Original Article

Comparison between the Effects of Acetaminophen, Dexmedetomidine, and Normal Saline Infusion on Pain Severity after Cataract Surgery

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Abstract

Background: Cataract surgery is one of the most common eye surgeries, which is currently performed under topical anesthesia using sedative medications. Dexmedetomidine and acetaminophen are good candidates for analgesia in other circumstances, however, this study aimed to evaluate the effect of dexmedetomidine or acetaminophen infusion and normal saline (NS) alone compared with the control group on the severity of pain in cataract surgery. **Materials and Methods:** In this parallel randomized controlled clinical trial, the effect of dexmedetomidine or acetaminophen infusion and NS on level of pain, vital signs, recovery status, and surgeon satisfaction during cataract surgery were assessed. One hundred and thirty-five patients between the age of 50–80 years undergoing cataract surgery were recruited on a consecutive basis and randomized into three groups receiving acetaminophen (15 mg/kg), dexmedetomidine (0.5 μgr/kg), and NS. Baseline vital signs, blood pressure, arterial oxygen saturation, respiratory and heart rate at certain time-points including the start of surgery, 5, 10, and 15 min after surgery, after arrival to the recovery room, 20, 40, 60 min after recovery were measured. Pain intensity and drugs side effects were also recorded after surgery. **Results:** Level of respiratory depression was higher in patients receiving dexmedetomidine. Heart rate and oxygen saturation percentage had no significant differences in the three groups as well as pain intensity. **Conclusions:** Acetaminophen was as effective as dexmedetomidine with lower side effects and higher surgeons' satisfaction, without any interference with cardiovascular and respiratory parameters. Acetaminophen infusion should be considered as an acceptable analgesic drug for cataract surgery.

Keywords: *Acetaminophen, cataract, dexmedetomidine, pain*

Introduction

Cataract surgery is one of the most common eye surgeries.[1]

Over time, with the development of cataract surgery, the anesthesia performed topically.[2,3] Although patient cooperation for immobilizing the eye would be needed in performing topical anesthesia, which may increase the patient's anxiety, this method is preferred to others due to the lack of need for painful injections for nerve block as well as fewer complications.[2,4,5]

Currently, this surgery is usually performed in advanced age under topical anesthesia and with the administration of sedative medications such as propofol, benzodiazepines, opioids, or a combination of them.[6-8] However, each of these drugs can cause complications such as respiratory depression, hypoxia, and apnea, which can interfere with the patient's cooperation and cause serious problems during surgery.[9]

An ideal sedative would be a drug that does not impose any dangerous side effects such as respiratory depression and hemodynamic instability and should also cause analgesia and forgetfulness for a short time during cataract surgery.[10,11]

Dexmedetomidine and acetaminophen are some of the drugs that can be used as routine compounds for analgesia during cataract surgery. Dexmedetomidine, a selective alpha 2 receptor agonist, is a sedative and analgesic, and its most important advantage is that it does not cause respiratory depression.[11-14] In addition, studies showed that it can reduce intraocular pressure, which gave it an additional advantage.[2]

Furthermore, intravenous acetaminophen has been shown to be an effective analgesic

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for mild to moderate pain. It is highly safe and its analgesic doses did not show any side effects. Moreover, it is not addictive and its analgesic properties are mainly due to inhibition of the cyclooxygenase pathway and probably due to its indirect effect on the central nervous system serotonergic system. Furthermore, it can easily pass the blood-brain barrier.[12,15-19]

However, there are many studies regarding the drugs used for anesthesia and analgesia in cataract surgery, and there are still problems associated with common drugs used for this purpose, therefore, efforts are still underway to evaluate the effect of other drugs with fewer side effects.[20] However, to the best of our knowledge, no study compared the effect of dexmedetomidine and acetaminophen on the postoperative patients' pain undergoing cataract surgery, while these two drugs were utilized in several studies during different types of surgeries and compared with other analgesic drugs. Given that the present study aimed to compare the effect of the infusion of two mentioned drugs, dexmedetomidine, and acetaminophen, on the level of pain, vital signs, recovery rate, and patient satisfaction undergoing cataract surgery.

Materials and Methods

Trial design

This randomized controlled clinical trial was designed in parallel format with an equal allocation ratio for two groups of the study. It has been approved by the Ethical Committee of Isfahan University of Medical Sciences with the code of 396314 and has been registered in www.irct.ir with code of IRCT20190208042654N4.

Study participants

There were 135 patients candidates for cataract surgery in the age of 50–80 years were recruited for this randomized controlled clinical trial study. The participants with an I or II physical health score according to the classification of the American Society of Anesthesiologists with willingness to participate were included.

In the case of dexmedetomidine or acetaminophen contraindication, allergies to any of the drugs used in the trial, blood coagulation problems, altered mental status, severe cardiovascular diseases, chronic obstructive pulmonary disease and having <50 or over 80 years of age the patients were not included. In case of any need to change the sedation method/surgical plan during surgery, the need for general anesthesia, they were excluded. This study was implemented in Feyz Hospital, Isfahan, Iran; participants and cataract surgeries were done in that hospital from December 2018 to October 2019.

Sample size

The sample size of 135 patients (45 patients in each group) was selected by random sampling technique from the mentioned population according to the sample size formula with 95% confidence interval for between-group comparisons, 80% test power, and considering the the mean ± standard deviation (SD) of the pain intensity after surgery in previous studies[7] that was equal to7.8 ± 7.4 and 11.1 ± 2.9 in the two groups receiving acetaminophen and dexmedetomidine, respectively, and the error level of 3.3 (the mean difference in pain between the two groups) [Figure 1].

Sampling and random allocation

The study population was selected on a consecutive basis. For the randomization of the participants, first, the principal investigator used the "Sealedenvelope" website to create blocks containing 9 individuals, containing three participants for each of three groups. Every participant had a unique code consisting of two letters and one number. This generated list remained confidential for participants, clinicians who enrolled the patients in the study, clinicians who injected the drugs, and the data analyzer. Patients have entered the study according to the generated list, after a full explanation of the study process and obtaining written consent.

All of the participants received IV midazolam 20 μg/kg, IV fentanyl 1 μg/kg, and IV ketamine 0.15 mg/kg during the cataract surgery intravenous sedation. In addition, tetracaine eye drop was used 5 min before surgery to induce local anesthesia in all groups. Patients were randomly divided into three groups based on their treatment. In Group A (Ace), acetaminophen was infused at a dose of 15 mg/kg within the first 15 min of surgery over 10 min. In Group B, dexmedetomidine (Dex) was infused at a dose of 0.5 μg/kg within the first 15 min of surgery over 10 min. In Group C, the infusion of normal saline (NS) was performed over 10 min. In all three groups, the given drug was diluted to reach a total volume of 100 ml. As part of blinding, used drugs in each group were previously prepared based on each patient weight and marked with their designated codes.

Measurements and outcomes

All patients were monitored with pulse oximetry and noninvasive blood pressure monitoring. During the procedure, the percentage of spo2, the number of breaths and heart rate per minute, and the systolic and diastolic blood pressure were recorded by a trained nurse in certain time-points including the start of surgery, 5, 10, and 15 min after starting of surgery, then at the beginning of recovery, 20, 40, 60 min after starting of recovery.

Pain intensity was evaluated and recorded immediately after surgery, 2 h, 4 h, and 6 h after moving to the recovery room and then at the time of discharge based on the Visual Analog Scale (VAS) with a range from 0 to 10. Note that, if the patient's pain intensity was reported higher than 3, pethidine at the dose of 0.5 mg/kg was administered. The

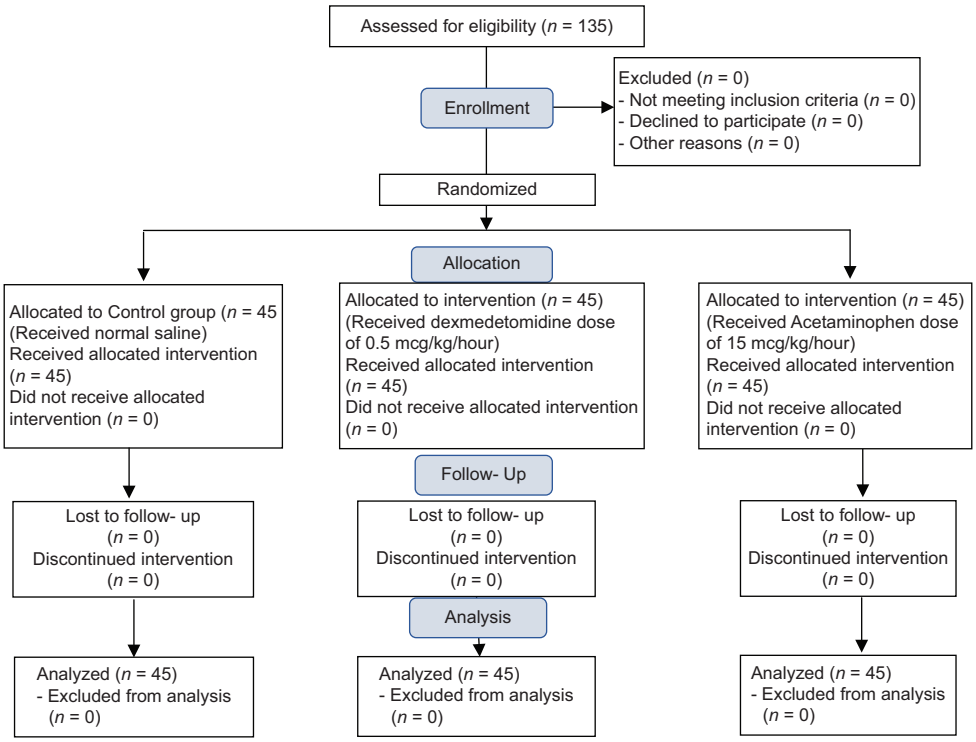

Figure 1: Study flowchart

VAS is a valid and reliable tool for measurement of acute pain and its alpha-Cronbach coefficient was determined as 0.97 in a previous study.[21] Furthermore, several studies in Iran have used this tool to measure pain intensity.[22,23]

Furthermore, the presence of severe nausea and any episode of vomiting after surgery was asked and recorded. In the case of complaints of severe nausea and any episode of vomiting, 0.05 mg/kg of intravenous ondansetron was administered. The time for the first narcotics request was recorded for each patient. The amounts of administered narcotics and ondansetron after the operation, as well as side effects of medications, including headaches, hypotension, bradycardia, and cough, were recorded. The satisfaction of ophthalmologists from the patient sedation during the operation was also recorded. Levels of satisfaction were defined as excellent (the patient's sedation and cooperation were complete), good (the patient cooperated despite unwanted and minor eye movements) and poor (there was a lot of unwanted eye movement during the operation and the patient did not cooperate). Finally, the Modified Aldrete Scale was used for deciding whether the patients should be moved to the ward from the recovery room. After transferring to the ward, the length of stay in the recovery room was recorded.

Statistical analysis

Qualitative variables were reported as count and percentage, where quantitative variables were reported as mean and SD. Kolmogorov–Smirnov test was used to assess the normality of variables. To compare the dichotomous variables between groups, Chi-square or Fisher's test was used, based on the normality of data. To compare different variables between groups one-way ANOVA test was used. To evaluate the variable changes over time, repeated measures analysis of variance for more than two time-points and paired *t*-test for comparing before and after were used. All of the Statistical analysis was performed using SPSS for Windows version 23. (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

This study was conducted on 135 cataract surgery patients under intravenous sedation at Feyz Hospital, Isfahan, Iran, from 2018 to 2019. Participants' demographic characteristics are shown in Table 1. The results showed that the three groups did not differ significantly in terms of age ($P = 0.63$), gender ($P = 0.47$), and history of drug use ($P = 0.20$). However, in terms of having underlying disease, in the Dex group, significantly more patients had these diseases ($P = 0.03$), which was adjusted in the following analysis.

After controlling the effect of underlying diseases, repeated measures analysis of variance did not show a significant difference between the three groups over time for systolic ($P = 0.35$) and diastolic ($P = 0.58$) blood pressures [Table 2 and Figure 2].

Next, we analyzed respiratory and pulse rates along with oxygen saturation by time and groups. Results showed a significant difference between the three groups regarding

respiratory rate ($P = 0.02$), where the higher reduction was seen in the Dex group than the other two groups. Although in terms of heart rate and oxygen saturation percentage, no significant differences were observed between the three groups ($P = 0.98$) [Table 3 and Figure 3].

Only one patient in the Dex group had nausea, who received intravenous ondansetron. The incidence of severe nausea did not show a significant difference between the three groups ($P = 0.99$), but the satisfaction of the surgeon from the patients' sedation in the Dex group was significantly lower ($P < 0.001$) than the two other groups. Furthermore, the recovery time in the Dex group was significantly longer ($P = 0.004$) compared to the two other groups [Table 4].

Finally, the mean of pain intensity did not show a significant difference between the three groups ($P > 0.05$), but the patients had experienced less pain in the acetaminophen group [Table 5]. None of the patients requested for narcotics.

Discussion

Pain is one of the most important predictors of return to normal activity after surgery.[24] Although the pain severity after cataract surgery is mild in most patients, results showed that 34% of patients had some pain and 9% had more than moderate pain (VAS > 4) in the first few hours after cataract surgery.[25] Our study aimed to compare the effect of infusion of two mentioned drugs, dexmedetomidine, and acetaminophen, also NS as a control group, on the severity of pain after surgery, vital signs, recovery time, and surgeon satisfaction undergoing cataract surgery. Based on our findings, acetaminophen was as effective as dexmedetomidine in controlling pain after cataract surgery. In some previous studies, better analgesia was reported in patients treated with dexmedetomidine compared to remifentanil, midazolam, saline, and placebo.[26-29] In a study conducted by Apan *et al*. on 90 patients undergoing cataract surgery, dexmedetomidine and midazolam infusion were compared regarding the pain intensity of patients during surgery. According to the results, the pain intensity of patients in the dexmedetomidine group was lower, and they suggested that it can be used as an alternative drug to cause analgesia during cataract surgery.[24] Hashemi *et al*. conducted a clinical trial study on 60 trauma patients who underwent outpatient diagnostic arthroscopy. Patients were randomly divided into two groups, one group received acetaminophen after arthroscopy and the other group received morphine for analgesia. The level of pain, nausea, and vomiting of patients was measured. They demonstrated that the level of pain did not differ

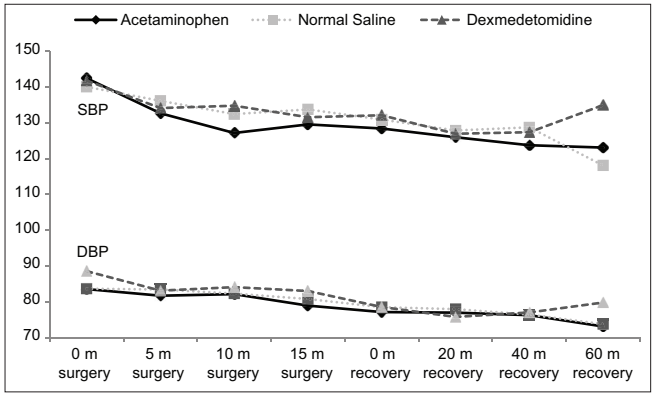

Figure 2: Trend of systolic and diastolic blood pressure changes by time and group

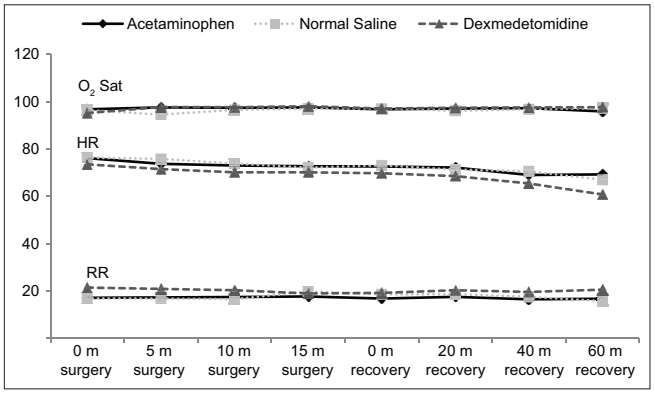

Figure 3: Trends in changes in heart rate, respiratory rate, and oxygen saturation (O_2 sat) by time and group

Table 1: Demographic characteristics of participants by study groups

Parameter	Acetaminophen (*n*=45), *n* (%)	Normal saline (*n*=45), *n* (%)	Dexmedetomidine (*n*=45), *n* (%)	Test	*P*
Age (years)	65.95±11.21	67.21±8.07	64.40±10.23	One-way ANOVA	0.63
Sex					
Male	22 (16.3)	27 (20)	22 (16.3)	Chi-Square	0.47
Female	23 (17)	18 (13.3)	23 (17)		
History of drug use					
Yes	11 (8.3)	11 (8.3)	18 (13.5)	Chi-Square	0.20
No	34 (25.6)	32 (24.1)	27 (20.3)		
Underlying disease					
Yes	11 (8.3)	8 (6)	19 (14.3)	Chi-Square	0.03
No	34 (25.6)	35 (26.3)	26 (19.5)		

Table 2: Mean and standard deviation of systolic and diastolic blood pressure of patients by time and group

Group	Mean±SD								*P*1 (time)	*P*2 (time × intervention)	*P*3 (intervention)
	Beginning of surgery	After starting of surgery			Beginning of recovery	After moving into the recovery room					
	0 min	5 min	10 min	15 min	0 min	20 min	40 min	60 min			
SBP											
Ace	142.51±21.66	132.66±18.28	127.21±20.79	129.56±20.66	128.44±19.23	126.00±15.99	123.78±13.54	123.10±15.38	0.21	0.91	0.35
NS	140.11±20.79	136.17±20.66	132.46±22.82	133.80±21.88	130.95±24.05	127.88±20.74	128.77±19.14	118.12±15.94	0.46		
Dex	141.82±28.10	134.17±35.72	134.80±24.67	131.58±29.30	132.15±27.82	127.00±21.58	127.40±22.09	135.00±26.73	0.69		
*P*4	0.88	0.81	0.32	0.78	0.72	0.90	0.61	0.16			
DBP											
Ace	83.53±9.198	81.68±10.73	82.10±11.41	78.90±10.95	77.11±14.07	76.95±10.56	76.25±9.70157	73.10±12.75	0.33	0.43	0.58
NS	83.66±9.05	83.42±11.88	82.32±11.49	80.79±11.68	78.48±13.533	77.95±11.56	76.40±10.72	73.75±10.71	0.42		
Dex	88.55±18.89	83.08±19.99	84.09±14.32	83.00±16.581	78.51±16.65	75.75±13.60	77.00±14.24	79.81±14.59	0.09		
*P*4	0.12	0.84	0.73	0.48	0.87	0.69	0.96	0.38			

*P*1, *P*2, *P*3: Significant at the level of 5% error of repeated measures, *P*4: Significant at the level of 5% error of one-way ANOVA. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, Ace: Acetaminophen, Dex: Dexmedetomidine, NS: Normal saline

Table 3: Mean and standard deviation of heart rate, respiration rate, and oxygen saturation of patients by time and group

Group	Mean±SD								*P*1 (time)	*P*2 (time × intervention)	*P*3 (intervention)
	Beginning of surgery	After starting of surgery			Beginning of recovery	After moving into the recovery room					
	0 min	5 min	10 min	15 min	0 min	20 min	40 min	60 min			
HR											
Ace	76.15±15.14	73.78±15.06	73.05±13.04	72.73±12.45	72.62±15.23	72.16±17.87	69.00±16.06	69.30±15.39	0.03	0.16	0.02
NS	76.35±15.03	75.82±16.84	73.85±15.85	72.18±16.95	73.08±15.25	71.34±15.44	70.59±14.06	67.00±15.99	0.18		
Dex	73.51±11.69	71.48±11.97	70.19±11.33	70.16±13.13	69.75±14.05	68.59±12.05	65.43±11.98	60.81±8.48	0.14		
*P*4	0.56	0.38	0.43	0.76	0.51	0.52	0.34	0.23			
RR											
Ace	17.11±3.64	17.26±3.44	17.42±3.65	17.63±4.13	16.80±2.88	17.51±5.94	16.46±2.99	16.70±3.46	0.48	0.83	0.98
NS	16.84±2.97	16.82±3.11	16.58±3.08	19.72±14.44	18.57±12.49	18.60±12.58	17.54±3.39	15.75±3.91	0.14		
Dex	21.43±4.48	20.86±5.77	20.30±5.95	18.93±6.28	19.18±5.71	20.27±5.24	19.56±4.74	20.56±4.81	0.47		
*P*4	<0.001	<0.001	0.001	0.68	0.35	0.32	0.007	0.02			
O_2 sat											
Ace	96.82±2.24	97.59±1.39	97.40±1.84	97.56±2.26	96.77±3.72	97.11±2.75	97.25±3.18	95.90±4.43	0.48	0.84	0.98
NS	96.51±2.19	94.58±13.48	96.55±2.01	97.06±3.97	97.08±6.53	96.16±3.07	96.77±2.54	97.28±2.05	0.39		
Dex	95.17±12.82	97.75±2.03	97.64±2.34	98.06±1.82	97.13±2.66	97.4±2.66	97.56±2.56	97.68±2.088	0.47		
*P*4	0.56	0.11	0.05	0.38	0.92	0.11	0.56	0.33			

*P*1, *P*2, *P*3: Significant at the level of 5% error of repeated measures, *P*4: Significant at the level of 5% error of one-way ANOVA. HR: Heart rate, RR: Respiratory rate, O_2 sat: Oxygen saturation, Ace: Acetaminophen, Dex: Dexmedetomidine, NS: Normal saline, SD: Standard deviation

Table 4: Distribution of frequencies of incidence of severe nausea, surgeon satisfaction and recovery time by the study groups

Parameter	Ace (*n*=45)	NS (*n*=45)	Dex (*n*=45)	Test	*P*
Severe nausea, *n* (%)					
Yes	0	0	1 (0.8)	Fisher's exact test	0.99
No	43 (33.6)	42 (32.8)	42 (32.8)		
Surgeon satisfaction, *n* (%)					
Excellent	34 (25.8)	29 (22)	13 (9.8)	Chi-square	<0.001
Good	10 (7.6)	14 (10.6)	8 (6.1)		
Bad	0	0	24 (18.2)		
Recovery time, mean±SD					
Mean	38.06±14.79	32.90±15.32	44.67±12.97	One-way ANOVA	0.004

Ace: Acetaminophen, Dex: Dexmedetomidine, NS: Normal saline, SD: Standard deviation

Table 5: Average pain severity of patients in the recovery room by groups

Group	Mean±SD		*P*1
	The severity of pain in recovery (1)	The severity of pain in recovery (2)	
Ace	0.56±0.54	0.51±0.50	0.53
NS	0.46±0.55	0.48±0.50	0.76
Dex	0.68±1.25	0.52±0.99	0.53
*P*2	0.48	0.97	

*P*1: Significant at the level of 5% error of paired *t*-test, *P*2: Significant at the level of 5% error of one-way ANOVA. Ace: Acetaminophen, Dex: Dexmedetomidine, NS: Normal saline, SD: Standard deviation

between the two groups, however, patients receiving acetaminophen did not show any drug side effects. They concluded that the use of intravenous acetaminophen after knee arthroscopy resulted in higher pain relief, reduced use of analgesics, and without any drug-related side effects such as nausea and vomiting. Furthermore, patients who received acetaminophen were more satisfied compared with patients who received morphine for analgesia.[30] In a double-blinded clinical trial by Alipour *et al*. 160 patients aged 50–80 years were randomly divided into two groups. At the beginning of surgery, one group received fentanyl and the other group received acetaminophen, and the level of pain and drug-related side effects were evaluated. They reported that acetaminophen is an effective drug in reducing postoperative pain in patients undergoing cataract surgery and also is safe and without serious side effects.[10]

No significant difference was observed between the three groups over time for heart rate, systolic, and diastolic blood pressure in our study. This result is similar to studies that compared the effect of dexmedetomidine to remifentanil, midazolam, and saline,[26,28] however, it is not consistent with another study that demonstrated statistically significant decreases in arterial pressures and heart rates associated with dexmedetomidine compared with the combination of propofol and alfentanil.[31]

Our results showed that the higher reduction in respiratory rate significantly occurred in the dexmedetomidine group in our study, whereas in terms of oxygen saturation (SpO2), heart rate, and blood pressure, no significant differences were observed between the three groups. The results of previous studies are still conflicting. While no statistically significant differences in oxygen saturation or respiratory rates were reported in studies evaluating the respiratory effects of dexmedetomidine compared to saline; midazolam and fentanyl; propofol and alfentanil; and ketamine and propofol,[15,16,32-35,29,31] some other studies showed inconsistent results when comparing dexmedetomidine to midazolam, placebo, and remifentanil.[9,28,36] Adverse respiratory events including the need for emergent intubation were not noted in any study.[37]

The incidence of nausea did not differ significantly between the three groups, and only one patient in the dexmedetomidine group reported nausea in our survey. Nausea is a known side effect of dexmedetomidine,[38] although there is no evidence about the incidence of this adverse effect to significant reports regarding the comparison of the some other analgesic drugs and placebo.[26,36,38]

Surgeon satisfaction is a key component in comparing sedative agents, especially in monitored anesthesia care, a form of anesthesia in which patient cooperation with the surgeon is critical. The surgeon satisfaction of the patients' sedation in the dexmedetomidine group was significantly lower than the two other groups in our study. Lower satisfaction was reported by surgeons when dexmedetomidine was compared to remifentanil.[9]

Our result demonstrated a tendency for prolonged recovery time in patients who received dexmedetomidine, which may limit its application in the ambulatory surgery setting. In some other studies, when compared to midazolam and propofol, patients treated with dexmedetomidine required longer times to achieve an Aldrete score of 9 or 10.[7,38]

Conclusions

We demonstrated that acetaminophen was as effective as dexmedetomidine with lower side effects and higher surgeon satisfaction, without any interference with

cardiovascular and respiratory parameters. Acetaminophen infusion should be considered an acceptable alternative for outpatient cataract surgery in elderly patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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