Arch Crit Care Med. 2015 August; 1(3):e6453. doi: 10.17795/accm-6453.

Published online 2015 August 31. **Research Article**

The Analgesic Effect of Morphine and Dexmedetomidine Intravenous Patient-Controlled Analgesia method to Control Pain After Open Cardiac Surgery: A Randomized Control Trial

Iman Ghandi,[1] Seyed Mostafa Alavi,[2,*] Turaj Babaee,[2] Behshid Ghadrdoost,[2] Hooman Bakhshandeh,[2] Mohsen Ziyaeifard,[2] Rasool Ferasatkish,[2] Zahra Faritous,[2] Alireza Jahangiri Fard,[3] and Maziar Mahjoubifard[4]

[1]Fellowship in Cardiac Anesthesiology, Razavi Cardiovascular Hospital, Mashhad, IR Iran
[2]Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran
[3]Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[4]Children and Adolescent Health Research Center Ali-ebn-e-abitaleb Hospital Zahedan University of Medical Sciences, Zahedan, Iran

[*]*Corresponding author*: Seyed Mostafa Alavi, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2123922154, E-mail: mostafa.alavi@gmail.com

Received 2015 July 01; **Accepted** 2015 August 15.

Abstract

Background: After major surgeries, such as abdominal or thoracic surgery, the majority of patients experience moderate to severe pain that may not be optimally controlled. Inadequate pain relief may lead to complications that can hinder rehabilitation and slow recovery.

Objectives: Post-operative pain is one of the most common complaints in surgery wards especially in open cardiac surgeries. The current study compared effectiveness of the patient controlled anesthesia (PCA) method, intravenously with morphine (MO) and dexmedetomidin (DEX) to reduce post-operative pain after open cardiac surgery.

Patients and Methods: The study was a double blind randomized clinical trial. One hundred candidates for open cardiac surgery were enrolled in the study and randomly assigned into two groups of MO and DEX. The patient-controlled intravenous analgesia (PCIA) pump was administered to all of the subjects, post-recovery, after insertion of catheter and filled with selected MO or DEX. Then visual analogue scale for pain severity was measured and recorded at 2, 4, 6, 8,10,12, 14, 16 and 18 hours post-operatively. SPSS V.16 was used for data analysis.

Results: Findings of the study showed a significant difference regarding the level of pain among the patients under treatment of MO and DEX at 2, 4, 6, 8, 10 and 12 hours after the surgery, whereas there was no significant difference at 14, 16 and 18 hours. However, the pain score was lower during the first 12 hours of follow-ups in both groups. Furthermore, intubation time in DEX-PCA group was shorter than that of MO group. It was also observed that the DEX pump group had required less intravenous morphine than MO pump group in the intensive care unit (ICU).

Conclusions: The study findings showed that post-operative pain was favorably reduced in both DEX and MO-PCIA groups after open cardiac surgery. Dexmedetomidin provides beneficial effects on pain control after cardiac surgery, with less adverse effects such as nausea, itching, atelectasis, intubation time, respiratory depression and intravenous morphine consumption.

Keywords: Morphine, Dexmedetomidine, Intravenous Patient-Controlled Analgesia, Open Cardiac Surgery, Pain Relief

1. Background

After major surgeries, such as abdominal or thoracic surgery, the majority of patients experience moderate to severe pain that may not be optimally controlled. Inadequate pain relief may lead to complications that can hinder rehabilitation and lengthen the recovery.

Analgesic methods vary and include intravenous, oral, rectal and regional that by peripheral nerve block are used for decades. The patient-controlled methods are considered by the recent trials. PCA is a method of allowing a person in pain to administer his own pain-relief. The infusion can be programed by the prescriber. If it is programmed and functioned as intended, the machine is unlikely to deliver an overdose of medication (1). These devices have various subtypes such as patient-controlled intravenous analgesia (PCIA), patient-controlled regional analgesia (PCRA) and patient-controlled epidural analgesia (PCEA). The initial investigations demonstrated good control of post-operative pain with a reduced incidence of side effects reported by patient-controlled analgesia (PCA) (2).

Hence, morphine is the most commonly used opioid for the relief of post-surgical pain. Despite widespread

use of morphine, it is associated with significant side effects such as respiratory depression, nausea and vomiting, urinary retention, prolonged and severe sedation and decreased gastrointestinal motility and ileus and accumulation of bile ducts in the liver and even in rare cases kidney failure. Nowadays, one of the preferred administration methods of this analgesic is patient-controlled intravenous analgesia (PCIA) (3).

Pain after cardiac surgery is serious due to multiple sources including: sternotomy and removal of the grafting vessels (4). Poor pain management in patients can cause significant complications such as cardiac ischemia due to stimulation of the sympathetic system, pulmonary complications such as atelectasis and pneumonia due to reduced ability to cough, venous thrombosis due to reduced and ultimately delayed mobility.

Moreover, non-steroidal anti-inflammatory drugs (NSAIDS) are other drug categories used as adjuvant therapy after cardiac surgery to control pain. These medicines may also cause significant complications that include increased risk of post-operative bleeding, gastrointestinal complications and renal dysfunction.

As mentioned above, adequate pain control after major surgeries such as cardiac surgery is so important that various methods such as continuous infusion administered by patients' desire or by patient controlled anesthesia (PCA) machines are tested (4). Nowadays, PCA method seems to be a good choice to control pain and effective to reduce consumption of opioid in the patients (3).

Dexmedetomitine is a potent, sedative, highly selective α-2 adrenergic receptor agonist which exhibits sympatholytic and analgesic effects with eight times more potent for the alpha-2 receptor than clonidine (5). The drug was approved by food and drug administration (FDA) as a short-term sedative (less than 24 hours) and analgesic in the critical care setting, particularly for use in the early post-operative period (6). As a sedative, dexmedetomidine has several advantages as follows: does not cause respiratory depression (7), causes easy arousability in the treated patients and they remain calm and cooperative (5). It is used to pre-medicate and sedate patients undergoing day care procedures with less adverse effects, and patients, typically, remain cooperative albeit being sedated (8, 9). The mean distribution half-life and the mean terminal half-life of dexmedetomidine are 8.6 minutes and 3.14 hours, respectively. Dexmedetomidine is metabolized in the liver, and excreted in urine (95%) and feces (4%) (10, 11).

Small-dose infusion of this drug in healthy volunteers has demonstrated sedation that can be easily reversed with verbal stimuli (12). Findings of the study by Candiotti et al., showed reduction of opioid analgesic and other anesthetic drugs in addition to dexmedetomidine in pain relief protocol (13).

Another study in 2003 by Herr et al., showed that DEX might be able to provide a safe sedation and lead to a significant reduction in the consumption of analgesics, beta-blockers, antiemetic, epinephrine, and diuretics (14).

In the current study, the analgesic effects of MO and DEX by PCIA method were compared for pain control after cardiac surgery. It was hypothesized that DEX provides beneficial effects on pain control after cardiac surgery, with less adverse effect. This hypothesis comes from the fact that using short-acting drugs is accompanied with less complication (especially respiratory depression) and accelerating the patient discharged from the intensive care unit.

2. Objectives

The review of literature demonstrated that none of the studies evaluated the effectiveness of continuous infusions of dexmedetomidine on the patients with open cardiac surgery by PCIA method; therefore, it is unclear whether MO or DEX is a better choice for the pain relief in these patients.

3. Patients and Methods

One-hundred candidates for open cardiac surgery with mean age of 46.86 $\pm$ 11.50 years old were studied. According to the American society of anesthesiologists' (ASA) physical status grading, these patients were graded I to III. The ASA physical status classification system was initially created in 1941 by ASA. Normal healthy patients were scored I and patients with mild and severe systemic disease were scored II and III, respectively (15).

Before operation, patients were instructed on the use of the PCA machine. The visual analogue scale (VAS: 0 = no pain, 10 = worst imaginable pain) was used for pain rate estimation. The patients were brought to the operation room after receiving the equal premedication which was the administration of morphine 0.1 mg/kg/IM with oral lorazepam 1 mg. Also, the anesthesia was inducted by remifentanil 1 μ/kg, midazolam 0.1 mg/kg and cisatracurium 0.15 mg/kg.

Anesthesia was maintained with remifentanil 0.1 - 0.05 μ/kg/minute, propofol 50 - 75 μg/kg/minute, midazolam 0.02 - 0.05 μ/kg/minute, cisatracurium and low dose of sevoflurane.

After surgery, patients were randomly divided into two groups. In the control group, before being transferred to the ICU ward, the intravenous patient-controlled anesthesia (IV-PCA) pump containing 0.2 mg morphine was inserted. The rate of morphine infusion in this pump was

4 mL per hour. In the second group, before being transferred to the ICU ward, the IV-PCA pump containing 0.2 μg dexmedetomidine was inserted.

The patients were transferred to ICU ward and extubated when they were hemodynamically stable, and then all the patients could receive infusion of medication via a PCIA pump in the first 24 hours. The setup regimen of pain relief with these devices was bolus doses of the drug with the locked out of time of 1 mL per 15 minutes, respectively.

Pain severity of the patients was evaluated via visual analog score two hours after extubation in ICU and with two hours intervals for six times. In this case, the patients presented the severity of their pain by a number from 1 to 10 of visual analogue scale (VAS) and the subjects who were not able to do this, the nurse selected the desired number according to the mimic of the patients' face denoting the illustration of VAS.

The other items investigated during the first 24 hours, included: Adverse effects of opioids (nausea, vomiting, pruritus, respiratory depression), time of extubation, the total amount of drug administered per subject, liver and kidney function tests, hemodynamic status of patients (blood pressure and heart rate), arterial blood gas (ABG) and chest X-ray (CXR). Finally, based on the collected data and statistical computations, the analgesic effects of MO and DEX and their complications were compared.

In the current study, patients with the following characteristics were excluded: ejection fraction (EF) < 30%, ASA > III, candidates of emergency surgery, intra-operative (ABPI) use, combined valvular surgery, impaired liver function (more than two folds of liver enzymes), renal dysfunction (cr > 2), drug addiction, sternum or rib fracture during surgery, presence of neurological complications, continuous unconsciousness and patients who did not cooperate with the authors.

3.1. Statistical Analysis

Collected data were transferred into SPSS version 16 and descriptive and analytical methods were used. Descriptive statistics included means, standard deviation and frequency distribution tabulations. In the current study, T-test and Chi-square test were used to gain analytical statistics.

3.2. Ethical Consideration

Every participant signed the informed consent letter and they were assured of the confidentiality of their recorded information. The trial was approved by committee of research ethics of Tehran University of Medical Sciences, as well. It was a randomized clinical trial conducted by sampling based on the target group selected from the patients referred to cardiac ward of Shahid Rajaei Hospital in Tehran after official admission.

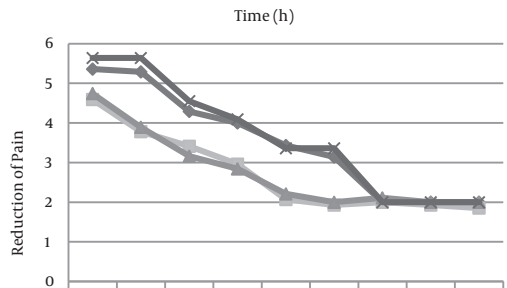
4. Results

One-hundred candidates for open cardiac surgery were studied, MO group patients (50 cases) with a mean age of 66.76 $\pm$ 6.08 (range 56 - 81 years) and DEX group (50 cases) with a mean age of 65.44 $\pm$ 5.22 (range 54 - 79 years). Therefore, most of the patients were 40-60 years and there was no significant difference between the groups regarding the age (P = 0.247). The summary of the results are shown in Table 1. According to Table 1, in case of pain scale, there was a significant difference among the patients under treatment between the groups at 2, 4, 6, 8, 10 and 12 hours measurements, after surgery. But this variable was not significantly different at 14, 16 and 18 hours. The results indicated that the reduction of pain was higher when DEX was used.

The analgesic effects of MO and DEX were compared in the patients according to the gender. As a result, DEX significantly reduced the pain among the male patients at 2, 4, 6, 8 and 10 hours after surgery. While, there was no significant difference between the genders at 14, 16 and 18 hours after surgery.

Among the female patients, DEX significantly reduced the pain at 2, 4, 6, 8, 10 and 12 hours after surgery. There was no significant difference between DEX and MO at 14 hours after surgery and variables related to 16 and 18 hours after surgery were not possible to examine. The summarized results in Figure 1 indicate the reduction of pain curves in the groups. According to Figure 1, injection of DEX reduced pain more than MO.

Figure 1. The Comparison Between the Two Studied Groups Regarding the Reduction of Pain



	2	4	6	8	10	12	14	16	18
Dex(Male)	5.36	5.29	4.29	4	3.43	3.14	2	2	2
Morphine(Male)	4.59	3.78	3.41	2.96	2.07	1.93	2	1.93	1.85
Dex(Female)	4.74	3.89	3.16	2.84	2.21	2	2.11	2	2
Morphine(Female)	5.64	5.64	4.55	4.09	3.36	3.36	2	2	2

Group DEX = Dexmedetomidine group, group MO = morphine group.

Table 1. Evaluation of Pain in the First Eighteen Hours After Surgery[a]

Post-Operation Time, h	Rate of Pain	T	df	P
2		4.26	98	0.000
MO	5.48 ± 0.974			
DEX	4.60 ± 1.09			
4		9.41	98	0.000
MO	5.44 ± 0.907			
DEX	3.80 ± 0.833			
6		6.27	98	0.000
MO	4.40 ± 0.808			
DEX	3.28 ± 0.970			
8		7.62	98	0.000
MO	4.04 ± 0.493			
DEX	2.84 ± 0.997			
10		7.20	98	0.000
MO	3.40 ± 0.926			
DEX	2.20 ± 0.728			
12		2.20	98	0.030
MO	2.24 ± 0.657			
DEX	2.00 ± 0.404			
14		1.00	98	0.320
MO	2.0 ± 0.000			
DEX	2.08 ± 0.566			
16		0.573	98	0.568
MO	2.00 ± 0.000			
DEX	1.96 ± 0.493			
18		1.00	98	0.320
MO	2.00 ± 0.000			
DEX	1.92 ± 0.566			

Abbreviations: DEX, dexmedetomidine group; MO, morphine.
[a] t-test for independent groups.

Moreover, the reduction of pain curves in male and female groups were compared. Based on Figure 1, in male and female groups, DEX affected the reduction of pain more than MO and in male-DEX group reduction of pain was more than the other groups.

Furthermore, three age groups were created, merging the five-year groups, to compare the effect of MO and DEX in terms of the age. Twenty patients in the age group of 51 - 60, sixty five patients in the age group of 61 - 70 and fifteen patients in the age group of 71 - 80 were evaluated. Based on the results of T-test for these independent groups, there was a significant difference among the 51 - 80 year old patients under the treatment of MO and DEX at 2, 4, 6, 8, and 10 hours after the surgery. But there was no significant difference between the groups at 12, 14, 16 and 18 hours after the surgery.

According to $P < 0.001$, the difference between the intravenous morphine consumption of the two groups was significant. Figure 2 indicates that the DEX pump group (4.22 ± 3.48) required less intravenous morphine than MO pump group (7.50 ± 4.15) in ICU.

According to Table 2, the relationship between the incidence of nausea and MO and DEX consumption was significant according to $\chi^2 = 19.39$ and $P = 0.000$. According

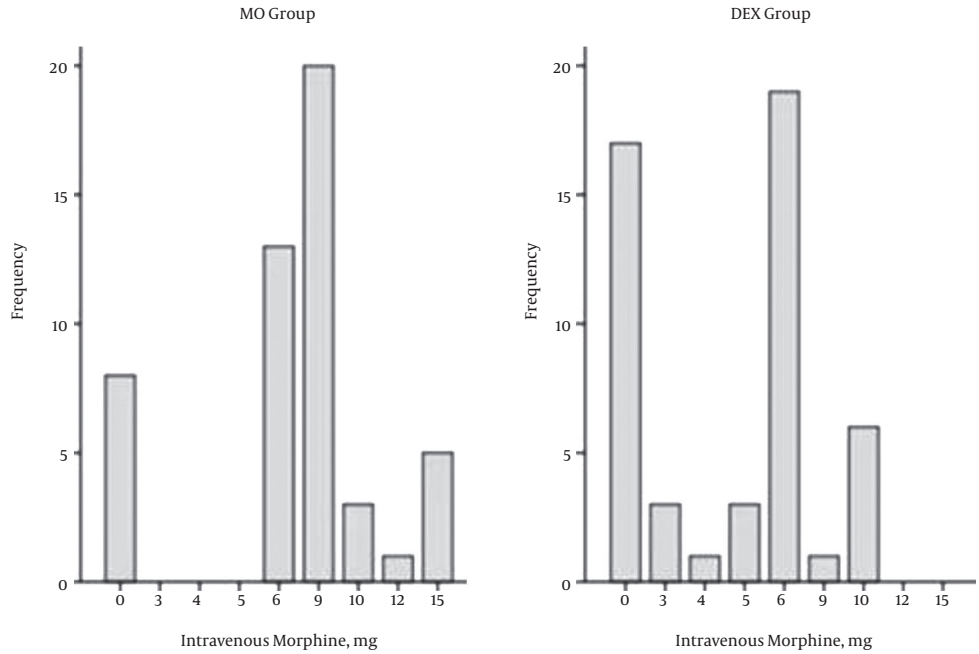


Figure 2. Amount of Intravenous Morphine in the Patients of Both Groups

to the adaptive Cramer coefficient, the rate of this relationship was C = 0.44.

Table 2. The Comparison Between the Adverse Effect in the Patients of the Study Groups

Adverse Effect	No. (%) in the DEX Group	No. (%) in the MO Group
Nausea		
Yes	13 (26)	35 (70)
No	37 (74)	15 (30)
Vomiting		
Yes	0 (0)	3 (6)
No	50 (100)	47 (94)
Itching		
Yes	4 (8)	19 (38)
No	46 (92)	31 (62)
Atelectasis		
Yes	23 (46)	34 (68)
No	27 (54)	16 (32)

Abbreviations: DEX, dexmedetomidine group; MO, morphine.

The relationship between incidence of vomiting and MO and DEX consumption was marginally significant according to $\chi^2 = 3.093$ and P = 0.079. The relationship between incidence of itching (pruritus) and MO and DEX consumption was significant according to $\chi^2 = 12.70$ and P = 0.000. According to the adaptive Cramer coefficient, the rate of this relationship was C = 0.356.

The comparison between adverse effects in DEX and MO groups suggest that in the DEX group, the nausea, itching and atelectasis decreased. Therefore, it could be concluded that the adverse effects in the DEX group were lower compared to the MO group.

Regarding atelectasis, the difference between the rate of atelectasis and MO and DEX consumption was significant. It was observed that the patients with MO pump experienced significantly more atelectasis (P = 0.026) than DEX group.

In the current study, the intubation time varied (in terms of minutes) between MO (437.50 $\pm$ 31.97) and DEX (377.06 $\pm$ 25.43) groups by T-test for independent groups. Based on the $t^2 = 10.37$ and P = 0.000, differences between the two groups were significant. This time in DEX group was shorter than MO group.

According to T = 1.59 and P = 0.115, the differences of EF in the two groups of MO (45.61 $\pm$ 2.62) and DEX (46.66 $\pm$ 3.80) were not significant.

Although, ASA variable could have 6 levels and was suitable for sequential methods (Mann-Whitney U test), since the current study had only two stages in practice, the Chi-square method was performed. According to Table 3, the relationship between ASA and MO and DEX consumption

was not significant based on $\chi^2 = 1.19$ and P = 0.275.

Table 3. The Comparison Between the Groups Based on ASA Grading

Variables	Grade	No. (%) DEX Group	No. (%) MO Group
ASA	II	10 (20)	40 (80)
	III	6 (12)	44 (88)

Abbreviations: ASA, American society of anesthesiologists; DEX, dexmedetomidine; MO, morphine.

5. Discussion

The present study aimed to evaluate the comparison of analgesic effect of PCIA-MO infusion and PCIA-DEX infusion on adequate pain control after cardiac surgery. It was observed that during the first 14 hours after the surgery, DEX reduced post-operative pain more than MO.

In agreement with the present study, Yacout et al. studied thirty adult ASA I-III patients admitted for the abdominal surgery under general anesthesia. They demonstrated that post-operative pain score was significantly lower in DEX group compared to placebo group during the early post-operative period with smaller amount of analgesic requirements in DEX group. DEX also reduced the post-operative pain score without delaying recovery from anesthesia (16).

The findings of Maldonado et al. suggested that post-operative sedation with DEX was associated with significantly lower rates of post-operative delirium and lower care costs (17).

Also, Gomez-Vazquez et al. reported that DEX provided a modest analgesic effect after knee arthroscopy, but the side effects of this drug, such as bradycardia and hypertension, may restrict the use of large bolus doses (18).

In another study, Mahmoud et al. evaluated the effect of DEX as an adjunct to PCA with morphine. They found out that post-operative 24-hour DEX infusion as an adjunct to PCIA with opioids might have a morphine-sparing effect as evidenced by the increase in morphine use on post-operative two days after the DEX infusion was stopped (19).

According to Hall et al., in a small population of volunteers with healthy cardiovascular systems, small doses of DEX provided sedation that could be easily reversed with verbal or physical stimuli (20).

In the present study, nausea, itching and intubation time were significantly lower in the DEX group than the MO group. While, vomiting, EF and ASA relation with DEX and MO were not significantly different. Compared to MO, DEX might be advantageous, especially in pain reduction. In addition to that, DEX had less adverse effect than MO.

Furthermore, DEX group had significantly lower rate of atelectasis that based on the above statements is justified and is a desirable outcome. Martin et al. and Flacke et al. reported that adverse effects and atelectasis, occurred more frequently in the control group, while it occurred more frequently in the dexmedetomidine group of the study (21, 22), and decrease in atelectasis was observed in other species following the administration of dexmedetomidine. That was corresponding with the current study findings.

One of the most important complications of opioids is respiratory depression via effects on the respiration center. Respiratory depression along with lower autonomic efforts of the patients' respiration which rises from the chest pain can lead to atelectasis, pulmonary collapse and increased risk of respiratory infections. Considering the fact that, patients with DEX pump need less intravenous morphine than the control group indicates the positive effect of DEX on reducing pain is more than that of morphine and consequently, the required intravenous morphine is less. Lin et al. studied the effect of combining dexmedetomidine and morphine for incremental PCA (IPCA) method in elderly people. Compared with group MO, patients in group DEX required 29% less morphine during the 0-24 hours post-operative period. The 4-24 hours incidence of nausea was significantly lower in DEX group. There was no bradycardia, hypotension, oversedation or respiratory depression. The addition of dexmedetomidine to IV PCA morphine resulted in superior analgesia, significant morphine sparing, less morphine-induced nausea and devoid of additional sedation and untoward hemodynamic changes (23). These findings are consistent with the current study results.

5.1. Conclusion

The results indicated that in a small population of volunteers with open cardiac surgery, small doses of dexmedetomidine provided more analgesia than morphine. Also, this supports the findings of the present study that DEX administration resulted in lower levels of nausea, itching, atelectasis, intubation time, respiratory depression and intravenous morphine response markers after surgery. This effect might prove useful in a post-operative setting or in the intensive care unit. It seems to be a safe method, with additional analgesic effects provides a satisfactory sedation level without any serious adverse effects after surgery.

Acknowledgments

Acknowledgments The authors wish to thank the vice chancellor of research of Shahid Rajaei hospital in Tehran

University of Medical Sciences for funding and supporting the current study, and all the other colleagues who participated in this research, and also, Zamen Salamati Co. for editing and proofreading of the manuscript.

Footnote

Authors' Contributions: Study concept and design: Iman Ghandi, conducting the project: Seyed Mostafa Alavi and Turaj Babaee, revising the manuscript: Behshid Ghadrdoost and Rasool Ferasatkish, collecting the data and review of the literature: Mohsen Ziyaeifard and Alireza Jahangirifard, data analysis and preparation of the Manuscript: Hooman Bakhshandeh, Zahra Faritous and Maziar Mahjoubifard.

References

1. Chambers J, Chearney LA, Romaine DS, Levy CB, Jewell CS. The facts on file encyclopedia of health and medicine. 2007 ;**3**.
2. White PF. Use of patient-controlled analgesia for management of acute pain. *JAMA.* 1988;**259**(2):243–7. [PubMed: 3275811].
3. Miller RD, Eriksson LI, Fleisher LA. Miller's anesthesia. 7 ed. Churchill livingstone; 2010. pp. 1662–4.
4. Kaplan JA, Rich DL, Lack CL, Konstadt SN. Kaplan's cardiac anesthosia. 5 ed. 3. Elsevier; 2006. pp. 1161–3.
5. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent).* 2001;**14**(1):13–21. [PubMed: 16369581].
6. Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. *Crit Care Med.* 1995;**23**(9):1596–600. [PubMed: 7664563].
7. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. *Drugs.* 2000;**59**(2):263–8. [PubMed: 10730549].
8. Aantaa R, Jaakola ML, Kallio A, Kanto J, Scheinin M, Vuorinen J. A comparison of dexmedetomidine, and alpha 2-adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery. *Br J Anaesth.* 1991;**67**(4):402–9. [PubMed: 1681840].
9. Alhashemi JA, Kaki AM. Dexmedetomidine in combination with morphine PCA provides superior analgesia for shockwave lithotripsy. *Can J Anaesth.* 2004;**51**(4):342–7. doi: 10.1007/BF03018237. [PubMed: 15064262].
10. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive caret. *Br J Anaesth.* 2002;**88**(5):669–75. [PubMed: 12067004].
11. Aantaa R, Scheinin M. Alpha 2-adrenergic agents in anaesthesia. *Acta Anaesthesiol Scand.* 1993;**37**(5):433–48. [PubMed: 8395129].
12. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology.* 1992;**77**(6):1125–33. [PubMed: 1361310].
13. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY, et al. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. *Anesth Analg.* 2010;**110**(1):47–56. doi: 10.1213/ane.0b013e3181ae0856. [PubMed: 19713256].
14. Herr DL, Sum-Ping S, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. *J Cardiothorac Vasc Anesth.* 2003;**17**(5):576–84.
15. Rampil I. The american society of anesthesiologists (ASA) anesthesiology. 1997 ;**87**(4):1026.
16. Yacout AG, Osman HA, Abdel-Daem MH, Hammouda SA, Elsawy MM. Effect of intravenous dexmedetomidine infusion on some proinflammatory cytokines, stress hormones and recovery profile in major abdominal surgery. *Alexandria J Med.* 2012;**48**(1):3–8.
17. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics.* 2009;**50**(3):206–17. doi: 10.1176/appi.psy.50.3.206. [PubMed: 19567759].
18. Gomez-Vazquez ME, Hernandez-Salazar E, Hernandez-Jimenez A, Perez-Sanchez A, Zepeda-Lopez VA, Salazar-Paramo M. Clinical analgesic efficacy and side effects of dexmedetomidine in the early postoperative period after arthroscopic knee surgery. *J Clin Anesth.* 2007;**19**(8):576–82. doi: 10.1016/j.jclinane.2007.06.013. [PubMed: 18083469].
19. Sadhasivam S, Boat A, Mahmoud M. Comparison of patient-controlled analgesia with and without dexmedetomidine following spine surgery in children. *J Clin Anesth.* 2009;**21**(7):493–501. doi: 10.1016/j.jclinane.2008.12.017. [PubMed: 20006257].
20. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg.* 2000;**90**(3):699–705. [PubMed: 10702460].
21. Martin E, Ramsay G, Mantz J, Sum-Ping ST. The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. *J Intensive Care Med.* 2003;**18**(1):29–41. doi: 10.1177/0885066602239122. [PubMed: 15189665].
22. Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, et al. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology.* 1987;**67**(1):11–9.
23. Lin TF, Yeh YC, Lin FS, Wang YP, Lin CJ, Sun WZ, et al. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth.* 2009;**102**(1):117–22. doi: 10.1093/bja/aen320. [PubMed: 18987053].