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Review

EVIDENCE-BASED STRATEGIES FOR MULTIMODAL POSTOPERATIVE PAIN MANAGEMENT

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SUMMARY – Surgery causes postoperative pain that should be immediately and effectively treated. Postoperative pain management is in central focus when planning postoperative treatment and is becoming the standard of care after surgical protocols – Enhanced Recovery after Surgery (ERAS). There are various serious complications associated with poorly controlled postoperative pain in adult surgical patients – cardiopulmonary complications, unplanned hospital admission, prolonged hospital stays, development of chronic pain, opioid side effects, opioid hyperalgesia and addiction. Studies have identified activation and sensitization of peripheral nociceptors and spinal dorsal horn neurons after surgical incision, and their specific mechanisms have been investigated. Basic scientific data and many clinical investigations suggest that different pain states result depending on the type and location of the incision, and that additional surgical procedures cause pain states of various severities in other sites. Supported by basic science, these observations have led to the development of the concept of procedure-specific postoperative pain management. The main value and novelty of procedure-specific postoperative pain management guidelines are that the guidelines are evidence-based, consider relevant patient characteristics, the role of anesthetic and surgical techniques, the balance between the invasiveness of the analgesic technique and the intensity of postoperative pain, as well as balance between analgesic efficacy and adverse event profile of the analgesic medications and procedures. In this review, the authors discuss the preventive and multimodal strategies of acute pain therapy, the pharmacotherapy of multimodal analgesia and local and regional techniques for specific surgical procedures.

Key words: *postoperative pain management; procedure-specific analgesia; multimodal and preventive analgesia; evidence-based data*

Introduction

Surgery causes postoperative pain that should be immediately and effectively treated. Postoperative pain management is in central focus when planning postoperative treatment and is becoming the standard of care after surgical procedures – Enhanced Recovery after Surgery (ERAS). Postoperative dynamic pain relief is very important for optimizing post operative recovery and reducing morbidity and chronic pain development[1]. Persistent postoperative pain is common and present in approximately 50% patients after thoracotomy, mastectomy and abdominal surgery, but it is

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even less well recognized that many patients develop chronic pain that might be a result of undertreated acute postoperative pain[1,2]. There are various serious complications associated with poorly controlled postoperative pain in the adult surgical patients – cardiopulmonary complications, unplanned hospital admission, prolonged hospital stays, development of chronic pain, opioid side effects, opioid hyperalgesia and addiction.

Despite many documented benefits and increased scientific evidence, postoperative pain has continued to be inadequately treated for decades. Opioids remain the cornerstone of perioperative pain management despite the fact that opioid misuse and abuse has reached epidemic status. According to the US Center for Disease Control, 130 deaths per day are attributable to prescribed opioid use[3].

Studies have identified activation and sensitization of peripheral nociceptors and spinal dorsal horn neurons after surgical incision, and their specific mechanisms have been investigated[4].

Spinal administration of many substances, e.g. N-methyl-D-aspartate (NMDA) receptor antagonists that prevent central sensitization in other pain modalities, did not produce similar effects after surgical incision, which can mean that incision causes a different form of spinal sensitization due to tissue trauma, local inflammation and nerve injury[4]. This makes it evident that central sensitization plays a vital role in the development of postoperative pain. Central sensitization can occur a short time after incision and have a significant impact on pain intensity[5]. Nerve injury as a primary cause of acute neuropathic pain after surgery is one of the critical risk factors for the development chronic postoperative pain[6].

After incision, peripheral C and A-delta fibers are sensitized and provoke spontaneous pain and heat and mechanical hyperalgesia in the early days after incision[5].

Pain after surgery is a unique and specific entity that is not a result of inflammatory process alone or isolated nerve injury[4]. Basic scientific data and many clinical investigations suggest that different pain states result depending on the type and location of the incision, and that different surgical procedures cause pain states of different severities in different locations. Supported by basic science, these observations have led to the development of the concept of procedure-specific postoperative pain management[7].

Procedure-specific postoperative pain management concept

Although scientific evidence on postoperative pain management has been rapidly growing, pain treatment after surgery is not successful. Confusing and conflicting evidence and lack of practical recommendations are important factors. Current postoperative pain treatment guidelines are generally "one size fits all", but it is well-known that pain characteristic such as type, location, intensity and duration vary after different surgical preocedures[1]. The methodological process for critical analysis of evidence and development of recommendations for procedure-specific analgesic interventions starts with performing a systematic reviews based on the protocol of the Cochrane Collaboration. In addition, well-designed, highly standardized prospective cohort studies could address a relevant clinical question[8]. It is necessary to confirm the clinical significance and safety of the analgesic techniques examined in the studies and determine whether the analgesic interventions improve postoperative patient outcomes.

The definition of procedure-specific postoperative pain management guidelines is that guidelines are evidence based take into consideration relevant patients characteristics, the role of anesthetic and surgical techniques, the balance between invasiveness of the analgesic techniques and the intensity of postoperative pain, as well as balance between analgesic efficacy and the adverse event profile of the analgesic medications and techniques[9]. Procedure-specific postoperative pain management guidelines emphasize the use of multimodal analgesia and preventive analgesia to block or reduce peripheral and central sensitizations and dynamic pain[10].

In summary, the Procedure-specific Postoperative Management Working Group (PROSPECT), which consist of an international collaboration of anesthesiologists and surgeons, is a process of optimizing postoperative pain treatment recommendations to provide healthcare professionals with practical procedure-specific guidelines to facilitate clinical decision-making across all stages of the perioperative period[10].

Preventive and multimodal analgesia

Several treatment concepts, including preventive and multimodal analgesia, have been developed to improve pain management and especially to prevent

chronic postsurgical pain. In preventive analgesia treatment, analgesic effects beyond its expected duration minimize peripheral and central sensitization induced by noxious stimuli during the whole perioperative period. Data from many reports confirm that preventive analgesia is a useful approach. To maximize the benefits of preventive analgesia strategies, it is important to continue the treatment in the postoperative period as long as the sensitizing stimulus persist. In order to prevent chronic postsurgical pain with a preventive analgesia approach, the best data are available for the use pharmacotherapy and regional anesthesia procedures such as multimodal analgesia.

Multimodal analgesia

Multimodal analgesia is the administration of a combination of analgesics with different modes or sites of action. It is a strategy that reduces opioids use and prescriptions through the use of non-opioid analgesics and local and/or regional analgesic techniques that have different mechanisms of action and have an opioid-sparing effect[11]. Multimodal analgesia regimens are both patient- and procedure-specific.

The main goals of multimodal analgesia are: 1) improvement of the patient experience through better pain control, 2) reduction of postoperative complications, morbidity and mortality, 3) reduction of health costs, and 4) decreased contribution to the global opioid epidemic[12].

Many studies have confirmed that multimodal analgesia increases patient satisfaction scores and permits earlier commencement of physical therapy and rehabilitations, improves mobilization and speeds up recovery in all surgical procedures. Multimodal analgesia must be integrated into a holistic and multidisciplinary approach throughout the postoperative period. At present, almost all approaches using enhanced recovery after surgery protocols include multimodal analgesia concepts as one component[13]. In this context, we will provide a detailed examination of multimodal analgesia pharmacotherapy, prescription of opioids and local and regional analgesic techniques.

Multimodal analgesia pharmacotherapy

Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 specific inhibitors (COX 2)

NSAIDs and COX-2-specific inhibitors are useful components of multimodal analgesia since they block the production of peripheral prostaglandin synthesis and tissue inflammation as well as significantly reducing peripheral sensitization as one of the primary causes of postoperative pain. Randomized controlled trials and their meta-analyses have shown that the use of celecoxib for all surgical procedures reduces pain scores and opioid consumption, expedites return of bowel function, return to normal daily activities and improves patients satisfaction1[4,15]. The COX-2 selective inhibitors have similar efficacy in the reduction of postoperative nausea and vomiting due to omission or opioid-sparing effects as nonselective NSAIDs, but they are superior in reducing other opioid adverse events[16]. The gastric ulceration rate was similar to placebo and significantly lower than nonselective NSAIDs in high-risk patients, even for short-term use[17].

COX-2 selective inhibitors have a more favorable side effect profile than nonselective compounds. Coxibs do not cause bronchospasm in patients with NSAID-exacerbated respiratory disease[18]. Coxibs lack platelet inhibition and cause less postoperative bleeding than nonselective NSAID drugs[19]. Kelley et al. reviewed 10,6279 patients undergoing breast and body contouring procedures, of whom 4,924 received ketorolac. Multivariable regression analysis demonstrated that ketorolac was not associated with hematoma, concluding that the benefits of NSAIDs use outweigh the risk[20]. In summary, the frequency of hematoma formation secondary to NSAIDs has been overestimated, with evidence supporting the use of NSAIDs in properly selected patients. Cardiovascular complications of coxibs, identified with refecoxib, were not registered with short-term use of parecoxib or long-term use of celecoxib[21,22]. Therefore, due to a number of reasons and evidence-based facts, the preoperative, intraoperative and postoperative incorporation of nonselective and especially selective COX-2 inhibitors into multimodal analgesia regimens is indispensable and recommended.

Acetaminophen

Acetaminophen has for a long time represented adequate perioperative analgesia choice with good efficacy for mild to moderate pain control and an opioid-sparing effect across all surgical procedures[23]. The mechanism of action is the inhibition of COX-mediated prostaglandin synthesis in the central nervous system and the activation of descending serotonergic

pathways. The safety profile of acetaminophen is excellent. The most concerning side effect is severe liver damage (above the maximum 4 gr/day dosage) For that reason, it is recommended to avoid acetaminophen in patients with known liver disease. According to a recent meta-analysis, there is no clear advantage of parenteral administration over oral administration for most selected patients for perioperative pain control[24]. The oral dosage protocols range from 500 to 1000 mg, usually with administration throughout the day. With that administration regimen, it is recommended not to use acetaminophen-opioid combination formulations for breakthrough pain, because of the risk of acetaminophen overdose. The effect of acetaminophen may be enhanced by the addition of NSAIDs, as that combination is more effective than either compound alone.

Dexamethasone

Dexamethasone reduces postoperative pain through its anti-inflammatory mechanism and is widely used in anesthetic practice to prevent nausea and vomiting, improve the quality of recovery and reduce fatigue[25]. In 2013, a meta-analysis demonstrated that postoperative patients have decreased pain scores and opioid consumption when dexamethasone is included as a multimodal adjunct[26]. Hyperglycemia and insulin therapy may require caution, but systematic reviews have concluded that the benefits from dexamethasone outweigh concerns of hyperglycemia, except for patients with non-regulated diabetes mellitus. There is no evidence that the use of dexamethasone correlates with increased postoperative wound infection or problems with wound healing[27].

Ketamine

Ketamine is a noncompetitive antagonist of the NMDA receptor when used in sub-anesthetic doses. Meta-analyses support the use of perioperative intravenous (IV) infusions of low-dose ketamine (in the range of around 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$) to improve analgesia, achieve an opioid-sparing effect and reduce opioid side effects such as postoperative nausea and vomiting[28]. Given mechanism of action of ketamine, the benefits of this drug are usually seen in patients after major surgeries that are suffering severe neuropathic pain (VAS >7/10), especially after thoracic, upper abdominal and major orthopedic surgery. In clinical practice, it is very important to note that NMDA receptor antagonists such as ketamine can reduce the development of opioid-induced hyperalgesia, especially after remifentanil use[29]. Ketamine is thus also a helpful analgesic in the treatment of patients with established opioid tolerance and high preoperative opioid use[30,31]. As another NMDA-receptor antagonist, magnesium has similar effects with regard to opioid-sparing and analgesia improvement[32,33]. Some clinical studies have confirmed the effect of perioperative ketamine in reducing the incidence of chronic postsurgical pain[28].

Gabapentinoids

Alpha-2-delta ligands pregabalin and gabapentin are also compounds which alleviate the state of secondary hyperalgesia due to central sensation in postoperative neuropathic pain. In this context, according to the evidence-based medicine, both compounds are important components of multimodal analgesia[34,35]. Data show that a single preoperative dose reduced pain scores, opioid consumption and adverse effects of opioids. The anxiolytic and anticonvulsant effect of these drugs is an additional beneficial factor[36]. A meta-analysis encompassing 18 studies and 1,181 patients demonstrated that perioperative gabapentin resulted in a 35% reduction in total opioid consumption and pain within the first 24 hours after surgery while simultaneously increasing early ambulation[37]. A large randomized controlled trial encompassing a variety of surgical procedures demonstrated the effectiveness of perioperative gabapentin toward supporting postoperative opioid cessation, with a regimen consisting of 1,200 mg preoperatively and 600 mg 3 times daily postoperatively (38). In burn victims, gabapentin is beneficial because of its ability to reduce burn-associated pruritus and opioid consumption[39,40].

Gabapentinoids are associated with several adverse effects including dizziness, somnolence and respiratory depression. Because of these side effects, gabapentinoids should only be used in patients with a high risk of chronic neuropathic postoperative pain when basic analgesics are contraindicated. The recommendation is to avoid or dose-reduce the medication in elderly patients with significant comorbidities, reduced lung function, chronic obstructive pulmonary disease or obstructive sleep apnea[41].

Alpha-2 adrenergic agonists

Alpha-2 agonists such as clonidine and dexmedetomidine are helpful compounds in perioperative multimodal analgesia, resulting in reduced pain intensity, opioid consumption and nausea. Because of potential adverse effects such as hypotension, bradycardia and possibly dose-dependent sedation, alfa -2 adrenergic agonists need to be used with caution[42].

In summary, we can say that pharmacotherapy of multimodal analgesia is supported by a large number of clinical studies. Perioperative use of ketamine, gabapentinoids and alfa-2 adrenergic agents reduces peripheral and central sensitization after surgical incision, and these medications are used in specific indications. The role of corticosteroids has not yet been fully elucidated and requires further investigation[4].

In acute pain treatment, the routine use of NSAIDs (the best choice seems to be a COX-2 selective medication), paracetamol and (e.g., before major procedures, in healthy patients) an alpha-2-delta ligand with rescue opioids has become the standard routine perioperative multimodal analgesia.

Local and regional analgesic techniques

The use of local and regional anesthesia is highly recommended as a standard of care in routine clinical practice of multimodal analgesia for a variety of surgical procedures[43]. Evidence shows that local anesthetics reduce opioid consumption, decrease postoperative nausea and vomiting, decrease pain scores, decrease the length of hospital stay, decrease rates of postoperative severe complications and decrease healthcare costs for almost all surgical procedures[44,45].

In recent years, the use of regional analgesia techniques performed only by anesthesiologists (e.g., neuraxial blocks) has diminished[46]. The use of perineural techniques is low. Possible reasons for the underuse of peripheral nerve blocks are lack of training, lack of resources (e.g., availability of ultrasound devices), and the brevity of duration of single-injection blocks[1]. Continuous peripheral nerve blocks extend the duration of analgesia, but their use in clinical practice is limited because of the technical difficulty of their application and the need for special personnel to manage them[1].

Recent evidence has shown that there is increasing use of interfascial plane blocks (e.g., transversus abdominis plane blocks, serratus plane blocks, quadratus lumborum blocks, erector spinae plane blocks, etc.)[47,48]. These blocks are technically easy to perform, efficient, safe and inexpensive. Moreover, surgical site infiltration techniques – local infiltration analgesia – are becoming increasingly popular[49,50]. Surgical site infiltration are easy to perform and less expensive, but with the drawback of a need for extensive administration of local anesthetic. The use of wound catheter techniques is rapidly growing because, as reported, they provide effective pain relief after major thoracic and abdominal surgery with almost no adverse effects[51,52]. The short duration of action for most local anesthetics (8-12 hours) might be overcome by catheter infusion techniques or the use of extended-release formulations of local anesthetics such as liposomal bupivacaine. Liposomal bupivacaine for regional blockade in the transversus abdominis plane is commonly used in abdominal wall reconstruction, demonstrating opioid reduction, decreased lengths of hospital stay and improved pain scores over traditional catheter-based infusion techniques without increases in wound complications[53].

For successful use of all these techniques, is very important that the surgeon is familiar with anatomy and injection techniques and is involved in a multidisciplinary approach in order to maximize the use of regional anesthesia in multimodal pain relief strategies. Joshi et al. emphasized that the persistent underuse of peripheral nerve blocks can be overcome by surgeon knowledge and administration of intraoperative interfascial plane blocks and surgical site infiltration[45].

Procedure-specific pain management guidelines

Procedure-specific pain management is based on data from many surgical procedures and clinical practices that is used to evaluate the benefits and risks of each analgesic technique. It is recommended that all surgical patients should receive "basic analgesics", which include acetaminophen and either an NSAID or a COX-2 specific inhibitor, unless there is a contraindication perioperatively[7,54]. In addition, patients should receive some form of local /regional anesthetic technique (e.g. surgical site infiltration, interfascial plane block). It is crucial to balance the invasiveness of the analgesic technique with the expected severity of postoperative pain, and balance the efficacy of the analgesic technique and potential adverse effects[7,54].

Early communication, complete information and patient engagement are necessary for multimodal analgesia to be most effective[12].

Recommendations summary for principles of multimodal analgesia[12]

Recommendations summary for principles of multimodal analgesia		
MULTIMODAL AGENT	**USEFUL INDICATIONS AND TIMING**	**IMPORTANT CONSIDERATIONS AND CONTRAINDICATIONS**
Local and regional anesthetic	• All patients should receive local and regional anesthetic	• Balance invasiveness of technique with severity of pain • Refresh providers on signs of local anesthetic toxicity
Nonsteroidal anti-inflammatory drugs and COX-2 selective COX-2 inhibitors	• Recommended for all patients unless contraindicated • Effective in scheduled manner preoperatively • Can be implemented in preoperative, intraoperative and postoperative set	• Contraindicated in chronic and acute kidney injury • COX-2 inhibitors should be avoided in patients with coronary artery disease • Does not increase bleeding complications
Acetaminophen	• Recommended for all patients unless contraindicated • Effective in "scheduled" manner • Perioperatively can be implemented in preoperative, intraoperative, and postoperative settings	• Do not exceed 4 g in 24 h • Use caution in patients with known liver disease • It is not recommended to prescribe combination opioid acetaminophen medications with a scheduled regimen to avoid inadvertent toxicity
Gabapentinoids	• Useful for operations at higher risk for persistent postoperative pain • Can be implemented in preoperative and postoperative settings.	• Adverse events include dizziness, somnolence and decreased respiration • Caution advised with elderly patients and those with reduced lung function. Dose adjusted for renal function
Dexamethasone	• Single intraoperative dose useful for analgesia and antiemetic prophylaxis • Consider especially for patients with history of PONV	Monitor for perioperative hyperglycemia, but no evidence to strongly support this as a contraindication

Conclusion

In conclusion, the current evidence-based data for the management of acute postoperative pain is significant. The procedure-specific pain management guidelines, PROSPECT, provide healthcare professionals with practical pain management recommendations to facilitate clinical decisions in the perioperative period.

Multimodal analgesia with non-opioid analgesic and local anesthetic techniques must be incorporated into every surgical procedure, with an opioid prescription for rescue analgesia – for breakthrough pain and not as a primary pain management strategy.

Standardization of procedure-specific protocols increases the efficiency of treatment. Clear communication and patient and surgeon engagement are necessary for multimodal analgesia to be most effective.

References

1. Rawal N. Current issues in postoperative pain management. Eur J Anaesthesiol. 2016;33(3):160-71.
2. Gerbershagen HJ, Pogatzki-Zahn E, Aduckhatil S, et al. Procedure-specific risk factor analysis for development of severe postoperative pain. Anesthesiology. 2014;120:1237-45.
3. Scholl L, Seth P, Karissa M, et al. Drug and opioid involved overdose deaths- United States 2013-2017. MMWRMor Mortal WklyRep. 2018; 67:1419-27.
4. Zahn PK, Pogatzki EM, Brennan TJ. Mechanisms of pain caused by incision. Reg Anesth Pain Med. 2002;27:514-6.

5. Zahn-Pogatzki EM, Segelecke D, Shug AS. Postoperative pain- from mechanisms to treatment. Pain Rep. 2017;2(2):e588.
6. Jain P, Padole D, Bakshi S. Prevalence of acute neuropathic pain after cancer surgery: a Prospective study. Indian J Anaesth. 2014;58:36-42.
7. Joshi GP, Kehlet H. Prospect Working Group. Guidelines for perioperative pain management: need for re-evaluation. Br J Anaesth. 2017;119:703-6.
8. Joshi GP, Kehlet H, Rawal N, et al. Guidelines for perioperative pain management: need for reevaluation. Special section – pain medicine editorial. 2017;119(4):720-22.
9. Fabritius ML, Mathiesen O, Wetterslev J, et al. Post – operative analgesia: focus has been on benefit – are we forgetting the harm? Acta Anaesthesiol Scand. 2016;60:839-41.
10. Girish P, Joshi GP, Stefan A, et al. Procedure-specific pain management and outcome stretegies. Best Practice Research Clinical Anesthesiology. 2014;28:191-201.
11. Rosero EB, Joshi GP. Preemptive, preventive multimodal analgesia: what do they really mean? Plast Reconstr Surg. 2014;134(4Suppl2):85-93.
12. Baker JC, Girish P, Joshi GP, et al. Basic and best practice of multimodal pain management for the plastic surgeon. Plast Reconstr Surg Glob Open. 2020;8:e2833.
13. Nanavati AJ, Prabhakr S. Fast – track surgery: toward comprehensive peri-operative care. Anesth Essays Res. 2914;8:127-33.
14. Gupta A, Jakobssonn J. Acetaminophen, nonsteroidal anti inflamatory drugs, and cyclooxygenase-2 selective inhibitors: an update. Plast ReconstrSurg. 2014;134(4Suppl2): 24-31.
15. Gan TJ, Joshi SZ, Zhao SZ, et al. Presurgical intravenous parecoxib soduim at follow up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduce opioid requirements and opioid adverse effects. Acta Anesthesiol Scand. 2004,48:1194-207.
16. Moore RA, Derry S, McQuay H, et al. Single dose oral analgetics for acute postoperative pain in adults. Cochrane Database Syst Rev. 2011;9:CD008659.
17. Goldstein JL, Kivitz AJ, Verburg KM, et al. A comparison of upper gastrointestinal mucosal effects of valdecoxib, naproxen and placebo in healthy elderly subjects. Aliment Pharmacol Ther. 2003;18:125-32.
18. Morales DL, Liphwort BJ, GuthirieB, et al. Safety risk for patients with aspirin exacerbated respiratory disease after acute exposure to selective nonsteroidal antiinflamatory drugs and COX-2 inhibitors: meta analysis of controlled clinical trials. J Allergy Clin Immunol. 2014;134:40-5.
19. Walker NJ, Jones VM, Kratky L, et al. Hematoma risk of nonsteroidal antiinflammatory drugs used in plastic surgery procedures: a systematic review and meta-analysis. Ann Plast Surg. 2019;82(Suppl5):437-45.
20. Kelley PB, Chung KC, Chung TT, et al. Postoperative ketolorac in breast and body contouring procedures: a nationwide claims analysis. Plastic Reconstr Surg. 2018;142472e-480e.
21. Shug S, Joshi GP, Camu E, et al. Cardiovascular safety of the cyclooxygenase -2 selective inhibitosrs parecoxib et valdecoxib in the postoperative setting. An analysis integrated data. Anesth Analg. 2009,108.299-307.
22. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen or ibuprofen for arthritis. N Engl J Med. 2016;375:2519-29.
23. Mc Nicol ED, Tzortzopoulou A, Cepeda MS, et al. Single-dose intravenous paracetamol and proparacetamol for prevention or treatment of postoperative pain: a systematic review and meta- analysis. Br J Anaesth. 2011;106:764-75.
24. Jabril F, Sharaby S, Mohamed A, et al. Intravenous versus oral acetaminophen for pain: systematic review of current evidence to support clinical decision making. Can J Hosp Pharm. 2015;68:238-47.
25. Murphy GS,Szokol JW, Greenberg SB, et al. Preoperative dexamethasone enhances quality of recovery after laparoscopic cholecystectomy: effect on in-hospital and postdischarge recovery outcomes. Anesthesiology. 2011;114:882-90.
26. Jwaldron NH, Jones CA, Can TJ, et al. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systemic review and meta-analysis. Br J Anaesth. 2013;110:191-200.
27. Polderman JAW, Fargang.Razi V, van Dieren S, et al. Adverse side- effects of dexamethasone in surgical patients – an abridged Cochrane systematic review. Anaesthesia. 2019;74:929-39.
28. Pogatzki Zahn EM, Neimeirer JS, Brennan TJ, et al. Persistent secondary hyperalgesia after gastrocnemius incision in the rat. Eur J Pain. 2002;6:295-305.
29. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth. 2011;58:911-23.
30. Barreveld AM, Correll DJ, Liu X, Max B, McGowan JA, Shovel L, et al. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. Pain Med. 2013;14:925-34.
31. Urban MK, Ya Deau JT, Wukovits B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. HSS J. 2008;4:62-5.
32. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113:639-46.
33. Murphy JD, Paskaradevan J, Eisler LL, Ouanes JP, Tomas VA, Freck EA, et al. Analgesic efficacy of continuous intravenous magnesium infusion as an adjuvant to morphine for postoperative analgesia: a systematic review and meta-analysis. Middle East J Anesthesiol. 2013;22:11-20-
34. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth. 2015;114:10-31.
35. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? a systematic review of efficacy and safety. Anesth Analg. 2007;104:1545-56.
36. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. Drugs Today (Barc). 2007;43:601-10.

37. Peng PW, Wijeysundera DN, Li CC. Use of gabapentin for perioperative pain control—a meta-analysis. Pain Res Manag. 2007;12:85-92.
38. Hah J, Mackey SC, Schmidt P, et al. Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: a randomized clinical trial. JAMA Surg. 2018;153:303-11.
39. Ahuja RB, Gupta R, Gupta G, et al. A comparative analysis of cetirizine,gabapentin and their combination in the relief of postburn pruritus. Burns. 2011;37:203-7.
40. Kaul I, Amin A, Rosenberg M, et al. Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: a retrospective chart review. Burns. 2018;44:414-22.
41. United State Food and Drug Administration Drug Safety Communication. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) when used with CNS depressants or in patients with lung problems.2019. Available at: https://www.fda.gov/drugs/drug-safety-andavailability/fda-warns-about-serious-breathing-problems-seizureand- nerve-pain-medicines-gabapentin-neurontin. Accessed May1, 2020.
42. Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology. 2012;116:1312-22.
43. Gabriel RA, Ilfeld BM. Use of regional anaesthesia for outpatient surgery within the United States: a prevalence study using a national database. Anesth Analg. 2018;126:2078-84.
44. Rivedal DD, Nayar HS, Israel JS, et al. Paravertebral block associated with decreased opioid use and less nausea and vomiting after reduction mammaplasty. J Sur Res. 2018;228:307-13.
45. Joshi GP, Kehlet H, Rawal N. Surgeon-administerd regional analgesia: need for communication and collaboration. Br J Anaesth. 2019;123:707-9.
46. Soffin EM,Lee BH, Kumar KK, et al. The prescription opioid crisis: role of the anaesthesiologist in reducing opioid use and misuse. Br J Anaesth. 2019;122:e198-208.
47. Kehlet H, Joshi GP. Systematic reviews and meta-analyses of randomized controlled trials on perioperative outcomes: an urgent need for critical reappraisal. Anesth Analg. 2015;121:1104-07.
48. Elsharkawy H, El-Boghdadly K, Barrington M. Quadratus lumborum block: anatomical concepts, mechanisms, and techniques. Anaesthesiology. 2019;33:322-35.
49. Kim DH, Oh YJ, Lee GH et al. Efficacy of ultrasound – guided serratus plane block on postoperative quality of recovery and analgesia after video-assisted thoracic surgery: a randomizd, triple blind, placebo- controlled study. Anesth Anlag. 2018;126:1353-61.
50. Pawa A, El-Boghdadly K. Regional anaesthesia by nonanesthesiologists. Curr Opin Anaesthesiol. 2018;31:586-92.
51. Kotemane NC, Gopinath N, Vaja R. Analgesic techniques following thoracic surgery: a survey of United Kingdom practice. Eur J Anaesthesiol. 2010;27:897-99.
52. Mungroop TH, Bond JM, Lirk P, et al. Preperitoneal or subcutaneous catheters as alternative for epidural analgesia in abdominal surgery. A systematic review and meta analysis. Ann Surg. 2019;269:252-60.
53. Roy CF, Azzi AJ, Davidson P. A review of wound infusion with local anesthetics in plastic surgery. Ann Plast Surg. 2019;83:317-24.
54. Joshi GP, Kehlet H. Postoperative pain management in the ear of ERAS: an overview. Best Prac Res Clin Anaesthesiol. 2019;33:259-67.

Sažetak

STRATEGIJE UTEMELJENE NA DOKAZIMA ZA MULTIMODALNO POSTOPERACIJSKO LIJEČENJE BOLI

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Operacija uzrokuje postoperativnu bol koju treba odmah učinkovito liječiti. Liječenje postoperativnom boli u središnjem je fokusu u planiranju postoperativnog liječenja i postaje standard skrbi nakon kirurških protokola - poboljšani oporavak nakon operacije (ERAS). Postoje razne ozbiljne komplikacije povezane s loše kontroliranom postoperativnom boli kod odraslih kirurških pacijenata – kardiopulmonalne komplikacije, neplanirani prijem u bolnicu, produljeni boravak u bolnici, razvoj kronične boli, opioidne nuspojave, opioidna hiperalgezija i ovisnost. Nakon kirurškog reza identificirana je aktivacija i senzibilizacija perifernih nociceptora i neurona dorzalnog roga kralježnice te su istraženi njihovi specifični mehanizmi. Osnovni znanstveni podaci i mnoga klinička istraživanja sugeriraju da ovisno o vrsti i mjestu reza dolazi do različitih bolnih stanja i da različiti kirurški zahvati uzrokuju bolna stanja različite jačine na različitim mjestima. Potpomognuta osnovnom znanošću, ova su opažanja dovela do razvoja koncepta liječenja postoperativne boli specifičnog zahvata. Glavna vrijednost i novost "Procedure-specific postoperative pain management" smjernica je da se smjernice temelje na dokazima, vode računa o relevantnim karakteristikama bolesnika, ulozi anestezijskih i kirurških tehnika, ravnoteži između invazivnosti analgetske tehnike i intenziteta postoperativne boli, kao i ravnotežu između analgetske učinkovitosti i profila nuspojava analgetičkih lijekova i tehnika. U ovom pregledu autori raspravljaju o preventivnim i multimodalnim strategijama terapije akutne boli, farmakoterapiji multimodalne analgezije te lokalnim i regionalnim tehnikama za specifične kirurške postupke.

Ključne riječi: *liječenje postoperativne boli, analgezija specifična za postupak, multimodalna i preventivna analgezija, podaci temeljeni na dokazima*