Slovenian Medical Journal

The incidence of chronic postoperative pain after major abdominal surgery

Incidenca kronične pooperativne bolečine po velikih abdominalnih operacijah

Matej Jenko, Neva Požar-Lukanović, Vesna Novak-Janković, Alenka Spindler-Vesel

Abstract

Background: Chronic postoperative pain, pain that cannot be explained by other causes and that persist more than 2 months after surgery, occurs in 10-50% of patients after major abdominal surgery. Its subgroup, chronic neuropathic pain is very resistant to treatment. Intraoperative application of epidural analgesia and infusion of dexmedetomidine may influence the incidence of chronic postoperative pain.

Method: Adult surgical patients from the Clinical Department of Abdominal Surgery, UMC Ljubljana, who were planned to undergo one of the following procedures: stomach surgery, pancreas surgery or large intestinal resections, were included in this prospective study. All patients had epidural analgesia and intraoperative dexmedetomidine infusion. Three months after the procedure, structured questionnaire was sent to the patients. The intensity and quality of pain were assessed. DN4 (Douleur Neuropathique 4) and painDetect questionnaires were used.

Results: We have received 42 (50%) properly filled DN4 questionnaires and 45 (53%) pain detect questionnaires. The incidence of chronic pain in our study was 25%, 7.1% of them had features of neuropathic pain (3 patients met criteria for neuropathic pain according to DN4).

Conclusion: Our prospective study suggests a possible favourable impact of intraoperative epidural analgesia and dexmedetomidine infusion on the incidence of chronic postoperative pain.

Izvleček

Uvod: O kronični pooperativni bolečini govorimo, kadar ne najdemo drugega vzroka za njen nastanek in ko traja dlje kot 2 meseca po operaciji. Pojavi se pri 10-50 % bolnikov po velikih abdominalnih operacijah. Podskupina kronične bolečine, ki jo je najtežje zdraviti, je kronična nevropatska bolečina. Medoperativna epiduralna analgezija in infuzija deksmedetomidina lahko vplivata na incidenco kronične pooperativne bolečine in na incidenco nevropatske bolečine.

Department of anaesthesiology, Division of Surgery, University Medical Centre Ljubljana, Ljubljana, Slovenia

Correspondence / Korespondenca: Matej Jenko, e: matej.jenko@kclj.si

Key words: dexmedetomidine; neuropathic pain; abdominal surgery

Ključne besede: deksmedetomidin; nevropatska bolečina; abdominalne operacije

Received / Prispelo: 18. 5. 2020 | **Accepted / Sprejeto:** 11. 11. 2020

Cite as / Citirajte kot: Jenko M, Požar-Lukanović N, Novak-Janković V, Spindler-Vesel A. The incidence of chronic postoperative pain after major abdominal surgery. Zdrav Vestn. 2021;90(11–12):596–602. **DOI:** https://doi.org/10.6016/ZdravVestn.3086

Metode: V prospektivno raziskavo smo vključili odrasle kirurške bolnike, sprejete na KO za abdominalno kirurgijo, pri katerih je bila načrtovana operacija želodca, operacija trebušne slinavke ali operacija črevesja. Vsi bolniki so imeli epiduralno analgezijo in medoperativno infuzijo deksmedetomidina. Tri mesece po operaciji smo bolnikom poslali vprašalnike. Ocenjevali smo jakost in vrsto bolečine. Za oceno smo uporabili DN4 (Douleur Neuropathique 4) in vprašalnik painDetect.

Rezultati: Prejeli smo 42 (50 %) pravilno izpolnjenih vprašalnikov DN4 in 45 (53 %) vprašalnikov painDetect. V naši raziskavi je bila incidenca kronične bolečine 25 %, nevropatske bolečine 7,1 % (3 bolniki so izpolnjevali merila za nevropatsko bolečino po vprašalniku DN4).

Zaključek: Rezultati naše prospektivne raziskave nakazujejo, da bi lahko medoperativna uporaba epiduralne analgezije in infuzije deksmedetomidina zmanjšala pojav pooperativne kronične bolečine.

1 Introduction

A significant amount of research is focused on the study of chronic postoperative pain, that is, pain that cannot be explained by another cause and that lasts for more than two months after surgery (1). Transient yet persistent pain caused by nerve damage can appear after surgery, however, other factors must also be present. Nerve damage will occur with each surgical procedure, but not all patients will develop persistent chronic pain. The following conditions increase the risk of chronic postoperative pain: previous pain (tolerance to opioids, hyperexcitability of the central nervous system), physical nerve damage (location of surgery, surgical technique), severe postoperative pain (inadequate analgesia, extensive tissue damage), depression, gender, genetics, delayed nerve regeneration (chemotherapy, radiation) (2).

Severe postoperative pain can cause hormonal and metabolic stress reactions, potentially leading to cardiovascular or other complications (3). Therefore, it is necessary to optimally treat perioperative pain early, inhibit the injury-induced transmission of the pain stimulus, and reduce the autonomic and somatic reflex response to pain. Epidural analgesia is optimal for major abdominal operations, as it has a lower endocrine and metabolic stress response compared to intravenous analgesia (4-10).

In chronic postoperative pain, the neuropathic component of pain is often present. It is characteristic of this form that transduction (change of a nociceptive stimulus into an electrical impulse) is missing in the physiological process of pain formation. This type of pain is difficult to treat due to changes in neurotransmitter and receptor characteristics along somatosensory and descending modulatory pathways (11). After abdominal surgery, chronic pain occurs in 10-50% of patients, of which up to 25% display the characteristics of neuropathic pain (12,13).

Chronic pain appears most frequently after amputations and inguinal hernia, breast, gallbladder and lung operations, but it can also appear after other types of surgery (14).

Perioperative epidural analgesia in combination with ketamine infusion has a beneficial effect on the reduction of acute postoperative pain and on the occurrence of chronic postoperative pain 12 months after surgery in patients who have undergone abdominal surgery (15). The usefulness of epidural analgesia itself has been confirmed by other studies (16).

Dexmedetomidine, a selective alpha-2 adrenoceptor agonist, reduces the interoperative use of anaesthetics, reduces the perioperative release of catecholamines and has anti-inflammatory activity (17-19). Peripheral administration of dexmedetomidine reduces mechanical and thermal hyperalgesia and postoperative pain (20).

Several studies have confirmed the beneficial effect of epidural analgesia or dexmedetomidine on the incidence of chronic postoperative pain in major abdominal surgery. The purpose of our study was to determine the incidence of chronic postoperative pain and neuropathic pain in patients who underwent major abdominal surgery and also received epidural analgesia and intraoperative dexmedetomidine infusion.

By monitoring various major abdominal operations, we could infer whether there were any differences in the incidence of chronic pain with respect to specific laparoscopic abdominal operations, the duration of surgery or complications.

2 Methods

The study involved 84 adult patients with an ASA (American Society of Anaesthesiologists) physical status classification score of 2-3 who underwent major

abdominal surgery (laparoscopic gastric, intestinal or pancreatic surgery) at the Department of Abdominal Surgery at the Medical Centre Ljubljana. Prior to surgery, a team member spoke with the patient obtaining their written consent. Patients with contraindications to epidural anaesthesia or planned postoperative admission to the intensive care unit (ICU) were not included in the study.

Upon admission to the operating theatre, an ECG was recorded, a cuff for non-invasive blood pressure measurement and pulse oximetry were set, intravenous cannulation was performed and a dexmedetomidine infusion (0.5 µg / kg / hour) was set. The epidural catheter was inserted in the left lateral position (Th 7-8, Th 9-10 for low anterior resection). For the introduction of anaesthesia, we used fentanyl or sufentanil, propofol or etomidate and rocuronium.

During surgery, we maintained normocapnia, normoxemia and normothermia.

Anaesthesia was maintained intravenously (with propofol and dexmedetomidine). The amount of propofol was titrated according to the value of the bispectral index (BIS). Analgesia was maintained with an epidural dose of levobupivacaine and sufentanil. If no additional analgesia was required during surgery, the epidural block was effective. Patients with insufficient epidural block were excluded from the study. A continuous epidural infusion of a local anaesthetic was set up during surgery, which the patients could self-regulate after surgery (patient control epidural analgesia, PCEA) (0.125% levobupivacaine 200 mL, morphine 4 mg, clonidine 0.075 mg; infusion rate 5 mL/h, bolus 5 mL, lockout time 30 minutes).

Muscle relaxation was monitored using TOF (Train of Four) and rocuronium dosage was administered as required. All patients received an intraoperative antiemetic.

The muscle block was interrupted with sugammadex or neostigmine at the end of surgery, according to the measured TOF values.

Toward the conclusion of surgery during the laparotomy closure, the dexmedetomidine infusion was stopped.

After surgery, the patients were monitored in the post-anaesthesia care unit and later transferred to the Department of Abdominal Surgery ICU.

Three months after the procedure, we sent each patient a DN4 (Douleur Neuropathique 4) and a painDetect questionnaire (20,21) to assess the intensity and quality of pain. We compared the responses of the painDetect questionnaire with the SF 36 questionnaire, which allowed us an approximate assessment of chronic pain (22). The collected responses were statistically processed with the IBM SPSS software 25 (New York, USA). The value of $p < 0.05$ was deemed statistically significant.

The study was approved by the Republic of Slovenia National Medical Ethics Committee (number 107/10/13, date of approval: 06.12.2013) and was registered on ClinicalTrials.gov (NCT02293473).

Table 1: Sensory dysfunction frequency, answers to the DN4 questionnaire.

Description of the type of pain or sensory dysfunction	Number of patients with a positive response (%)
Burning pain	3 (7.1)
Painful cold	2 (4.8)
Electric sock	1 (2.4)
Tingling	11 (26.2)
Pins and needles	4 (9.5)
Numbness	2 (4.8)
Itching	4 (9.5)
Hypoesthesia to touch	0 (0)
Hypoesthesia to pinprick	0 (0)
Pain increased by brushing	0 (0)
Presence of four or more signs in the same patient (meets the criteria for neuropathic pain)	3 (7.1)

Table 2: The painDetect questionnaire analysis (numerical scale from 0 to 10).

Variable	Mean (standard deviation), minimum - maximum
Pain intensity at a particular time	1.2 (± 1.4), 0 - 5
Most severe pain in the last four weeks	5.3 (± 2.7), 1 - 10
Average pain in the last four weeks	2.2 (± 1.6), 0 - 7

Table 3: Type of pain according to the painDetect questionnaire.

Variable	Frequency (%)
Persistent pain with slight fluctuations	12 (26.7)
Persistent pain with pain attacks	19 (42.2)
Pain attacks without pain between them	6 (13.3)
Pain attacks with pain between them	4 (8.9)
Missing answers	4 (8.9)

3 Results

Of the 84 patients who were sent questionnaires, we received 45 (53%) responses. 42 (50%) patients returned both the DN4 and painDetect questionnaires fully completed. The results are presented in Tables 1, 2, and 3. Of those who returned both, the mean age was 65 (± 12) years; average weight 64 (± 10 kg). 17 had an ASA score of 2, and 25 had an ASA score of 3. 20 (48%) were male, and 22 (53%) were female. Two of the 84 patients had pancreatic surgery but did not return the questionnaires. The results for the other two subgroups of patients (patients after gastric surgery and after bowel surgery) are in Table 4. All patients included underwent surgical laparotomy. Laparoscopic surgeries were not included in the study. The incidence of chronic pain was 25% (11 patients), the characteristics of neuropathic pain were reported by three patients 7.1%.

4 Discussion

Chronic postoperative pain was present in 25% of patients in our study, which is consistent with data from the literature (22).

The incidence of neuropathic pain was 7.1% and none of the patients rated their pain at more than 7 on a numerical scale of pain, which is a slightly lower proportion in terms of intensity and proportion of neuropathic

Table 4: Results for a subset of patients in the study.

Type of surgery	Gastric surgery	Bowel surgery	
Number of patients	16	26	Total 42
Duration of surgery	123 min (IQR 35 min)	130 min (IQR 40 min)	p=0.122 (Mann - Whitney U test)
Number of patients admitted to the ICU	1	0	p=0.381 (chi-squared test)
Number of patients re-admitted to the ICU	1	5	p=0.380 (chi-squared test)
Number of patients with insulin-dependent diabetes (number of these patients with neuropathic pain)	3 (0)	2 (1)	p=0.352 (chi-squared test)
Average length of hospital stay	9 (IQR 3)	9 (IQR 4,5)	p= 0.651 (Mann - Whitney U test)
Number of patients who met the criteria for neuropathic pain	2	1	p=0.547 (chi-squared test)

Legend: IQR – interquartile range.

pain than in comparable studies (1,12,13). The DN4 and painDetect questionnaires indicated that most pain patterns are not of neuropathic origin (Table 3) (23). Different studies have used different, directly incomparable methods, which, however, describe a higher incidence of chronic postoperative pain than in our study. In a study by Joris et al., the incidence was 17% after laparoscopic colorectal surgery and similarly after laparotomies (12). In laparoscopic gynaecological operations, the reported incidence of clinically significant neuropathic pain is low at approximately 5%. It occurs due to damage to the iliohypogastric-ilioinguinal nerve when suturing the fascia, which occurs less frequently than in open surgery (24). Persistent postoperative neuropathic pain remains a poorly recognized clinical problem. The chronicity and persistence of this type of pain is often very limiting and has a strong impact on the patient, both psychologically, physically, economically and emotionally (25).

The results of other research show that epidural analgesia significantly reduces the incidence of chronic neuropathic postoperative pain, to 17.6% (16). This is higher with epidural analgesia than in our study, possibly indicating the beneficial effect of dexmedetomidine. Our patient's mean age was higher than in other studies, and the incidence of chronic postoperative pain is increased in elderly patients. However, patients requiring postoperative intensive care in whom the incidence of chronic and neuropathic pain is higher (26) were excluded from our study. Some studies report a comparable incidence of chronic neuropathic pain with epidural analgesia alone (22,27).

The lower incidence of postoperative chronic pain could be affected by the beneficial effect of dexmedetomidine infusion during surgery (20). Its analgesic component is mediated through spinal and supraspinal mechanisms, as α2 adrenergic receptors are found in the brain in the locus coeruleus and in the posterior horns of the spinal cord. Binding of dexmedetomidine to the α2 adrenergic receptor activates the G protein, which prevents calcium from entering the cell, inhibiting the release of norepinephrine. At the same time, potassium ions enter the cell, which reduces the cell's susceptibility to depolarization and thus inhibits the transmission of pain stimuli (28-30). The main analgesic effect of dexmedetomidine is its action on α2 adrenergic receptors in the locus coeruleus (28,29). After nerve damage, it reduces hyperalgesia and inhibits microglia activation and signal-regulated kinase in the dorsal horn of the spinal cord (18,19). The anti-inflammatory effect of dexmedetomidine is also beneficial (31). By stimulating α2 adrenergic receptors and inhibiting necrosis factor κB, it inhibits the release of inflammatory cytokines, particularly interleukin 6, interleukin 8, and tumour necrosis factor α (32-37).

We did not find differences in the incidence of chronic postoperative pain in the individual subgroups of patients (gastric, bowel surgery). The level of epidural catheter insertion depended on the expected surgery level and maximum pain. However, the type of surgery itself, its duration and postoperative complications do not show differences in the incidence of chronic postoperative or neuropathic pain. Our sample size was too small to analyze the effect of comorbidities on chronic postoperative pain (13,23). The literature data shows that one in five patients (20%) with insulin-dependent diabetes develops chronic postoperative pain.

4.1 Study limitations

In our study, 53% of patients returned the questionnaires. There is a possibility that responses were sent only by patients who had a favourable surgical treatment outcome, giving falsely positive results. Due to the small sample size, it was relatively difficult to estimate the expected confidence interval of the incidence of chronic pain. Patients with chronic neuropathic pain can display specific symptoms: depression, sleep disorders and similar disorders are more common, which may explain why some patients did not return their questionnaires. This could increase the incidence of neuropathic pain by a factor of 4 and, accordingly, the incidence of chronic postoperative pain. In our study, we also did not analyze psychological factors such as depression, which plays an important role in the development of chronic postoperative pain. Due to the observational nature of the study, it was not possible to estimate the proportional contributions of epidural analgesia or dexmedetomidine to the reduction of chronic postoperative pain. Compared to foreign studies, a possible beneficial effect of a different surgical technique cannot be ruled out.

5 Conclusion

The purpose of our study was to assess the incidence of postoperative chronic pain and neuropathic pain after major abdominal surgery. The results of our study might indicate a beneficial effect of perioperative epidural analgesia and dexmedetomidine on the incidence of chronic postoperative pain.

Conflict of interest

None declared.

References

1. Macrae WA, Davies H. Chronic postsurgical pain. In: Crombie IK. Epidemiology of pain. Seattle: IASP Press; 1999. pp. 125-42.
2. Cousins MJ, Gallagher RM. Persistent post-surgical pain. In: Cousins MJ, Gallagher RM. Fast facts: Chronic and cancer pain. 2nd ed. Oxford: Health Press Limited; 2011. pp. 84-91.
3. Frank E, Sood OP, Torjman M. Postoperative epidural analgesia foolowing radical retropubic prostatectomy. J Surg Oncol. 1998;67:117-20. DOI: 10.1002/(SICI)1096-9098(199802)67:2<117::AID-JSO8>3.0.CO;2-D PMID: 9486783
4. Ben-David B, Swanson J, Nelson JB, Chelly JE. Multimodal analgesia for radical prostatectomy provides better analgesia and shortens hospital stay. J Clin Anesth. 2007;19(4):264-8. DOI: 10.1016/j.jclinane.2006.12.003 PMID: 17572320
5. Stenseth R, Bjella L, Berg EM, Christensen O, Levang OW, Gisvold SE. Thoracic epidural analgesia in aortocoronary bypass surgery. II: effects on the endocrine metabolic response. Acta Anaesthesiol Scand. 1994;38(8):834-9. DOI: 10.1111/j.1399-6576.1994.tb04014.x PMID: 7887107
6. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology. 1995;82(6):1474-506. DOI: 10.1097/00000542-199506000-00019 PMID: 7793661
7. Stevens R, Mikat-Stevens M. Does the anaesthetic techique affect recovery of bowel function after radical prostatectomy? Br J Anaesth. 1998;80:551-2.
8. Gruber EM, Tschernko EM, Kritzinger M, Deviatko E, Wisser W, Zurakowski D, et al. The effects of thoracic epidural analgesia with bupivacaine 0.25% on ventilatory mechanics in patients with severe chronic obstructive pulmonary disease. Anesth Analg. 2001;92(4):1015-9. DOI: 10.1097/00000539-200104000-00039 PMID: 11273942
9. Jayr C, Thomas H, Rey A, Farhat F, Lasser P, Bourgain JL. Postoperative pulmonary complications. Epidural analgesia using bupivacaine and opioids versus parenteral opioids. Anesthesiology. 1993;78(4):666-76. DOI: 10.1097/00000542-199304000-00009 PMID: 8466067
10. Clark F, Gilbert HC. Regional analgesia in the intensive care unit. Principles and practice. Crit Care Clin. 2001;17(4):943-66. DOI: 10.1016/S0749-0704(05)70188-3 PMID: 11762269
11. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. BMJ. 2014;348:f7656. DOI: 10.1136/bmj.f7656 PMID: 24500412
12. Joris JL, Georges MJ, Medjahed K, Ledoux D, Damilot G, Ramquet CC, et al. Prevalence, characteristics and risk factors of chronic postsurgical pain after laparoscopic colorectal surgery: retrospective analysis. Eur J Anaesthesiol. 2015;32(10):712-7. DOI: 10.1097/EJA.0000000000000268 PMID: 26086282
13. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101(1):77-86. DOI: 10.1093/bja/aen099 PMID: 18434337
14. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology. 2000;93(4):1123-33. DOI: 10.1097/00000542-200010000-00038 PMID: 11020770
15. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology. 2005;103(4):813-20. DOI: 10.1097/00000542-200510000-00020 PMID: 16192774
16. Bouman EA, Theunissen M, Bons SA, van Mook WN, Gramke HF, van Kleef M, et al. Reduced incidence of chronic postsurgical pain after epidural analgesia for abdominal surgery. Pain Pract. 2014;14(2):E76-84. DOI: 10.1111/papr.12091 PMID: 23758753
17. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia. 1999;54(12):1136-42. DOI: 10.1046/j.1365-2044.1999.01114.x PMID: 10594409
18. Ramsay MA. Bariatric surgery: the role of dexmedetomidine. Seminars in Anesthesia. Semin Anesth. 2006;25(2):51-6. DOI: 10.1053/j.sane.2006.02.004
19. Huang X, Deng R, Tu W, Hu Z. Dexmedetomidine reduces neuropathic pain in a rat model of skin/muscle incision and retraction. Asian J Surg. 2017;40(1):35-40. DOI: 10.1016/j.asjsur.2015.10.009 PMID: 27131956
20. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36. DOI: 10.1016/j.pain.2004.12.010 PMID: 15733628
21. Keller T, Freynhagen R, Tölle TR, Liwowsky I, Möller P, Hüllemann P, et al. A retrospective analysis of the long-term test-retest stability of pain descriptors of the painDETECT questionnaire. Curr Med Res Opin. 2016;32(2):343-9. DOI: 10.1185/03007995.2015.1125869 PMID: 26636376
22. Bouman EA, Theunissen M, Bons SA, van Mook WN, Gramke HF, van Kleef M, et al. Reduced incidence of chronic postsurgical pain after epidural analgesia for abdominal surgery. Pain Pract. 2014;14(2):E76-84. DOI: 10.1111/papr.12091 PMID: 23758753
23. Gerbershagen HJ, Dagtekin O, Rothe T, Heidenreich A, Gerbershagen K, Sabatowski R, et al. Risk factors for acute and chronic postoperative pain in patients with benign and malignant renal disease after nephrectomy. Eur J Pain. 2009;13(8):853-60. DOI: 10.1016/j.ejpain.2008.10.001 PMID: 19010073
24. Shin JH, Howard FM. Abdominal wall nerve injury during laparoscopic gynecologic surgery: incidence, risk factors, and treatment outcomes. J Minim Invasive Gynecol. 2012;19(4):448-53. DOI: 10.1016/j.jmig.2012.03.009 PMID: 22560041
25. Shipton E. Post-surgical neuropathic pain. ANZ J Surg. 2008;78(7):548-55. DOI: 10.1111/j.1445-2197.2008.04569.x PMID: 18593408
26. Sadatsune EJ, Leal PC, Clivatti J, Sakata RK. Chronic postoperative pain: pathophysiology, risk factors and prevention. Rev Dor. 2011;12(1):58-63. DOI: 10.1590/S1806-00132011000100013
27. Keller T, Freynhagen R, Tölle TR, Liwowsky I, Möller P, Hüllemann P, et al. A retrospective analysis of the long-term test-retest stability of pain descriptors of the painDETECT questionnaire. Curr Med Res Opin. 2016;32(2):343-9. DOI: 10.1185/03007995.2015.1125869 PMID: 26636376
28. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative analgesic agent. Proceedings (Baylor University Medical Center. 2001;14(1):13-21. DOI: 16369581/#:~:text=10.1080/08998280.2001.11927725. PMID: 16369581
29. Arcangeli A, D'Alò C, Gaspari R. Dexmedetomidine use in general anaesthesia. Curr Drug Targets. 2009;10(8):687-95. DOI: 10.2174/138945009788982423 PMID: 19702517
30. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth. 2006;53(7):646-52. DOI: 10.1007/BF03021622 PMID: 16803911
31. Kamibayashi T, Maze M, Weiskopf RB, Weiskopf RB, Todd MM. Clinical uses of alpha2 -adrenergic agonists. Anesthesiology. 2000;93(5):1345-9. DOI: 10.1097/00000542-200011000-00030 PMID: 11046225
32. Zhang J, Wang Z, Wang Y, Zhou G, Li H. The effect of dexmedetomidine on inflammatory response of septic rats. BMC Anesthesiol. 2015;15(1):68. DOI: 10.1186/s12871-015-0042-8 PMID: 25929655

33. Bulow NM, Colpo E, Pereira RP, Correa EF, Waczuk EP, Duarte MF, et al. Dexmedetomidine decreases the inflammatory response to myocardial surgery under mini-cardiopulmonary bypass. Braz J Med Biol Res. 2016;49(4):e4646. DOI: 10.1590/1414-431X20154646 PMID: 26909786

34. Liu W, Yu W, Weng Y, Wang Y, Sheng M. Dexmedetomidine ameliorates the inflammatory immune response in rats with acute kidney damage. Exp Ther Med. 2017;14(4):3602-8. DOI: 10.3892/etm.2017.4954 PMID: 29042954

35. Tang C, Huang X, Kang F, Chai X, Wang S, Yin G, et al. Intranasal dexmedetomidine on stress hormones, inflammatory markers, and postoperative analgesia after functional endoscopic sinus surgery. Mediators Inflamm. 2015;2015:939431. DOI: 10.1155/2015/939431 PMID: 26199465

36. Kawasaki T, Kawasaki C, Ueki M, Hamada K, Habe K, Sata T. Dexmedetomidine suppresses proinflammatory mediator production in human whole blood in vitro. J Trauma Acute Care Surg. 2013;74(5):1370-5. DOI: 10.1097/TA.0b013e31828db978 PMID: 23609293

37. Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. Crit Care Med. 2004;32(6):1322-6. DOI: 10.1097/01.CCM.0000128579.84228.2A PMID: 15187514