Original Article

Comparing Effectiveness and Safety of Intravenous Atropine with Topical Tetracaine in Preventing and Relieving Oculocardiac Reflex in Patients Undergoing Strabismus Surgery: A Randomized Clinical Trial

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Abstract

Background: Oculocardiac reflex (OCR) is one of the serious complications following surgical therapeutic procedures for strabismus. Various medications have been tested to prevent or mitigate this complication. We aimed to compare the effect of intravenous atropine and topical tetracaine on the incidence and severity of OCR in strabismus surgery.

Materials and Methods: In this triple-blind randomized clinical trial study, 120 patients who were candidates for strabismus surgery were randomly assigned to receive intravenous atropine, topical tetracaine, or artificial tears as the control. The incidence of OCR and its severity along with the changes in hemodynamic conditions were compared across the groups.

Results: The incidence rate of OCR in the groups receiving atropine, tetracaine, and the control was found to be 17.5%, 25.0%, and 32.5% in the releasing phase without any difference, respectively ($P = 0.303$); however, it was 2.5%, 7.5%, and 25.0%, respectively, in the cutting phase, indicating a lower rate in the group receiving tetracaine ($P = 0.004$). Similarly, there was no difference in the severity of OCR across the three study groups in the releasing phase ($P = 0.666$); however, in the cutting phase, OCR was revealed to be milder in the group receiving atropine as compared to other groups ($P = 0.033$). Prescribing atropine led to higher mean systolic blood pressure and mean arterial pressure during surgery.

Conclusion: The injection of atropine can effectively reduce the incidence of OCR during strabismus surgery and reduce its severity if this reflex occurs.

Keywords: Atropine, oculocardiac reflex, strabismus, tetracaine

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Introduction

Strabismus surgery is surgery of the ocular muscle to correct the deviation of the eye with different goals such as strengthening the ocular muscle, weakening this muscle, or changing muscle functions.[1] This surgery is the third most common eye surgery in the United States, and no exact epidemiology has been reported from Iran. Studies on Iranian children have shown that the overall incidence of this surgery ranged 2–3.1% in the different regions of our country.[2-4] Despite high successfulness, strabismus surgery may be accompanied with some potential complications

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including incomplete and excessive correction, globe rupture, orbital bleeding, muscle detachment, anterior segment ischemia, tendon capsule prolapse and conjunctival cyst, infectious conjunctivitis, oculocardiac reflex (OCR), and post-operative nausea and vomiting.[5] The OCR or Aschner reflex was first proposed by Aschner in 1908, defining a reduction of more than 20% of heart rate following pressure on the eyeball.[6] OCR is one of the complications of strabismus surgery, which occurs due to pressure on the eyeball and a decreased heart rate[6,7] and causes side effects such as sinus bradycardia, tachycardia, arrhythmia, and even cardiac arrest.[6] The incidence of OCR in strabismus surgeries is very different, ranging from 14 to 90% with the average range of 67.9%, so strabismus surgery is a common and important risk factor for OCR.[6] Various factors such as the anesthesia treatment strategy and drugs used in strabismus surgery are associated with OCR risk.[8,9] Anesthetic drugs used can affect the severity and incidence of OCR, and among these drugs, atropine can be used before or during strabismus surgery to prevent the treatment of severe bradycardia and cardiac arrest.[9]

Atropine is used to increase the heart rate and reduce salivation in surgery, which is usually used intravenously or intramuscularly, and its mechanism of action is to block acetylcholine receptors. It is also available as a drop in the treatment of uveitis and amblyopia.[10] Atropine is a drug used in strabismus surgeries that are given intravenously to treat a decrease in heart rate before or during these surgeries. Recent studies suggest that atropine is an effective drug in reducing the side effects of these operations, such as bradycardia and hypotension.[11] However, not many studies have been done on its effectiveness in preventing OCR, especially compared to other treatments.

Tetracaine eye drops are mainly used to treat eye pain and corneal anesthesia. Tetracaine controls the passage of sodium beyond the cell membrane and reduces the action potential depolarization phase by competing with calcium in sitting on neuronal membrane receptors. These effects stop the onset and conduction of nerve waves by reversibly stabilizing the membrane of nerve cells as a result of reducing the permeability of this membrane to sodium ions. Tetracaine drops have been shown to reduce stress ocular pain after strabismus surgery.[12]

Due to the dangerous effects of OCR during strabismus surgery on one hand and the lack of sufficient studies to compare the effectiveness of common treatments including atropine and tetracaine drops to prevent and reduce the incidence of OCR during strabismus surgery on the other hand, in this study, we decided to compare the effect of intravenous atropine and topical tetracaine on the incidence and severity of OCR in strabismus surgery and compare it with the control group.

Materials and Methods

In this triple-blind randomized clinical trial study, patients who were candidates for strabismus surgery referred to Feyz Hospital in Isfahan in 2016 and 2017 were included in the study.

At the confidence level of 95%, the power of the test is 80%, and taking into account the results of the previous study[13] regarding the prevalence of bradycardia in the atropine and control groups equal to 13% and 40%, respectively, the sample size was calculated to 40 cases in each group.

All patients aged 2 to 64 years and candidates for strabismus surgery under general anesthesia with class I and II according to American Society of Anesthesiologists (ASA) criteria; without hypersensitivity to atropine, tetracaine, and artificial tears; without history of cardiovascular diseases; and without history of using cardiovascular drugs during the 3 months before the study were included. Exclusion criteria were the occurrence of any event that led to the patient being admitted to the ICU or changing the method of anesthesia and the death of the patient. Conscious written consent was received from all patients before entering the study. The study protocol was approved by the Ethical Committee in Isfahan Medical Sciences Research (approval code: IR.MUI.MED.REC.1399.332). It was also registered in the clinical trial system of Iran (Code: IRCT20150106020588N8).

A total of 120 eligible patients undergoing strabismus surgery were randomly selected. Then they were divided into three groups receiving intravenous atropine, tetracaine eye drops, and the control by Random Allocation software. Demographic information of patients including age and sex and clinical information including mean arterial pressure and heart rate at the time before induction of anesthesia, during surgery, and after surgery were recorded by a medical student in a specific checklist for each patient. The patient's blood pressure and heart rate were recorded using vital sign monitoring devices in operating rooms. The anesthesia method was the same in all three groups and was performed using sodium thiopental (5 mg/kg), atracurium (0.5 mg/kg), and fentanyl (2 mg/kg) and maintained using propofol (100 mg/kg/min). Immediately after the eye was prepared and the surgeon allowed access to the operation site, in the tetracaine group, 0.5% topical tetracaine (4 drops in 4 directions) was poured on the eyeball and 1 cc of sterile normal saline intravenous injection was injected. In the atropine group, 0.5 mg of intravenous atropine, the volume of which was increased to 1 cc by sterile normal saline, and 4 drops of artificial tears were poured on the eyeball in 4 directions. In the control group, 4 drops of artificial tears in four directions and 1 cc of sterile normal saline intravenous injection are also given intravenously [Figure 1]. The incidence of a heart rate drop of more than 20% of baseline during surgery along with eye muscle strain was identified and recorded as OCR. Severity of OCR in the stages of muscle release and incision during surgery was based on the percentage of reduction in heart rate by 20 to 30% as mild, 30 to 40% as moderate, and above 40% as severe. In case of OCR in any amount, the intervention was first stopped, and if it does not improve within 10 to 20 seconds, atropine (15

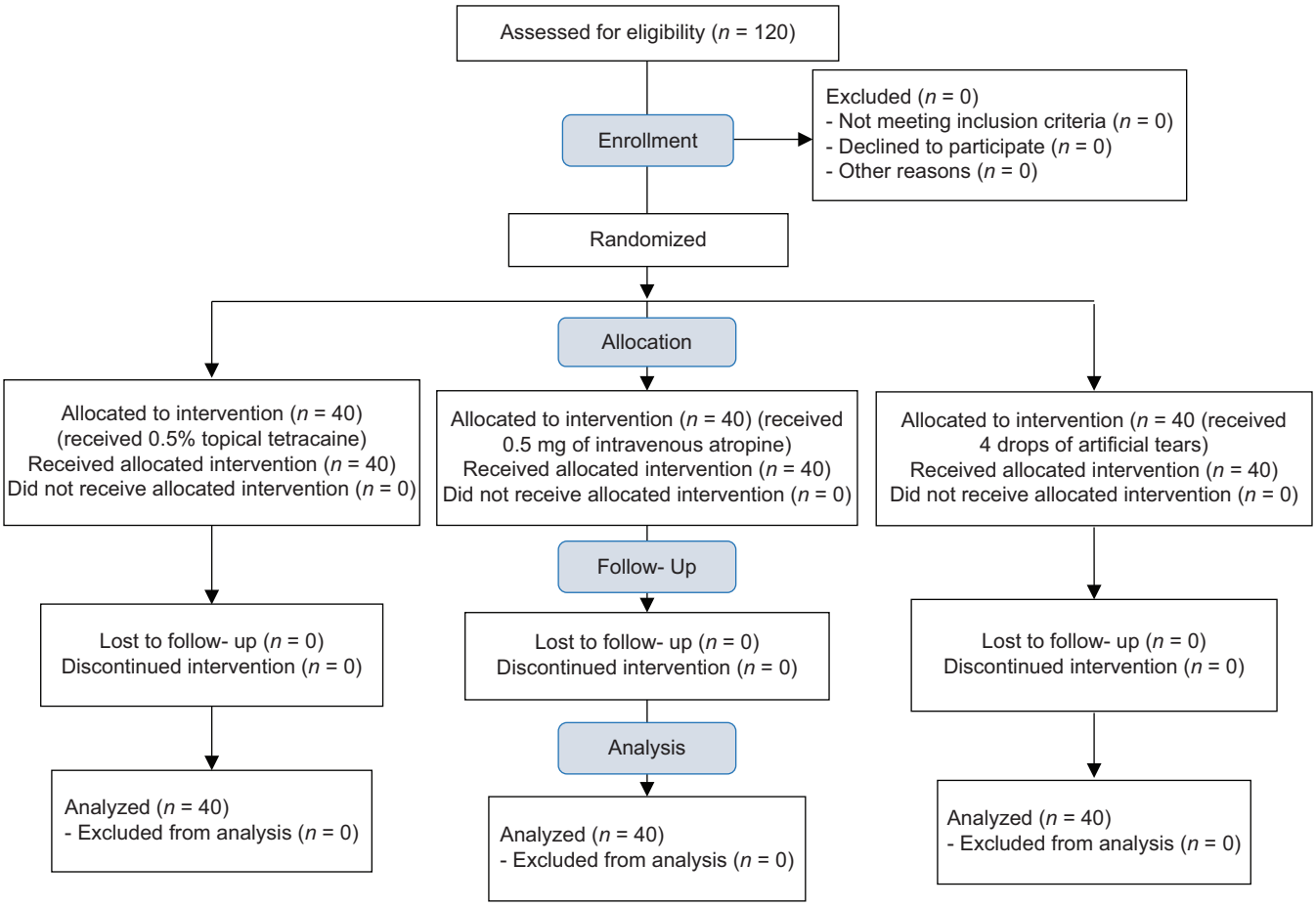

Figure 1: Consort chart

micg/kg) up to a maximum of 40 micg/kg was prescribed until the heart rate improves every 3 minutes, and the time of improving the patient's heart rate was recorded. In case of hypotension, a decrease in SPO2, or any of the OCR events, cardiotonic drugs such as ephedrine or epinephrine were used, and if necessary (a heart rate less than 25% with the presence of hypotension), cardiac massage and resuscitation were performed. In all three groups, in both release and cutting phases, the severity of OCR was recorded. Other hemodynamic information of patients was also collected using a designed checklist. In order to make the study blindness, the person prescribing the drugs was different from the person collecting and analyzing the information.

Finally, the data were analyzed with SPSS (ver. 26). The data were expressed as mean ± SD and frequency (%). Inferential statistical analysis was performed using the Kolmogorov–Smirnov test to determine the normality of the data distribution, the one-way analysis of variance (ANOVA) to compare quantitative variables between three groups at each follow-up time, and the repeated measures ANOVA to compare means across variables over the time in each group. In addition, the Chi-square test was used to compare the distribution of qualitative variables between the two groups. In all analyses, a significance level < 0.05 was considered.

Results

Overall, 120 patients were included into our trial, who were randomly assigned to receive atropine, tetracaine, or artificial tears as the control. The three groups were similar in average age, gender, and ASA score [Table 1].

In assessing hemodynamic parameters, we found no difference across the three groups in the mean heart rate, respiratory rate, and mean diastolic blood pressure before, within, and after operation [Table 2]. Also, the mean systolic blood pressure and mean arterial pressure were similar in the three groups before and after operation. However, the group receiving atropine experienced significantly higher mean systolic blood pressure and mean arterial pressure during surgery as compared to other study groups.

The incidence rate of OCR in the groups receiving atropine, tetracaine, and the control was found to be 17.5%, 25.0%, and 32.5% in the releasing phase without any difference, respectively ($P = 0.303$); however, it was 2.5%, 7.5%, and 25.0% in the cutting phase, respectively, indicating a lower rate in the group receiving tetracaine ($P = 0.004$). Similarly, there was no difference in the severity of OCR across the three study groups in the releasing phase ($P = 0.666$); however, in the cutting phase, OCR was revealed to be

milder in the group receiving atropine as compared to other groups ($P = 0.033$) [Table 3].

Discussion

The results of this study also showed that the use of intravenous atropine in addition to reducing the incidence of this reflex can significantly reduce its severity in the surgical cutting phase of strabismus compared to tetracaine eye drops. Additionally, intravenous atropine can be associated with increased systolic blood pressure and mean arterial pressure during strabismus surgery. In a study conducted by Rahimi *et al.*,[14] the effect of tetracaine with artificial tears on the reduction and severity of OCR in patients undergoing strabismus surgery was compared. The results of their study show that similar to our study, tetracaine drops significantly reduced the incidence of OCR during the cutting phase of strabismus surgery compared to artificial tears and were also associated with less intensity of this reflex. However, contrary to our study, they did not compare and contrast intravenous atropine with tetracaine drops.

In this regard, Rahimi Varposhti *et al.*[13] showed that the incidence and severity of OCR in the cutting phase were more in placebo or synthetic teardrop group than in tetracaine eye drop group. In addition, the duration of OCR recovery and atropine consumption did not differ between two groups. In a general summary, they stated that tetracaine eye drops only reduce the incidence and severity of OCR in the phase of strabismus surgery.

Another study by Espahbodi *et al.*[11] in 2015 to examine the effect of ketamine compared to atropine on the incidence of OCR in patients undergoing eye surgery found that in the ketamine-receiving and atropine-receiving group, 20% and 43% of OCR occurred, respectively, contrary to the results of our study. Anninger *et al.*[15] conducted a study in Philadelphia in 2007 on the effect of tetracaine on ocular pain after strabismus in 88 children who were candidates

Table 1: Baseline characteristics of patients in the three groups

Characteristics	Atropine group	Tetracaine group	Control group	*P*
Age, year	27.55±13.61	26.70±12.03	15.15±12.09	0.66*
Gender				
Male	18 (45.0)	21 (52.5)	22 (55.0)	0.64**
Female	22 (55.0)	19 (47.5)	18 (45.0)	
ASA score				
I	35 (87.5)	34 (85.0)	34 (85.0)	0.93**
II	5 (12.5)	6 (15.0)	6 (15.0)	

*: Significance level obtained from the one-way analysis of variance test comparing the mean of the variables between the three groups.
**: Significance level obtained from Chi-square test to compare variable frequency distribution between three groups

Table 2: Comparison of the mean hemodynamic parameters over follow-up time between the three groups

Characteristics	Atropine group	Tetracaine group	Control group	P^1
Systolic blood pressure				
Before surgery	126.44±9.78	125.80±10.50	123.32±11.06	0.382
During surgery	125.25±9.220	121.67±9.27	118.42±11.06	0.011
After surgery	125.52±7.15	122.75±11.14	121.20±10.85	0.140
P^2	<0.001	<0.001	<0.001	
Diastolic blood pressure				
Before surgery	77.35±8.51	78.05±8.81	77.17±8.56	0.891
During surgery	74.82±8.08	72.67±7.46	70.80±7.41	0.066
After surgery	76.07±8.60	74.37±8.92	75.17±8.96	0.695
P^2	<0.001	<0.001	<0.001	
Mean arterial pressure				
Before surgery	93.70±7.90	93.96±8.38	92.55±8.97	0.733
During surgery	91.63±7.31	89.00±5.76	86.67±7.22	0.006
After surgery	92.55±7.30	90.50±8.59	90.51±8.93	0.441
P^2	<0.001	<0.001	<0.001	
Heart rate				
Before surgery	81.47±9.40	80.45±7.44	83.87±10.37	0.230
During surgery	79.35±8.63	76.95±7.94	78.87±10.38	0.450
After surgery	80.47±9.41	77.45±7.44	80.87±10.39	0.191
P^2	0.003	<0.001	<0.001	
Respiratory rate				
Before surgery	15.25±2.20	14.15±2.32	14.72±2.25	0.090
During surgery	14.98±2.33	14.05±1.30	14.22±2.15	0.456
After surgery	14.26±1.79	13.98±1.29	13.78±2.00	0.576
P^2	0.263	0.258	0.362	

1: The significance level obtained from the one-way analysis of variance test comparing the mean of the variables between the three groups in each of the follow-up times. 2: The significance level obtained from the analysis of repeated measures ANOVA comparing the mean of the variable over time in each of the three groups

Table 3: Frequency severity of OCR between the three groups

Characteristics	Atropine group	Tetracaine group	Control group	P*
Releasing phase				
No OCR	33 (82.5%)	31 (77.5%)	27 (67.5%)	0.66
Mild OCR	4 (10.0%)	4 (10.0%)	7 (17.5%)	
Moderate OCR	2 (5.0%)	3 (7.5%)	2 (5.0%)	
Severe OCR	0 (0%)	0 (0%)	0 (0%)	
Cutting phase				
No OCR	39 (97.5%)	37 (92.5%)	30 (75.0%)	0.030
Mild OCR	1 (2.5%)	2 (5.0%)	3 (7.5%)	
Moderate OCR	0 (0%)	1 (2.5%)	4 (10.0%)	
Severe OCR	0 (0%)	0 (0%)	3 (7.5%)	

*: Significance level obtained from Chi-square test to compare variable frequency distribution between three groups

for strabismus. Tetracaine was found to reduce the occurrence and severity of ocular stress pain after surgery.[14] Another study showed that the incidence of OCR in the remifetanil group was 58.3% and in the ketamine group was 28.3%.[15]

In addition, it is worth mentioning that although atropine inhibits the reflex, it can result in cardiac arrhythmia. The advantages of topical anesthesia include rapid recovery of vision, cost-effectiveness, and avoiding complications that might occur following injection by needle. Therefore, it seems that the local administration of tetracaine can be significant in controlling OCR.[16]

The afferent signals are transmitted through the short and long ciliary nerves to the ciliary ganglion and then, through the ophthalmic branch of the paired (trigeminal) nerve, to the gastrin node. Stimulation of this node, in most cases, increases parasympathetic activity, followed by severe bradycardia or other arrhythmias such as atrioventricular block, ventricular ectopy, and even asystole. The incidence of this reflex during eye surgery is between 16 and 85%.[17] However, the most common manifestation of OCR is sinus bradycardia, and its occurrence in children can be very dangerous and fatal. It should be noted that retrobulbar block and anticholinergic drugs are also used to block OCR.[18,19] It seems that low incidence of OCR following the use of atropine can be judged by its related anticholinergic effect.

In this study, the small size of the sample and the lack of comparison of different doses of atropine and tetracaine can be considered as limitations; however, few studies have compared these two drugs, and from this point of view, it can be considered a strong point. Therefore, in order to evaluate more accurately and generalize the results to larger populations, it is suggested to conduct more studies similar to the present study.

Conclusion

The results of our study show that intravenous injection of atropine can effectively reduce the incidence of OCR during strabismus surgery and reduce its severity if this reflex occurs. However, more studies are suggested to evaluate the effectiveness of this treatment, especially compared to other treatments to reduce this reflex as well as other arrhythmias during strabismus surgery.

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Conflicts of interest

There are no conflicts of interest.

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