



Prevention of Chronic Post-Surgical Pain

Introduction

Chronic pain occurring after a surgical procedure has received special attention since its first description by Macrae just more than 20 years ago [19]. Almost 40 million people undergo surgery each year. Among them, one patient out of 10 will develop chronic postsurgical pain (CPSP), and one patient out of 100 will suffer severe CPSP which will negatively affect his/her quality of life. In 35 to 57% of the patients enduring CPSP, a neuropathic component [20] is present which increases pain severity and worsens the quality of life [1]. Reports from the recently developed “transitional pain services” support these findings [2].

The transition from acute to chronic pain is a complex process, involving multiple mechanisms at different levels [3]. Current knowledge suggests mechanisms in relation to both peripheral (at the site of tissue trauma) and central (spinal and supraspinal) sensitization [4]. Drugs have been studied as preventive strategies, including drugs which target spinal excitatory process and/or display anti-inflammatory properties able to modulate the release of pro-inflammatory mediators by peripheral immune and central glial cells [21]. Because the intensity and duration of acute postoperative pain has often been found as a major risk factor of CPSP, attention has often focused on the control of acute postoperative pain as preventive strategy [5].

Prevention of Chronic Pain After Surgery

Surgery constitutes one of the main causes of chronic pain and, since it is often scheduled and, thus, predictable, this makes preventive strategies easier to apply. However, most studies investigated the use of drugs (or regional anesthesia techniques) only in the immediate perioperative period or just before surgery. From these data, there is only limited evidence showing that any perioperative agent can consistently reduce the risk of CPSP [6]. Another critical aspect is a non-selected preventive approach by treating all patients similarly; stratified prevention in only those patients being at high risk for chronification might increase preventive success. Because risk assessment is – at least in part – possible, such studies need to be performed in the future.

Mechanistically, N-Methyl-D-Aspartate (NMDA) receptor antagonists play a pivotal role in central plastic changes and in spinal/cortical potentiation contributing to chronic pain. They also modulate inflammation. Perioperative intravenous ketamine reduces postoperative analgesic consumption and pain intensity. Until now, perioperative ketamine has been identified as one of the interventions carrying possible benefit in prevention, particularly in case of highly painful procedures e.g. orthopedic surgery [7] and patients with preoperative pain and opioid consumption [8,9]. A large randomized controlled trial (called “ROCKeT trial”) is currently ongoing to assess these findings [10]. Preventive effect

of methadone, an opioid with unique properties including NMDA receptor antagonism, which intraoperative administration reduces postoperative pain up to 30 days is currently studied [11].

Gabapentinoids given during the perioperative period, including pregabalin and gabapentin, have a mild effect on postoperative pain but reduce opioid requirements. Gabapentinoids don't appear to prevent CPSP development [12] but might affect the incidence of CPSP with a neuropathic component [12].

Intravenous lidocaine may be used, i.e. as an alternative to epidural analgesia, to reduce postoperative pain and improve recovery but effects on acute pain are limited [13]. A recent meta-analysis supports the use of perioperative lidocaine infusion to reduce CPSP development at 3 months post-surgery, and particularly after breast cancer surgery [14]. Regarding other routes of local anesthetics administration, epidural anesthesia may reduce CPSP after thoracotomy and regional techniques after breast cancer surgery; continuous wound infiltration also may decrease CPSP after cesarean delivery and iliac crest bone graft harvesting [15, 22]. Very few studies have been published so far with clonidine, dexmedetomidine, nefopam or other antihyperalgesic drugs.

Finally, the benefit of antidepressant drugs for the prevention of acute and CPSP has been debated [16]. Recent publications suggest that perioperative duloxetine might improve the quality of recovery and reduce CPSP development in patients presenting preoperative central sensitized state [17].

What is mainly undefined is the dose and duration of treatment required for almost every treatment option. A balance between efficacy and safety should be considered and risk adaptation for patients should be made as usual. All drugs discussed here are off label for the perioperative use. Thus, patients need to be informed and have to consent.

Drugs and regional analgesia techniques are not the only choices for preventing chronification. In fact, it is very important to realize that chronification of pain is a biopsychosocial process requiring a multidisciplinary approach. For chronic pain after surgery, the exact contribution of each aspect and biopsychosocial intervention strategies required to prevent them need to be proven in the future.

Conclusion

Pain prevention, both severe acute pain and CPSP development, remains an area of unmet clinical need. Some major reasons for preventive strategies failure are already known like the lack of treatment individualisation [7,17] and the duration of preventive treatment application [17]. Moreover, the chronic intake of postoperative opioids which may contribute to pain persistence deserves further considerations. The aforementioned findings question the relationship between acute pain control and CPSP development. They also support the need for patient stratification and argue for a close follow up of targeted patients supporting the role of transitional pain services [18]. An important step has been done by the inclusion of chronic pain, regardless of its origin, in the next International Classification of Diseases (ICD-11) [1]. Hopefully, that will increase the visibility of CPSP and will promote research in the field as well as the development of preventive strategies.

REFERENCES

1. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, et al. (2019) The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain* 160: 45-52.
2. Tiippana E, Hamunen K, Heiskanen T, Nieminen T, Kalso E, et al. (2016) New approach for treatment of prolonged postoperative pain: APS Out-Patient Clinic. *Scand J Pain* 12: 19-24.
3. Glare P, Aubrey KR, Myles PS (2019) Transition from acute to chronic pain after surgery. *Lancet* 393: 1537-1546.
4. Pogatzki-Zahn EM, Segelcke D, Schug SA (2017) Postoperative pain-from mechanisms to treatment. *Pain Rep* 2: e588.
5. Gilron I, Vandenkerkhof E, Katz J, Kehlet H, Carley M (2017) Evaluating the Association Between Acute and Chronic Pain After Surgery: Impact of Pain Measurement Methods. *Clin J Pain* 33: 588-594.
6. Steyaert A, Lavand'homme P (2018) Prevention and Treatment of Chronic Postsurgical Pain: A Narrative Review. *Drugs* 78: 339-354.
7. McNicol ED, Schumann R, Haroutounian S (2014) A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* 58: 1199-1213.
8. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, et al. (2010) Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* 113: 639-646.
9. Nielsen RV, Fomsgaard JS, Nikolajsen L, Dahl JB, Mathiesen O (2019) Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: A randomized clinical trial of opioid-dependent patients. *Eur J Pain* 23: 455-460.
10. Schug SA, Peyton P (2017) Does perioperative ketamine have a role in the prevention of chronic postsurgical pain: the ROCKet trial. *Br J Pain* 11: 166-168.
11. Murphy GS, Szokol JW (2019) Intraoperative Methadone in Surgical Patients: A Review of Clinical Investigations. *Anesthesiology* 131: 678-692.
12. Martinez V, Pichard X, Fletcher D (2017) Perioperative pregabalin administration does not prevent chronic postoperative pain: systematic review with a meta-analysis of randomized trials. *Pain* 158: 775-783.
13. Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, et al. (2015) Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev*: CD009642.
14. Bailey M, Corcoran T, Schug S, Toner A (2018) Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. *Pain* 159: 1696-1704.
15. Weinstein EJ, Levene JL, Cohen MS, Andreae DA, Chao JY, et al. (2018) Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. *Cochrane Database Syst Rev* 6: CD007105.
16. Wong K, Phelan R, Kalso E, Galvin I, Goldstein D, et al. (2014) Antidepressant drugs for prevention of acute and chronic postsurgical pain: early evidence and recommended future directions. *Anesthesiology* 121: 591-608.
17. Koh IJ, Kim MS, Sohn S, Song KY, Choi NY, et al. (2019) Duloxetine Reduces Pain and Improves Quality of Recovery Following Total Knee Arthroplasty in Centrally Sensitized Patients: A Prospective, Randomized Controlled Study. *J Bone Joint Surg Am* 101: 64-73.
18. Katz J, Weinrib A, Fashler SR, Katznelzon R, Shah BR, et al. (2015) The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. *J Pain Res* 8: 695-702.
19. Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. *Pain*. 1998;76(1-2):167-71
20. Haroutunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain*. 2013 Jan;154(1):95-102.
21. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database Syst Rev*. 2013 Jul 24;(7):CD008307.
22. Hussain N, Shastri U, McCartney CJL, Gilron I, Fillingim RB, Clarke H, Katz J, Juni P, Laupacis A, Wijeyesundera D, Abdallah FW. Should thoracic paravertebral blocks be used to prevent chronic postsurgical pain after breast cancer surgery? A systematic analysis of evidence in light of IMMPACT recommendations. *Pain*. 2018 Oct;159(10):1955-1971.

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