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Original Article

Evaluating sedative effects of dexmedetomidine and morphine in the patients with opioid use disorder undergoing cataract surgery

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Abstract: Background: Considering that patients with opioid dependence are at higher risk of inadequate sedation during operations, and the rescue analgesia in these patients are usually greater than the general population; the aim of this study was comparison of sedation quality of dexmedetomidine and morphine in patients with opioid use disorder undergoing cataract surgery. Methods: This clinical trial was conducted on 60 patients with opioid use disorder underwent cataract surgery that were referred to Feiz Hospital, Isfahan, Iran in 2018. Patients were randomly divided into two groups as the dexmedetomidine group started 1 μg/kg dexmedetomidine in 10 minutes before surgery and then continued with 0.5 μg/kg/h while the morphine group received 0.1 mg/kg of morphine before surgery. Sedation score, pain intensity, hemodynamic parameters, analgesic request and side effects were compared in the two groups. Results: There was no significant differences between groups based on Ramsay score before, during and after surgery ($P > 0.05$), the pain intensity in the morphine group was significantly lower during the recovery period than dexmedetomidine group, the duration of recovery and sedation in the morphine group was significantly more than the dexmedetomidine group, and nausea and vomiting and eye pain in the morphine group were significantly higher than dexmedetomidine ($P < 0.05$). Conclusion: Morphine usage was more effective in pain relief than dexmedetomidine in patients with opioid use disorder undergoing cataract surgery, but the complications and recovery time were higher in morphine usage. Also the sedation was similar in both groups.

Keywords: Morphine, dexmedetomidine, cataract, sedation, postoperative pain, opioid use disorder

Introduction

Cataract is one of the most common eye diseases seen in older adults that mostly need to surgery [1]. The incidence of cataract in individuals over the age of 40 in the United States was reported to be 20.5 million [2]. Cataract surgery mostly need to sedation and sedation aids relaxing the patients during the infusion of the analgesics and also the surgery [3]. Sedation demonstrates various aspects in different individuals and might be associated with considerable risks regarding the condition of the patient. Opioid use disorder is an essential factor that should be considered seriously in the field of anesthesiology as the people with opioid use disorder might require higher doses of anesthetics in comparison with the healthy people for their anesthesia [4, 5]. Morphine is considered one of the most important analgesic drugs and is considered to be a strong opioid with sedative effects. Morphine is an appropriate medication for pain relief, which is used during and after the surgical procedures [6]. In the elderly with opioid use disorder, morphine should be used with great caution as its complications might be serious. Two of the most critical complications of morphine are the suppression of the respiratory system, as well as hemodynamic disorders, which should be closely monitored in the elderly with opioid use disorder [7]. Dexmedetomidine is an alpha-2 agonist and displays its anti-nociceptive effects in the central nervous system through stimulating

alpha2-adrenoceptors [8]. This drug is another important drug used for anesthesia that has both analgesic and sedative effects, fewer side effects, and fewer effects on patient's hemodynamics in comparison with other drugs [9]. In some study compared effect of morphine and dexmedetomidine on sedation that dexmedetomidine have sedation effect such as morphine and other opium [10, 11].

There are currently limited studies that investigated the effect of morphine and dexmedetomidine in the field of anesthesiology, and up to the date, no study has evaluated the effects of these two drugs in cataract surgery candidates in patients with opioid use disorder. Therefore, considering the prevalence of cataract and the importance of analgesia in the cataract surgery, and also concerning the significance of the opioid use disorder and its effects on the course of anesthesia, this study aimed to determine and compare the sedative effects of morphine and dexmedetomidine in the patients with opioid use disorder undergoing cataract surgery candidates.

Materials and methods

Study design

This double-blind, randomized clinical trial study evaluated 60 cataract surgery candidates who referred to Feiz Hospital in Isfahan, Iran, in 2018. The Ethics Committee of Isfahan University of Medical Sciences has approved this study (Approval code: IR.MUI.MED.REC. 1397.367).

Inclusion criteria were: 1. Patients candidate to cataract surgery, 2. At least 18 years of age, 3. American Society of Anesthesiologists score or ASA I or II, 4. Opioid use disorder more than at least 12 months (consumed 390 mg/day opium). In addition, patients were diagnosed based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and based DSM-5 criteria, all patients were mild to moderate opioid use disorder. DSM-5 Criteria for Diagnosis of Opioid Use Disorder is included 11 questions about symptoms of using opioid and this disorder is divided into 3 severity of mild (2-3 symptoms), moderate (4-5 symptoms) and severe (6 and more symptoms) [12].

Informed written consent was taken of patients and their companions for participation in the study.

Patients who had an underlying disease or uncontrolled systemic illness (such as kidney failure, heart failure, etc.) were not included in the study.

Exclusion criteria were modification of anesthesia method and the failure of the patient's follow-up until 12 hours after the end of the surgical operation.

After selecting the patients, they were divided into two groups as the morphine group and dexmedetomidine group using the random allocation software.

Anesthesia protocol

The dexmedetomidine group was received intravenous fentanyl at the dose of 1 μg/kg, midazolam at the dose of 0.01 mg/kg and dexmedetomidine at the dose of 1 mg/kg infusion during 10 minutes and then at the dose of 0.5 μg/kg during the operation. The morphine group received fentanyl at the dose of 1 μg/kg, midazolam at the dose of 0.01 mg/kg and morphine at the dose of 0.1 mg/kg, and before the start of sedation and after initiating the monitoring protocols, all patients received topical Tetracaine 0.5% eye-drop.

To assess the sedation level during the surgery, we used the Ramsay sedation scale, with a target score of 2 to 3. To decrease the potential risk for hypotension within the surgery, patients were well hydrated with the ringer lactate solution at the dose of 5 ml/kg before receiving the study medications. If they did not achieve level 2 or 3 scores according to the Ramsay scale, propofol at the dose of 30-60 μg/kg was injected intravenously every twominutes to reach the mentioned criteria (**Table 1**).

Before surgery, patient-monitoring devices were adjusted and the changes in the hemodynamic parameters (including the heart rate, respiratory rate, mean arterial blood pressure and arterial blood oxygen levels), electrocardiographic changes and sedation score were measured the at 10^{th}, 20^{th}, and the first 30^{th} minute of surgery and at first, 30^{th} and 60^{th} minute of PACU admission. Also, the severity of pain was

Table 1. The sedation scale of patients based on the Ramsay criteria

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

evaluated according to the visual analog scale [13]. This scale is a visual criterion using which the severity of nausea and pain is determined with a score ranging from 0 to 10 (so that score one is the lowest and score 10 is the highest score for the severity of ever experienced pain). VAS was evaluated at the first, 30th and 60th minutes of the patient's admission to PACU. Duration of anesthesia, surgery and PACU stay, frequency of drug-related complications and the score of the satisfaction of the patient and the surgeon (using criteria 0 to 10) was also recorded.

If the patient's pain intensity was more than three according to the VAS, intravenous pethidine at the dose of 0.5 mg/kg was administered. Moreover, we recorded the additional dosage of the additional administered opioid and the sedative (propofol at the dose of 30 μg/kg in cases of intraoperative sedation score below 2) in both groups after the surgery. Also, if patients had severe nausea (VAS score above 3) and vomiting, they received oral ondansetron at a dose of 0.05 mg/kg. Its consider that opioid consumption in both group was similar and balanced and opioid consumption was more than at least 12 months (consumed 390 mg/day opium) in all patients.

Statistical analysis

The sample size was measured based on 95% confidence interval and power calculation of 0.84, also the which was according similar study, standard deviations of sedation score were S1 = 0.7 and S2 = 1.2 and mean differences was the was considered as 0.7 [14]. Subsequently the sample size was 30 individuals for each group.

Data were analyzed using SPSS software v.22. Independent t-test and Chi-square were used to compare the groups, and repeated measure ANOVA were used to compare the changes of study variables in different times. The quantitative data were expressed as mean and standard deviation, and the qualitative variables were showed as frequency and percentage. *P*-value < 0.05 was considered as significant threshold.

Results

Demographical

In this study, the patients were divided into two groups: morphine group (23 males and 7 females) and dexmedetomidine group (26 males and 4 females); there was no significant difference between the groups regarding the age, sex and ASA score (P > 0.05) (**Table 2**).

Hemodynamics

Also, there was no significant difference between the groups regarding the systolic and diastolic blood pressure, respiratory rate, heart rate and oxygen saturation at the 10th, 20th and the 30th minute of the surgery, and at the first, 30th and the 60th minute of the PACU admission (P > 0.05). Based on repeated measure ANOVA, changes of systolic, and diastolic blood pressure, respiratory rate, heart rate, and oxygen saturation in the before, during and after surgery were significant in both groups (P < 0.001) (**Table 3**).

Sedation, pain and complication

There was no significant difference between the groups considering the Ramsay scoring prior to the surgery, during of the surgery, and after surgery (P > 0.05) (**Table 4**).

The mean pain intensity at the post-operative time, including the first, 30th and the 60th minute of the PACU admission was significantly lower in the morphine group in comparison with the dexmedetomidine group (P < 0.05). On the other hand, according to the repeated measure ANOVA, after the operation, pain reduction was significant in the two groups (P < 0.001). There was no significant difference between the groups regarding to the frequency of the need for the analgesic drug and their doses (P > 0.05). Nausea and vomiting and eye pain occurred significantly higher in the morphine

Table 2. Demographic variables studied between two groups

Variables		Morphine group	dexmedetomidine group	*P*-value
Age (years) (mean ± SD)		61.86 ± 12.48	58.20 ± 12.55	0.26*
Gender	Male	(76.7%) 23	(86.7%) 26	0.25**
	Female	(23.3%) 7	(13.3%) 4	
ASA	I	(73.3%) 22	(66.7%) 20	0.38**
	II	(26.7%) 8	(33.3%) 10	

*independent t test, **Chi Square test. ASA: American Society of Anesthesiologists.

Table 3. Hemodynamic variables studied between the two groups

Variables		Morphine group (mean ± SD)	dexmedetomidine group (mean ± SD)	*P*-value*
Systolic blood pressure (mmHg)	Before intervention	122.89 ± 14.30	120.03 ± 14.96	0.46
	The first 10 minutes of operation	115.68 ± 14.78	118.66 ± 14.04	0.84
	The first 20 minutes of operation	113.46 ± 11.26	114.13 ± 11.03	0.81
	The first 30 minutes of operation	114.60 ± 9.83	111.93 ± 10.55	0.31
	Admission to recovery	113.23 ± 8.68	112.60 ± 10.01	0.79
	The first 30 minutes of recovery	116.33 ± 11.55	117.10 ± 10.41	0.79
	60 minutes first recovery	120.10 ± 10.77	117.26 ± 11.59	0.33
	P-value to Difference over time**	< 0.001	< 0.001	
Diastolic blood pressure (mmHg)	Before intervention	69.06 ± 10.77	69.36 ± 15.42	0.93
	The first 10 minutes of operation	69.46 ± 12.25	67.76 ± 14.71	0.62
	The first 20 minutes of operation	65.44 ± 8.66	68.70 ± 10.91	0.21
	The first 30 minutes of operation	67.06 ± 9.11	64.73 ± 5.90	0.24
	Admission to recovery	70.27 ± 10.69	69.82 ± 10.16	0.87
	The first 30 minutes of recovery	71.96 ± 7.46	74.63 ± 10.82	0.16
	60 minutes first recovery	72.23 ± 11.65	68.86 ± 10.12	0.23
	P-value to Difference over time**	< 0.001	< 0.001	
Respiratory rate in minutes	Before intervention	21.76 ± 4.36	22.66 ± 5.09	0.46
	The first 10 minutes of operation	20.26 ± 1.33	20.23 ± 3.40	0.96
	The first 20 minutes of operation	19.70 ± 1.72	20.06 ± 1.22	0.34
	The first 30 minutes of operation	23.43 ± 3.49	22.86 ± 3.91	0.55
	Admission to recovery	21.33 ± 2.52	20.60 ± 1.77	0.21
	The first 30 minutes of recovery	20.26 ± 2.09	19.53 ± 1.59	0.14
	60 minutes first recovery	20.46 ± 2.50	20.63 ± 3.10	0.82
	P-value to Difference over time**	< 0.001	< 0.001	
Heart rate per minute	Before intervention	76.90 ± 14.30	73.43 ± 13.36	0.33
	The first 10 minutes of operation	76.23 ± 13.32	72.56 ± 12.77	0.28
	The first 20 minutes of operation	76.06 ± 10.24	72.66 ± 12.21	0.41
	The first 30 minutes of operation	76.70 ± 11.65	74.16 ± 12.18	0.53
	Admission to recovery	75.73 ± 10.61	73.90 ± 12.25	0.98
	The first 30 minutes of recovery	74.88 ± 9.33	74.95 ± 13.21	0.98
	60 minutes first recovery	73.36 ± 9.70	75.50 ± 12.24	0.67
	P-value to Difference over time**	< 0.001	< 0.001	
Saturation of oxygen (percent)	Before intervention	95.30 ± 2.36	96.46 ± 1.75	0.13
	The first 10 minutes of operation	95.80 ± 1.47	96.36 ± 2.22	0.24
	The first 20 minutes of operation	95.56 ± 1.83	96.23 ± 2.66	0.26
	The first 30 minutes of operation	95.63 ± 2.65	96.33 ± 2.56	0.30
	Admission to recovery	96.23 ± 2.09	96.40 ± 2.55	0.78
	The first 30 minutes of recovery	95.73 ± 2.11	96.66 ± 2.61	0.20
	60 minutes first recovery	95.50 ± 2.35	96.75 ± 2.63	0.23
	P-value to Difference over time**	< 0.001	< 0.001	

*independent t test, **Repeated measure ANOVA.

Table 4. Sedation score of patients in two groups of study at different times

Variables			Morphine	dexmedetomidine	*P*-value*
Sedation score	Before intervention	Anxious or restless or both	29 (96.7%)	28 (93.3%)	0.50
		Cooperative, orientated and tranquil	1 (3.3%)	2 (6.7%)	
	The first 10 minutes of operation	Cooperative, orientated and tranquil	3 (10%)	8 (26.7%)	0.10
		Responding to commands	25 (83.3%)	12 (73.3%)	
		Brisk response to stimulus	2 (6.7%)	0	
	The first 20 minutes of operation	Cooperative, orientated and tranquil	8 (26.7%)	11 (36.7%)	0.10
		Responding to commands	18 (60%)	19 (63.3%)	
		Brisk response to stimulus	4 (13.3%)	0	
	The first 30 minutes of operation	Cooperative, orientated and tranquil	4 (13.3%)	9 (30%)	0.08
		Responding to commands	23 (76.7%)	21 (70%)	
		Brisk response to stimulus	3 (10%)	0	
	Admission to recovery	Anxious or restless or both	26 (86.7%)	28 (93.3%)	0.34
		Cooperative, orientated and tranquil	4 (13.3%)	2 (6.7%)	
	The first 30 minutes of recovery	Anxious or restless or both	28 (93.3%)	29 (96.7%)	0.50
		Cooperative, orientated and tranquil	2 (6.7%)	1 (3.3%)	
	60 minutes first recovery	Anxious or restless or both	29 (96.7%)	30 (100%)	0.50
		Cooperative, orientated and tranquil	1 (3.3%)	0	

*Chi Square.

group compared to the dexmedetomidine group ($P < 0.05$). Also, there was no significant difference between the groups based on patient satisfaction ($P = 0.61$). The duration of sedation and the PACU stay was significantly higher in the morphine group than in the dexmedetomidine group ($P < 0.05$), but there was no significant difference between the two groups concerning the duration of the surgery ($P = 0.11$) (**Table 5**).

Discussion

Based on the results of this study, patients who received morphine and dexmedetomidine had similar sedative effects, and the intensity of post-operative pain in the morphine group was relatively lower than that of the dexmedetomidine group. However, complications such as nausea, vomiting, and eye pain were observed in patients treated with morphine, and these two drugs didn't demonstrate significant differences regarding patient satisfaction. Besides, the duration of sedation and the PACU stay in the dexmedetomidine group was shorter than that of the morphine group.

Halaweh et al. studied the effect of dexmedetomidine and morphine on the need for narcotics for up to 24 hours in patients undergoing laparoscopic surgery. They concluded that there was no significant difference between the use of morphine and dexmedetomidine regarding the need for paracetamol and morphine. They also concluded that using dexmedetomidine was effective in reducing the need for morphine up to 24 hours after the surgery [10]. In our study, the results showed that there was no difference between the groups regarding the frequency of post-operative need for analgesics and their doses.

In a study by Shehabi et al. who reviewed and compared the effects of dexmedetomidine and morphine during cardiac surgery, it was concluded that the use of dexmedetomidine did not reduce the risk of delirium after cardiac surgery, but reduced the duration of delirium, led to a sufficient sedation and decreased the need for vasopressors. However, compared to morphine, it caused more bradycardia [11]. In our study, dexmedetomidine had similar sedation to morphine.

In another study on patients undergoing a cesarean section intratecal administration of dexmedetomidine (5 μg) increased the duration of the sensory and motor nerve block, morphine-like antinociceptive effect, and decreased shivering compared to morphine (100 micrograms) [15]. In our study, the efficacy of dexmedetomidine-induced analgesia was lower in comparison with morphine. Also, complications such as nausea, vomiting, and eye pain occurred fewer in the dexmedetomidine group.

Table 5. Other variables studied between two groups

Variables		Morphine group	dexmedetomidine group	*P*-value
Pain intensity (mean ± SD)	Admission to recovery	5.83 ± 1.17	6.66 ± 0.88	0.003*
	The first 30 minutes of recovery	4.16 ± 1.34	5.03 ± 0.99	0.006*
	The first 60 minutes first recovery	3.20 ± 0.71	4.26 ± 0.90	0.001 > *
	P-value	0.001 > **	0. 001 > **	
Rescue analgesia		(16.7%) 5	(26.7%) 8	0.14***
analgesic dosage (mg) (mean ± SD)		26.01 ± 15.16	35.62 ± 7.28	0.19*
Complications	nausea and vomiting	(36.7%) 11	0	0.001 > ***
	eye pain	(16.7%) 5	0	0.02***
Patient Satisfaction		7.66 ± 1.24	7.50 ± 1.27	0.61*
Duration (mean ± SD) (minute)	surgery	41.50 ± 5.54	38.76 ± 7.29	0.11*
	Sedation (anesthesia)	61.67 ± 5.07	47.86 ± 6.16	0.001 > *
	PACU stay	79.83 ± 19.51	66.66 ± 11.84	0.003*

*independent t test, **Repeated measure ANOVA, ***Chi Square.

Lin et al. concluded that adding dexmedetomidine to morphine could result in more analgesia, the requirement of lower amounts of morphine, decreased rates of morphine-induced nausea, and more sedation and the prevention of hemodynamic changes [16]. In our study, nausea and vomiting were observed less frequently in the group treated with dexmedetomidine.

In another study, Ghandi et al. compared the preventive effect of dexmedetomidine and morphine for pain relief in patients undergoing cardiac surgery and concluded that the use of both drugs is effective in reducing post-operative pain, but dexmedetomidine demonstrated better effect on pain control, fewer side effects such as nausea, itching, atelectasis, elongation of intubation, respiratory depression, and the need for anti-sedatives [17]. In our study, both drugs were effective in reducing post-operative pain, and the rate of complications in the dexmedetomidine group was lower than that of morphine group.

Another study evaluated the effects of dexmedetomidine in patients undergoing retinal surgery and revealed that using dexmedetomidine would cause effective sedation, without side effects such as respiratory depression, and this drug is safe and selective for retinal surgeries [18]. In our study sedation effect of dexmedetomedine was similar to morphine and also this sedation was effective and without complication.

Some of the remarkable limitations of our study are low sample size, short follow-up duration, and not including other factors that might have effects in this field. But on the other hand, it can be noted that our study is the first research ever to investigate the effects of dexmedetomidine and morphine in patients undergoing cataract surgery, especially in patients with opioid use disorder. One of the key differences between our research and other studies was that our study patients were all patients with opioid use disorder, and therefore, morphine had better effects on these individuals.

Conclusion

Theree disorder has a better effect on reducing paifore, according to the results of this study and other similar investigations, the use of both dexmedetomidine and morphine might have a good effect on pain relief and sedation, also the sedation was similar in dexmedetomidine and morphine during and after surgery but using morphine in patients with opioid usn of the patients compared to the dexmedetomidine, and on the other hand, the side effects of morphine were considerably more than that of dexmedetomidine. It seems that due to a large number of studies with contradictory results on various factors affecting the quality of sedation and pain during and after surgery [19-21], further investigations are needed in this regard.

Disclosure of conflict of interest

None.

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