi, Y., Du, F., Xue, Z., Cang, J., Miao, C., & Zhang, X. (2021). The effect of perineural dexamethasone on rebound pain after ropivacaine single-injection nerve block: a randomized controlled trial. *BMC anesthesiology*, 21 (1), 47. <https://doi.org/10.1186/s12871-021-01267-z>

- [19] Morita, S., Oizumi, N., Suenaga, N., Yoshioka, C., Yamane, S., & Tanaka, Y. (2020). Dexamethasone added to levobupivacaine prolongs the duration of interscalene brachial plexus block and decreases rebound pain after arthroscopic rotator cuff repair. *Journal of shoulder and elbow surgery*, 29 (9), 1751–1757. <https://doi.org/10.1016/j.jse.2020.04.019>
- [20] Woo, J. H., Lee, H. J., Oh, H. W., Lee, J. W., Baik, H. J., & Kim, Y. J. (2021). Perineural dexamethasone reduces rebound pain after ropivacaine single injection interscalene block for arthroscopic shoulder surgery: a randomized controlled trial. *Regional anesthesia and pain medicine*, 46 (11), 965–970. <https://doi.org/10.1136/rapm-2021-102795>
- [21] Watanabe, K., Tokumine, J., Yoroze, T., Moriyama, K., Sakamoto, H., & Inoue, T. (2016). Particulate-steroid betamethasone added to ropivacaine in interscalene brachial plexus block for arthroscopic rotator cuff repair improves postoperative analgesia. *BMC anesthesiology*, 16 (1), 84. <https://doi.org/10.1186/s12871-016-0251-9>
- [22] Yu, L., Zhou, Q., Li, W., Zhang, Q., Cui, X., Chang, Y., & Wang, Q. (2022). Effects of Esketamine Combined with Ultrasound-Guided Pectoral Nerve Block Type II on the Quality of Early Postoperative Recovery in Patients Undergoing a Modified Radical Mastectomy for Breast Cancer: A Randomized Controlled Trial. *Journal of pain research*, 15, 3157–3169. <https://doi.org/10.2147/JPR.S380354>
- [23] Hwang, J. T., Jang, J. S., Lee, J. J., Song, D. K., Lee, H. N., Kim, D. Y., Lee, S. S., Hwang, S. M., Kim, Y. B., & Lee, S. (2020). Dexmedetomidine combined with interscalene brachial plexus block has a synergistic effect on relieving postoperative pain after arthroscopic rotator cuff repair. *Knee surgery, sports traumatology, arthroscopy: official journal of the ESSKA*, 28 (7), 2343–2353. <https://doi.org/10.1007/s00167-019-05799-3>
- [24] Touil, N., Pavlopoulou, A., Barbier, O., Libouton, X., & Lavand'homme, P. (2022). Evaluation of intraoperative ketamine on the prevention of severe rebound pain upon cessation of peripheral nerve block: a prospective randomised, double-blind, placebo-controlled study. *British journal of anaesthesia*, 128 (4), 734–741. <https://doi.org/10.1016/j.bja.2021.11.043>
- [25] Zhu, T., Gao, Y., Xu, X., Fu, S., Lin, W., & Sun, J. (2020). Effect of Ketamine Added to Ropivacaine in Nerve Block for Postoperative Pain Management in Patients Undergoing Anterior Cruciate Ligament Reconstruction: A Randomized Trial. *Clinical therapeutics*, 42 (5), 882–891. <https://doi.org/10.1016/j.clinthera.2020.03.004>
- [26] McNicol, E. D., Ferguson, M. C., & Schumann, R. (2021). Single-dose intravenous ketorolac for acute postoperative pain in adults. *The Cochrane database of systematic reviews*, 5 (5), CD013263. <https://doi.org/10.1002/14651858.CD013263.pub2>
- [27] Rao, J., Gao, Z., Qiu, G., Gao, P., Wang, Q., Zhong, W., Wang, Y., & Li, Y. (2021). Nalbuphine and dexmedetomidine as adjuvants to ropivacaine in ultrasound-guided erector spinae plane block for video-assisted thoracoscopic lobectomy surgery: A randomized, double-blind, placebo-controlled trial. *Medicine*, 100 (32), e26962. <https://doi.org/10.1097/MD.00000000000026962>
- [28] Burke, S. M., & Shorten, G. D. (2010). Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. *Anesthesia and analgesia*, 110 (4), 1180–1185. <https://doi.org/10.1213/ANE.0b013e3181cf949a>
- [29] Giancesello, L., Pavoni, V., Barboni, E., Galeotti, I., & Nella, A. (2012). Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. *Journal of neurosurgical anesthesiology*, 24 (2), 121–126. <https://doi.org/10.1097/ANA.0b013e31823a885b>
- [30] Zhou, Q., Yu, L., Yin, C., Zhang, Q., Tai, Y., Zhu, L., Dong, J., & Wang, Q. (2022). Effect of Transauricular Vagus Nerve Stimulation on Rebound Pain After Ropivacaine Single Injection Femoral Nerve Block for Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Journal of pain research*, 15, 1949–1958. <https://doi.org/10.2147/JPR.S370589>
- [31] Xuan, C., Yan, W., Wang, D., Li, C., Ma, H., Mueller, A., Chin, V., Houle, T. T., & Wang, J. (2022). Efficacy of preemptive analgesia treatments for the management of postoperative pain: a network meta-analysis. *British journal of anaesthesia*, 129 (6), 946–958. <https://doi.org/10.1016/j.bja.2022.08.038>
- [32] Zhang, L. K., Li, Q., Quan, R. F., & Liu, J. S. (2021). Is preemptive analgesia a good choice for postoperative pain relief in lumbar spine surgeries?: A meta-analysis of randomized controlled trials. *Medicine*, 100 (13), e25319. <https://doi.org/10.1097/MD.00000000000025319>
- [33] Wang, C., Fu, H., Wang, J., Huang, F., & Cao, X. (2021). Preemptive analgesia using selective cyclooxygenase-2 inhibitors alleviates postoperative pain in patients undergoing total knee arthroplasty: A protocol for PRISMA guided meta-analysis of randomized controlled trials. *Medicine*, 100 (7), e24512. <https://doi.org/10.1097/MD.00000000000024512>
- [34] Muñoz-Leyva, F., Cubillos, J., & Chin, K. J. (2020). Managing rebound pain after regional anesthesia. *Korean journal of anesthesiology*, 73 (5), 372–383. <https://doi.org/10.4097/kja.20436>
- [35] Stone, A., Lirk, P., & Vlassakov, K. (2022). Rebound Pain After Peripheral Nerve Blockade-Bad Timing or Rude Awakening?. *Anesthesiology clinics*, 40 (3), 445–454. <https://doi.org/10.1016/j.anclin.2022.03.002>
- [36] Williams, B. A., Bottegall, M. T., Kentor, M. L., Irrgang, J. J., & Williams, J. P. (2007). Rebound pain scores as a function of femoral nerve block duration after anterior cruciate ligament reconstruction: retrospective analysis of a prospective, randomized clinical trial. *Regional anesthesia and pain medicine*, 32 (3), 186–192. <https://doi.org/10.1016/j.rapm.2006.10.011>