Original Article

The Effect of Dexmedetomidine Infusion after Craniotomy on Sedation, and Its Complications in the Intensive Care Unit and Its Comparison with the Control Group

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Abstract

Introduction: The purpose of this study was to evaluate the effect of administering dexmedetomidine on pain and hemodynamic parameters of patients after craniotomy.

Materials and Methods: The present study is a randomized clinical trial that was performed on 60 patients undergoing craniotomy. The basic information of the patients was collected, their vital signs were recorded, and after the completion of the surgery, the intervention group received dexmedetomidine, and the control group received a normal saline infusion. Then, at the 30th minute and 4th, 8th, 12th, 16th, 20th, and 24th hour after the patient's admission to the recovery, the degree of sedation in the patients and the satisfaction of the patient's nurse based on the pain Visual Analogue Scale were evaluated. Data were analyzed using SPSS software.

Results: There was no significant difference between the two groups regarding age, sex, systolic and diastolic blood pressure, heart rate, and oxygen saturation, at the 30th minute and 4th, 8th, 12th, 16th, 20th and 24th hour and sedation level at 12th, 16th and 20th hour after the patient's admission to the recovery ($P > 0.05$). Sedation level and the scores of the satisfaction of the patient's nurse in the dexmedetomidine group were significantly higher than in the control group ($P < 0.001$).

Conclusion: The use of dexmedetomidine is associated with better sedation scores in the first 8 hours after the patient's admission to the recovery and pain Visual Analogue Score (VAS) compared to the placebo. Hemodynamic parameters were similar between the two groups.

Keywords: Dexmedetomidine, Craniotomy, Visual analog scale, Placebo, Hemodynamics

Introduction

Craniotomy refers to a set of surgeries used for treating a vast spectrum of neurological disorders, including cerebral tumors, brain's vascular diseases (hematoma, aneurysm and vascular malformations), skull fractures, external bodies, edema or cerebral infection as well as for diagnosis (such as placement of intracerebral electrodes) [1].

Amongst the important goals of the anesthesia team during craniotomy surgery is the preservation of the stable cerebral hemodynamics, prevention of the patients' sudden awareness, and also prevention of acute cerebral edema. Severe excitations during craniotomy constantly stimulate the sympathetic system and lead to notable changes in the arterial blood pressure and the brain's blood circulation. These cerebrovascular changes can cause an increase in the intracerebral pressure and a decrease in the cerebral perfusion pressure following which ischemia may be induced especially in patients with the disordered autonomic systems. Therefore, controlling the hemodynamic reactions along with the maintaining of the least sympathetic excitations is amongst the most important interventions for preserving the stability of the cerebral hemostasis. Moreover, this issue is of great importance from the perspective of the acceleration of recovery following anesthesia in operated patients, particularly in patients with hypertension [2, 3].

The other important challenge before the anesthesia team following craniotomy surgery is pain control. Although it seemed in the past that the pain of the intra-skull surgeries is lesser than that of the other surgeries, some studies have demonstrated that about 80% of the patients report intermediate to severe pain within 48 hours following

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craniotomy and this is indicative of their not being completely cured [4-6].

Many of the physicians make limited use of opioids for pain control but, due to the possibility of the emergence of respiratory depressions, hypercapnia, and increase in the intracerebral pressure following their use, the high dosages of the opioids are not usually prescribed, and their use is most frequently made of lower dosages of opioids. After the prescription of insufficient drug dosages, post-surgery symptoms like edema, hemorrhage, long hospitalization, and so forth usually emerge and the mortality rates are increased due to the subsequent sympathetic reactions [7].

Considering the problems related to the use of opioids, non-opioid analgesics are extensively used for the reduction of post-craniotomy pains. These drugs also show the opioid-related symptoms but for a lesser amount and, at the same time, the post-surgery symptoms are rendered more limited following their consumption [8].

Dexmedetomidine is a sedative alpha-2 agonist drug and is categorized as a clonidine-class drug with its difference with clonidine being an eight-time tendency for binding with alpha-2 receptors in contrast to alpha-1 adrenoceptor [9, 10].

The stimulation of the alpha-2 receptor exerts a relieving and painkilling effect on the entire body and, on the other hand, causes a reduction in the palpitation through corroboration of the vagus nerves' effect. Furthermore, the agonistic effect of alpha-2 on autonomic ganglions brings about reductions in the sympathetic signals and resultantly causes vasodilation due to the reduction of the sympathetic effects; in higher dosages, it causes vasoconstriction due to its influence on the veins' smooth muscles [9-11].

One of the useful properties of dexmedetomidine is that it can be used intravenously, intramuscular, subcutaneously, nasally, and alveolar, and rectally or orally [9].

In children, this drug is extensively applied for preventing delirium and pain following surgery as well as for managing the symptoms and signs of opioids' quitting [12].

Numerous studies have shown that dexmedetomidine can be used surely within the first 24 hours after craniotomy. The suggested dosage for dexmedetomidine is a bolus injection for 1.0 µg.kg for ten minutes followed by a preserving injection for 0.2-0.7µg.kg within 20 to 30 minutes before the end of the surgery [13].

Despite a great many of the studies about the effectiveness of dexmedetomidine in preserving the stability of the cerebral hemodynamics and induction of painlessness, some studies have shown the identicalness of the effect of dexmedetomidine and other anesthesia-inducing drugs like propofol or ketamine. Considering the conflicting results in the comparison of dexmedetomidine and these drugs, on the one hand, and the need for a drug that, meanwhile being safe, exerts strong effects on the preservation of the patients' hemodynamics stability and painlessness, on the other hand, the present study intends to investigate the effect of dexmedetomidine administration on patients' pain as well as the parameters of their hemodynamics' stability following craniotomy.

Materials and Methods:

The present study is a random clinical trial that was conducted on the craniotomy candidates who had referred to Al-Zahra (may Allah hail on her) Hospital in Isfahan in 2017-2018. The study has been confirmed under the ethical code number … by the Medical Ethics Committee of Isfahan's Medical University and it has been approved under the code number … in the Research Vice Chancellorship of Isfahan's Medical Sciences Department as a dissertation. Use was made of a simple and convenience sampling method herein and the study sample volume was comprised of 25 individuals (placed in an intervention group and an evidence group) considering the results of the prior similar studies, a test power of 80% and a unit level of error stemming from the mean pain feeling in the two groups. The study inclusion criteria were: patients' being in an age range from 20 to 80; being a candidate for craniotomy, patients' being intubated after surgery, being placed under mechanical respiration for 24 hours,, and filling the consent letter for taking part in the study. The study exclusion criteria were: surgery duration below 30 minutes, cardiac-respiratory arrest, the the existence of sensitivity to drugs, the existence of third-degree heart block, palpitation below 45, systolic pressure below 80 mmHg and not being willing for continuing participation in the study. After acquiring the required permits from the Medical Ethics Committee and Research Vice Chancellorship of Isfahan's Medical Department, the patients were selected based on the study's inclusion and exclusion criteria. In this regard, the patients were seminally presented with the necessary explanation about the study and its implementation method, and written consent letters were acquired for participation in the study. In the next stage, the patients' demographic information, including age, gender, history of special diseases, history of cardiac diseases,, and smoking, were collected using a questionnaire by the study's implementer. Then, the patients were randomly allocated to two 30-person groups, namely the intervention group that received dexmedetomidine and the evidence group that received normal saline. All of the selected patients were subjected to constant heart monitoring at the beginning of the entry into the operation room and their systolic and diastolic blood pressures, a number of palpitations, and percentage of arterial blood oxygen (SPO2) were recorded. After the termination of the surgery, the intervention group intravenously received dexmedetomidine in a dosage of 1µg.kg in the diluted and soluble manner in a volume of 20 cc for ten minutes with the repeated administration of a dosage equal to 0.5µg.kg.hr. The evidence group, as well, was

subjected to intravenous infusion of normal saline for an amount of 20 cc for 10 minutes followed by the repeated infusion of 0.5 ml/kg/hr. Then, in minute 30 after entry into recovery and at the hours four, eight, twelve, sixteen, twenty, and twenty-four after entry into recovery, the sedation levels of the patients who had been transferred following recovery into ICU were measured based on Richmond's agitation-sedation scale. This scale is an instrument for investigating the sedations status or agitation status of the individuals and it is an effective tool in the intensive care units for determining the dosage of the sedatives. The reliability and validity of this tool have been investigated in Iran by Tadrisi et al. and the results have been promising. On the other hand, the amount of the patients' satisfaction following surgery was evaluated based on a visual analog scale which is one of the simplest and most useful instruments available for assessing the amount of post-surgery pain and it enables reporting of a spectrum from pain's nonexistence to most severe pain and it has been investigated in various studies in Iran and acceptable reliability and validity rates have been proved for it. It is noteworthy that midazolam for an amount of 0.5mg/kg or fentanyl for an amount of 2μg/kg is considered for injecting to the patients in case of the observation of fighting in the patients during anesthesia or in case of the recording of scores above 4 based on Richmond's scale. All of the information recorded for the statistical analysis was inserted into a software package.

Data Analysis:

All of the information recorded in the computer was analyzed using IBM SPSS Statistics for Windows, version 24.0, Armonk, NY: IBM Corp. The quantitative data was evaluated by the use of an independent t-test. The qualitative data, as well, was analyzed using the chi-square test. The quantitative data have been exhibited in the form of mean and standard deviation and the qualitative data, as well, have been shown in the form of numbers and percentages within the format of the following Tables. The significance level, as well as defined in the form of a P-value<0.05.

Results:

In this study, the patients were divided into two groups, namely the group receiving dexmedetomidine (19 men and 11 women) and the control group (14 men and 16 women). There was observed no significant difference between the patients in terms of age and gender (P>0.05). There was found a significant difference between the two groups in terms of the sedation level within the first half after recovery and at hours four and eight after an operation in such a way that the sedation levels of the dexmedetomidine group's patients were significantly more subtle than those of the control group's patients (P<0.001). However, there was not found a significant difference between the two groups based on the sedation levels at hours 12, 16, and 20 after recovery (P>0.05). the mean satisfaction rate of the patients in the dexmedetomidine group was significantly higher than that of the patients in the control group (P=0.005) (Table 1).

Table 1: The Variables Studied in the Patients of the Two Groups

Variables			Dexmedetomidine Group	Control Group	P-value
Age			60.33±12.91	57.03±12.61	0.77*
Gender	Male		19 (63.3%)	14 (46.7%)	0.19**
	Female		11 (36.7%)	16 (53.3%)	
VAS-based Satisfaction Rate			6.90±2.07	3.30±1.29	0.005*
Sedation Level	Half an Hour after Recovery	0-4	5 (16.7%)	28 (93.3%)	0.001>**
		-1 to -2	18 (60%)	2 (6.7%)	
		-3 to -4	6 (20%)	0	
		-5	1 (3.3%)	0	
	4 Hours Later	0-4	13 (43.3%)	29(96.7%)	0.001>**
		-1 to -2	15(50%)	1(3.3%)	
		-3 to -4	1(3.3%)	0	
		-5	1(3.3%)	0	
	8 Hours Later	0-4	18(60%)	30(100%)	0.001**
		-1 to -2	11(36.7%)	0	
		-5	1(3.3%)	0	
	12 Hours Later	0 to 4	26(86.7%)	30(100%)	0.11**
		-1 to -2	3(10%)	0	
		-3 to -4	1(3.3%)	0	
	16 Hours Later	0-4	28(93.3%)	30(100%)	0.24**
		-1 to -2	2(6.7%)	0	
	20 Hours Later	0-4	29(96.7%)	30(100%)	0.50**
		-1 to -2	1(3.3%)	0	
	24 Hours Later	0-4	30()	30()	-

*The Comparison between Groups based on Independent t-test
**The Comparison between Groups based on Chi-square Test

There was no significant difference between the two groups in terms of the systolic and diastolic blood pressure, palpitation, and percentage of oxygen saturation in half an hour after recovery and at hours 4, 8, 12, 16, 20, and 24 after it (P>0.05) (Table 2).

Table 2: Hemodynamic Variables Studied for both of the Groups

Variables		Dexmedetomidine Group	Control Group	P-value*
Systolic Blood Pressure	Half an Hour after Recovery	121.27±15.34	118.34±13.04	0.57
	4 Hours Later	116.34±14.52	115.03±14.92	0.64
	8 Hours Later	115.26±11.02	115.66±10.95	0.80
	12 Hours Later	114.20±10.34	112.43±11.91	0.26
	16 Hours Later	113.76±9.03	115.01±13.20	0.05
	20 Hours Later	117.20±11.26	119.36±11.41	0.86
	24 Hours Later	117.53±11.10	117.58±10.78	0.68
Diastolic Blood Pressure	Half an Hour after Recovery	68.50±11.39	73.75±17.52	0.08
	4 hours later	67.86±12.36	71.60±15.76	0.32
	8 Hours later	66.03±8.36	63.86±12.14	0.06
	12 Hours later	67.40±9.62	69.21±11.25	0.42
	16 Hours later	70.75±9.98	68.68±11.04	0.84
	20 Hours later	71.13±9.05	73.44±10.82	0.35
	24 Hours later	70.63±10.48	73.58±12.85	0.40
Palpitation	Half an Hour after Recovery	85.46±17.26	84.23±14.67	0.45
	4 hours later	86.20±16.57	81.93±15.65	0.84
	8 Hours later	80.03±16.10	79.56±15.81	0.92
	12 Hours later	80.26±14.36	77.06±19.56	0.24
	16 Hours later	75.62±14.46	73.66±15.65	0.85
	20 Hours Later	79.03±12.64	76.14±13.38	0.83
	24 Hours Later	75.72±13.09	69.89±13.28	0.69
Oxygen saturation percentage	Half an Hour after Recovery	99.80±0.61	99.70±0.79	0.25
	4 Hours Later	99.86±0.50	99.85±0.52	0.88
	8 Hours Later	99.89±0.45	100.0±0.00	0.10
	12 Hours Later	99.89±0.45	99.92±0.27	0.65
	16 Hours Later	99.89±0.45	99.92±0.27	0.65
	20 Hours Later	99.88±0.47	99.92±0.27	0.60
	24 Hours Later	99.84±0.50	99.92±0.27	0.27

*The Comparison between Groups based on Independent t-test

Discussion:

The results of our study indicated that the sedation levels within half an hour after recovery as well as the first four and eight hours after entry into recovery were higher in the group that received dexmedetomidine in comparison to the group that had received normal saline; no significant difference was observed between the two groups in this regard in hour 12 after recovery. Besides, the scores of VAS in the patients who had been given dexmedetomidine signify the higher satisfaction of the patients following the use of this drug in comparison to the control group. This finding means that dexmedetomidine has been effective in the early hours after surgery in relieving the pains and sedating the patients who had been subjected to craniotomy. The similarity of the results obtained following the comparison of the systolic and diastolic blood pressure, heart palpitation, and percentage of oxygen saturation in various hours after entry into recovery between the dexmedetomidine group and the control group, as well, is reflective of the non-considerable effect of this drug on the hemodynamics of craniotomy patients herein. Therefore, considering the sedative nature of this drug along

with its limited effects on the stability of the patients' hemodynamics in contrast to placebo, dexmedetomidine can be recounted as a safe and effective drug to be administrated following craniotomy.

Based on the results obtained in a study by Jadhav et al. who investigated the effect of dexmedetomidine on craniotomy patients, it has been found out that the drug's use is followed by a significant reduction in the mean palpitation rate, diastolic blood pressure, and mean arterial blood pressure in the patients as compared to the receivers of placebo; no significant difference has been found therein regarding the systolic blood pressure between the patients who had received dexmedetomidine and those who had received placebo [3].

In our study, the diastolic blood pressure and the mean heart palpitation of the dexmedetomidine receivers have been similar to those of the placebo receivers hence the present study's findings are not consistent with what has been obtained by Jadhav et al. but consistent with their findings of SPO2 and systolic blood pressure. The reason for these differences might be the difference in the measuring of the parameters, differences in the measurement times, the difference in anesthesia methods, and possible differences in the background diseases in the patients of the two studies. In the study by Batra et al., the effect of dexmedetomidine was investigated as a pain-reliever during intracranial surgeries and the results indicated that the vital signs, including HR and mean arterial blood pressure, have been similar during the surgery and only extubation time has been found longer in the control group than the group that had been administrated with dexmedetomidine [14].

Additionally, the mean arterial blood pressure was found higher in the control group than the dexmedetomidine receivers from the minute 60 after craniotomy till the minute 240 after that. These results are not consistent with the results of our study in that the vital signs have been similar in both of the groups after surgery and it might be due to the difference in the time of dexmedetomidine administration, drugs administrated during anesthesia as well as their dosages. On the other hand, the results of the study by Peng et al. who investigated the effect of dexmedetomidine on post-craniotomy pain are consistent with the results of our study. They showed that the palpitation and blood pressure statuses of the patients from the group that had received a placebo as well as the group that had been administrated with dexmedetomidine are similar. Also, the investigation of the pain intensity in the patients who had been given dexmedetomidine in their study indicated that the amount of pain in this group has been lower than that in the group that received placebo; this finding is following what has been found herein [15].

In opposite, Muller et al. compared the effectiveness of dexmedetomidine along with propofol and showed that the heart palpitation and mean blood pressure have undergone notable changes in the group that had received dexmedetomidine and also that dexmedetomidine is not alone as effective as fentanyl. Additionally, administration of dexmedetomidine has been found associated with the instability in the hemodynamic properties and longer duration of recovery time in their study. The difference in the type of the intervention and its time might be one possible and important reason for the difference between our study's results and the results obtained in the study by Muller et al. [16].

The study by Lu et al. investigated the effect of dexmedetomidine on the quality of the patients' sleeping following surgery in ICU and it was found out that the patients who had received dexmedetomidine have been improved in terms of their sleeping quality in comparison to the patients from the control group. Moreover, their RASS scores were reported higher than the control group in terms of the regional sedation and sleeping quality improvement. The other thing found by them was the mean arterial blood pressure, heart palpitation as well as breathing rate's similarity in both the intervention and control groups [17].

Despite differences in the study type, patients' type, and their diseases, the above findings are following our study's results. The results of the present study are also consistent with the findings of the study by Chen et al. [18].

They also similarly demonstrated that, as compared to placebo, the administration of dexmedetomidine has been accompanied by more effective anesthetic effects and sleeping quality improvement following hysterectomy operation. Despite the differences in the placebo type as well as operation duration, these results are consistent with the findings of our study. As a drug effective for sedation in long and short runs, dexmedetomidine is applied for many of the patients and, in contrast to propofol or midazolam, it has been generally indicative of a more effective sedation span though different studies have offered various results in this regard [19].

Sedation is of particular importance for managing the anxiety and agitation of the patients following various surgeries, particularly in the patients hospitalized in ICU, and sedatives are prevalently applied as important tools in this regard [20].

Dexmedetomidine can be utilized for inducing regional sedation and preserving the patients' consciousness status according to the need for responding to the questions of the treatment personnel within a logical level [21].

Because this drug has high potency for binding to alpha-2 receptors, it may result in the occurrence of vasoconstriction, vasodilation as well as bradycardia [22].

The increase in the drug's dosage has been accompanied by the increase in the blood pressure and the lower dosages are followed by low blood pressure hence its mechanism of action is related to the sympatholytic activity stemming from

dexmedetomidine. Furthermore, the reduction in the heart palpitation following the use of high dosages of dexmedetomidine may be also observed and this can be justified considering the effect of this drug on the sympathetic system that was explained above [19].

Although the sedative effect of dexmedetomidine has not been specified, the investigations have shown that the excitation of the pre and post-synoptic alpha-2 receptors created in the spinal cord, as well as the brain pons' locus coeruleus, are involved in the internal paths of the sleep induction hence the mechanism of dexmedetomidine's action is different with that of the pain-relieving drugs like propofol that influences the gamma-aminobutyric acid's secretion system [23].

Changes in the perception and reduction of the anxiety following the consumption of this drug are, on the other hand, associated with the sedating and pain-relieving effects stemming from this drug and add to the complexity of recognizing the paths of the sedation and pain-relieving paths of this drug [23, 24].

Therefore, future studies can consider these complexities and concentrate on special intervention groups such as anxiety-controlled groups to contribute to the clarification of the abovementioned mechanism of action.

Amongst the present study's constraints, the relatively low study sample volume and consideration of only a unit center for the selection of the study participants can be pointed out. A craniotomy may reach indication following various disorders and stress originating from the various surgery times can influence these disorders and the conditions of each operation may influence the results following the administration of dexmedetomidine. Since the surgeries are different and the time of each has not been investigated in this study, the generalization of the results to the whole society would be more complicated. The other limitation of this study is the non-investigation of the anesthesia-inducing and maintaining substances in the surgeries carried out on various patients. Besides, despite the consideration of the administration of sedative when needed by the patients, the amount and frequency of the administration have not been compared for the two groups. Considering the abovementioned constraints, on the one hand, and the importance of performing more detailed evaluations about dexmedetomidine for finding the results with lower complexity in line with the generalization of them to the whole society, on the other hand, more extensive research with a larger sample volume is recommended in this regard in future.

Conclusion:

The use of dexmedetomidine is accompanied by the improvement of the Visual Analogue Scale (VAS). The sedation scores have been considerably better following the administration of dexmedetomidine within the first half an hour and after 4 and 8 hours after entry into recovery compared to the placebo group based on Richmond's scale. The hemodynamic parameters of the patients who had received dexmedetomidine have been similar in all the times after recovery to those of the placebo-receivers.

References

1. Wang L, Shen J, Ge L, Arango MF, Tang X, Moodie J, *et al*. Dexmedetomidine for craniotomy under general anesthesia: a systematic review and meta-analysis of randomized clinical trials. J. Clin. Anesth. 2019;54:114-25.
2. Tanskanen P, Kyttä J, Randell T, Aantaa R. Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomized, and placebo-controlled study. BJA: Br. J. Anaesth. 2006;97(5):658-65.
3. Jadhav N, WasekarN, Wagaskar V, Kondwilkar B, Patil R. Use of dexmedetomidine in patients undergoing craniotomies. J. Clin. Diagn. Res.: JCDR. 2017;11(1): UC01.
4. Gottschalk A, Berkow LC, Stevens RD, Mirski M, Thompson RE, White ED, *et al*. Prospective evaluation of pain and analgesic use following major elective intracranial surgery. J. Neurosurg. 2007;106(2):210-6.
5. Klimek M, Ubben JF, Ammann J, Borner U, Klein J, Verbrugge SJ. Pain in neurosurgically treated patients: a prospective observational study. J. Neurosurg. 2006;104(3):350-9.
6. Nair S, Rajshekhar V. Evaluation of pain following supratentorial craniotomy. Br. J. Neurosurg. 2011;25(1):100-3.
7. Basali A, Mascha EJ, Kalfas I, Schubert A. Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2000;93(1):48-54.
8. Durieux ME, Himmelseher S. Pain control after craniotomy: off balance on the tightrope? J. Neurosurg. 2007;106(2):207-8.
9. Sottas CE, Anderson BJ. Dexmedetomidine: the new all-in-one drug in paediatric anaesthesia? Curr. Opin. Anaesthesiol. 2017;30(4):441-51.
10. Kamibayashi T, Maze M. Clinical uses of α2-adrenergicagonists. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2000;93(5):1345-9.
11. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs. 2000;59(2):263-8.
12. Tobias JD. Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU. J. Opioid Manag. 2006;2(4):201-5.
13. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. Rev. Bras. Anestesiol. 2012;62(1):125-33.
14. Batra A, Verma R, Bhatia V, Chandra G, Bhushan S. Dexmedetomidine as an anesthetic adjuvant in intracranial surgery. Anesth. Essays Res. 2017;11(2):309.
15. Peng K, Jin XH, Liu SL, Ji FH. Effect of Intraoperative Dexmedetomidine on Post-Craniotomy Pain. Clin. Ther. 2015;37(5):1114-21.e1.
16. Muller S, Borowics SM, Fortis EA, Stefani LC, Soares G, Maguilnik I, *et al*. Clinical efficacy of dexmedetomidine alone is less than propofol for conscious sedation during ERCP. Gastrointest. Endosc. 2008;67(4):651-9.
17. Lu W, Fu Q, Luo X, Fu S, Hu K. Effects of dexmedetomidine on sleep quality of patients after surgery without mechanical ventilation in ICU. Medicine (Baltimore). 2017;96(23):e7081.
18. Chen Z, Tang R, Zhang R, Jiang Y, Liu Y. Effects of dexmedetomidine administered for postoperative analgesia on sleep quality in patients undergoing abdominal hysterectomy. J. Clin. Anesth. 2017;36:118-22.
19. Keating GM. Dexmedetomidine: A Review of Its Use for Sedation in the Intensive Care Setting. Drugs. 2015;75)10):1119-30.
20. Altshuler J, Spoelhof B. Pain, agitation, delirium, and neuromuscular blockade: a review of basic pharmacology, assessment, and monitoring. Crit. Care Nurs. Q. 2013;36(4):356-69.
21. Colin PJ, Hannivoort LN, Eleveld DJ, Reyntjens KM, Absalom AR, Vereecke HE, *et al*. Dexmedetomidine pharmacokinetic-

pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation. Br. J. Anaesth. 2017;119(2):200-10.
22. Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics, and Pharmacodynamics of Dexmedetomidine. Clin. Pharmacokinet. 2017;56(8):893-913.
23. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics, and Pharmacodynamics of Dexmedetomidine. Clin. Pharmacokinet. 2017;56(8):893-913.
24. Kim DJ, Kim SH, So KY, Jung KT. Effects of dexmedetomidine on smooth emergence from anaesthesia in elderly patients undergoing orthopaedic surgery. BMC anesthesiology. 2015;139:15.