Comparing the Preventive Effect of 2 Percent Topical Lidocaine and Intravenous Atropine on Oculocardiac Reflex in Ophthalmological Surgeries Under General Anesthesia

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Original Article

ABSTRACT

Background: The current study aimed to determine preventive effect of 2 percent topical xylocaine on oculocardiac reflex in ophthalmological surgeries except strabismus, including retinal detachment and vitrectomy with scleral buckling under general anesthesia.

Methods: A randomized controlled clinical trial was carried out on 150 patients aged 18-90 years undergoing ophthalmological surgeries under general anesthesia. Samples randomly divided into the experimental group (received four drops of 2 percent topical xylocaine instilled in desired eye) and control group (received 0.5 mg atropine sulfate injection). Systolic, diastolic and mean arterial blood pressure of patients and baseline heart rate were recorded. They were compared regarding the incidence of bradycardia, heart rate less than 60 beats/minute, hypotension and blood pressure less than 90 mm/Hg. Data were analyzed by Statistical Package for the Social Sciences software version 20 using Chi-square and ANOVA.

Results: The difference between two groups was not statistically significant regarding demographic and basic variables. The incidence of bradycardia in both groups was respectively (90.7 percent vs. 17.3 percent), heart rate less than 60 beats/minute (40 percent vs. 13.3 percent), hypotension (76 percent vs. 32 percent) and blood pressure less than 90 mmHg was (28 percent vs. 8 percent). Accordingly, the differences between both groups were statistically significant ($P > 0.001$).

Conclusions: The preventive impact of topical xylocaine upon oculocardiac reflex in ophthalmological surgeries such as retinal detachment and vitrectomy with scleral buckling under general anesthesia was less effective than that of atropine injection. Therefore, to avoid this reflex in high-risk patients, injecting atropine would be safer.

Keywords: Anesthetics, atropine, oculocardiac reflex, ophthalmologic surgical procedures, topical, xylocaine

INTRODUCTION

Trigeminocardiac reflex is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnea and gastric hyper motility under stimulation of any sensory branches of the trigeminal nerve.[1] Sensory terminals of the trigeminal nerve sends nerve signals, due to the extra-ocular muscle stretch or increased intraocular pressure, from the ciliary ganglions of ophthalmic branch of the trigeminal nerve to the sensory nerve cells within forth ventricle, which in the efferent pathway vagus nerve goes to the heart and lead to bradycardia, reduced cardiac conduction and cardiac contractility.[2-4] This reflex, which is caused by the vagal stimulation is classically named oculocardiac reflex. It occurs through ophthalmic branch of trigemino nerve.[5-7] Although this reflex commonly occurs during the strabismus surgeries, it can possibly happen in other ophthalmological surgeries.[8-16] Previous interventions which have been applied to prevent this reflex in strabismus surgeries were either atropine or xylocaine or both.[17-21] Intravenous (IV) atropine blocks peripheral muscarinic receptors in the heart; moreover, xylocaine Hydrochloride (retro bulbar) blocks the conduction in the ciliary ganglion in the afferent pathway of the reflex arc.[2,22] Although atropine inhibits the reflex, but it can result in cardiac arrhythmia.[23] The advantages of topical anesthesia include rapid recovery of vision, cost effectiveness and avoiding complications that might occur following injection by needle.[24-37] In addition, risk factors for this reflex are hypercapnia, hypoxia, acidosis, sedation and drugs.[38,39] In the study of Ruta *et al*. 2 percen t xylocaine has been proved to be effective in controlling oculocardiac reflex while applying topically upon rectus muscles in strabismus surgeries.[40] In another study in which topical anesthesia has been used instead of general anesthesia for strabismus surgeries, the prevalence of oculocardiac reflex has been rarely reported.[41,42] In a study upon patients undergoing retinal and strabismus surgeries, to assess the effects of topical xylocaine compared with placebo, occurrence of this reflex was significantly reduced.[43] In another study, in scleral buckling under general anesthesia, applying local xylocaine in opened conjunctiva has reduced prevalence of the reflex.[44] Since 2 percent topical xylocaine is not commonly applied in ophthalmological surgeries under general anesthesia and also most of these patients are old and generally take beta blockers and calcium channel blockers, hence this study carried out in Feiz Medical Center science with the aim of comparing the preventive impact of 2 percent topical xylocaine and IV atropine on oculocardiac reflex in ophthalmological surgeries under general anesthesia.

METHODS

In a double-blind randomized clinical trial study, after obtaining approval from Research Ethics Committee of Isfahan University of Medical sciences, 150 patients aged of 18-90 years, were enrolled in the study. At first, aim of the study was explained to the participants and their written informed consent was obtained. Study samples were patients undergoing ophthalmological surgeries such as retinal detachment and vitrectomy with scleral buckling in Feiz Medical Center affiliated to the Isfahan University of Medical Sciences. The inclusion criteria are defined as patients between the ages of 18-90, candidate for retinal detachment surgery and vitrectomy and not allergic to xylocaine and similar compounds. On this basis, patients who had taken any drugs or any substance which have interaction with xylocaine or atropine, patients with cardiac arrest and those who needed any other ophthalmological surgeries except the two above mentioned ones as inclusion criteria in this study. Among 150 patients who met the inclusion criteria, 75 patients assigned to each group, by means of a sample size formula to compare two ratios (occurrence of Occulo Cardiac Reflex in both groups), with a confidence level of (95 percent), power of (80 percent) and the prevalence of OCR that assumed 30 percent[40] in the experimental group based on the literatures and 50 percent in the control group due to uncertainty of the prevalence. Patients were randomly allocated into two experimental and control group by means of Randomization Allocation Software (RAS) randomly assign subjects to different trial groups by computer. In the experimental group patients received xylocaine drop which instilled in desired eye. Likewise in the control group received IV atropine. Fluid therapy in both groups was equal. Once patients were transferred and positioned on an operating table,

monitoring equipment's such as electrocardiograph, pulse oximetry and blood pressure cuff were connected. Induction of anesthesia was done by applying 4 milligram/kg thiopental sodium, 0.035 milligram/kg midazolam, 1.5 microgram/kg fentanyl and 0.6 milligram/kg atracurium. After tracheal intubation, anesthesia continued by a combination of 50 percent of N_2O in O_2 and 1.5 percent isoflurane. When anesthesia started, four drops of 2 percent xylocaine with an interval of 2 minute during 10 minute was instilled into the desired eye of the patients in the experimental group.[45-48] In the control group, 0.5 mg atropine was injected along with anesthesia induction. Tidal volume and respiratory rate of samples were adjusted 10 milliliter/kg and 12 times/minute, respectively. Afterwards, during the operation, by monitoring of end-exhaled carbon dioxide was monitored and maintained 25-35 by adjusting respiratory rate and tidal volume. Furthermore, heart monitoring and pulse oximetery was performed to evaluate and record heart rate, arterial oxygen saturation, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure. Arterial oxygen saturation was maintained over 95 percent; in addition, in case of reducing the heart rate lesser than 20 percent of baseline, it was considered as bradycardia and recorded in the questionnaire.[14] At the end of the operation, memory of monitoring equipment was checked and the minimum and maximum heart rate were recorded in the questionnaire by one of the researcher. For the purpose of double- blinding in this study, neither the technician who recorded the memory nor the patients were aware of the administered treatment and patient group. In case of reducing heart rate to less than 60 beats/minute, manipulation by the surgeon was stopped and 0.5 mg atropine injected. If needed, it was repeated after 3 minute. In case of dropping systolic blood pressure to lesser than 30 percent of baseline, it was recorded as hypotension and in case of dropping the systolic blood pressure to less than 90 mmHg, it was treated by reducing the anesthetic drugs and extra fluid therapy. In the case that did not response to the treatment, 5 mg of ephedrine was injected and also repeated as needed. At the end of anesthesia, the residual effect of muscle relaxants was reversed by applying 0.02 milligram/killogram of atropine and 0.05 milligram/kilogram of neostigmine. Patient was extubated after full consciousness. Data were collected, edited and analyzed by Statistical Package for the Social Sciences software version 20. Statistical tests used to analyze data are Chi-square test (for comparison of frequency distribution of qualitative variables between two groups) and repeated measures ANOVA for comparison of hemodynamic variables during study. In this study, the amounts of $P < 0.05$ were considered to be significant.

RESULTS

A total of 154 patients were recruited to the study and four of them were excluded [Figure 1]. In Table 1, distribution of demographic characteristics and underlying variables has been shown for samples of two groups. According to the table, no significant differences were observed between two groups regarding the distribution of these variables.In Table 2, the mean and SD of hemodynamic indexes of samples in both groups are shown. ANOVA with repeated observations showed that the mean of changes in heart rate of samples who received xylocaine and atropine is significantly different = 0.003). However, blood pressure changes between two groups were not significantly different. The mean of minimum heart rate was (60.1 ± 9.2) in xylocaine group and (71.2 ± 13.5) in atropine group. According to the *t*-test, the difference between two groups was significant (= 0.001). In addition, the mean of maximum heart rate in both experimental and control groups were (88.9 ± 16.8) and (97 ± 16.5) respectively. *T*-test indicated that the difference between these two groups is significant ($P = 0.002$).In Table 3, the frequency distribution of complications in two groups who received xylocaine and atropine has been indicated. In this regard, the incidence of bradycardia, dropping heart rate to less than 60 beat/minute, hypotension and dropping the blood pressure to the less than 90 mmHg in the xylocaine group was significantly more than that of atropine group; moreover, non-sinusoidal rhythm and cardiac arrest did not happen to any patients of the two groups. For six patients who received xylocaine, atropine was also applied. Furthermore, six patients in xylocaine group (8 percent) and seven patients in atropine

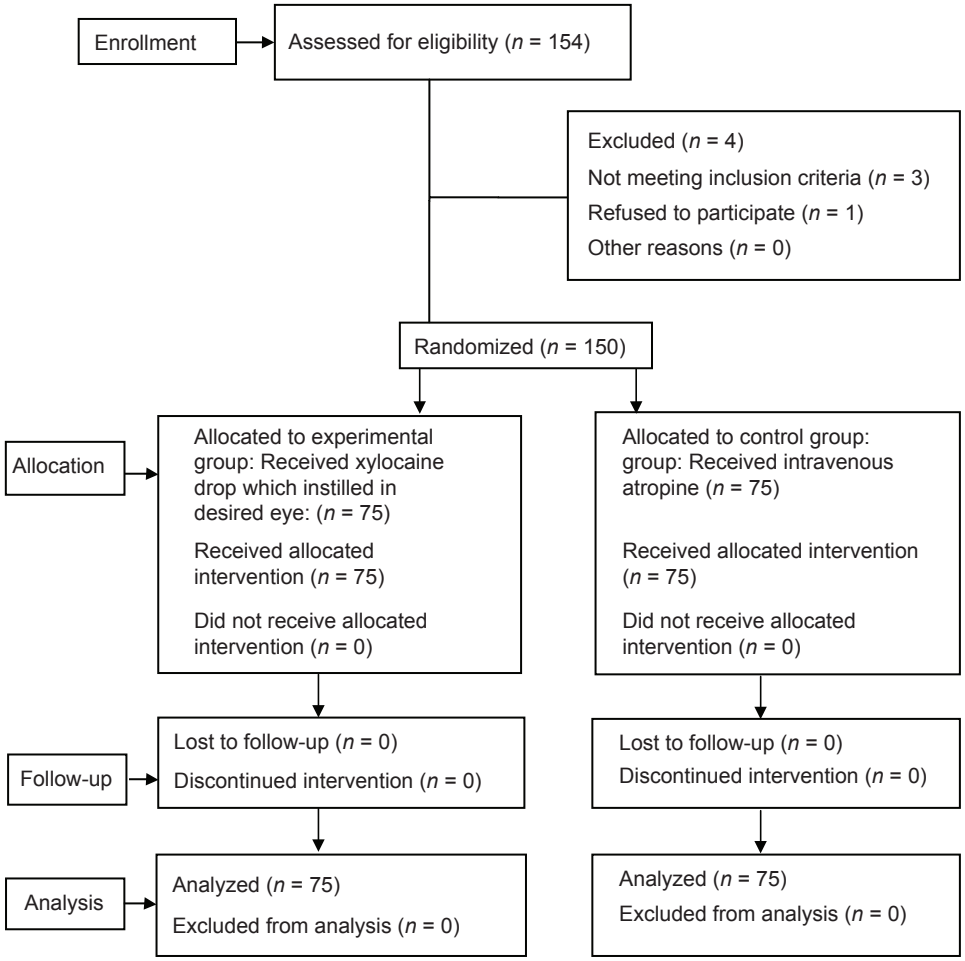

Figure 1: CONSORT diagram showing the flow of participants through each stage of the study

Table 1: Distribution of demographic variables in two groups

Variable	Group level	Xylocaine	Atropine	*P*
Age	Year	57.4 (14.5)	53.8 (16.3)	0.16
Sex	Male	41 (54.7)	48 (64)	0.25
	Female	34 (45.3)	27 (36)	
Weight	Kilogram	67.13 (13.6)	70.1 (9.5)	0.13
Type of surgery	Deep vitrectomy	53 (70/7)	60 (80)	0.19
	Retinal detachment	22 (29/3)	15 (20)	
Duration of operation	Minute	101.9 (25.7)	103.8 (28.7)	0.68
Taking beta-blocker	Yes	17 (22.7)	11 (14.7)	0.21
	No	58 (77.3)	64 (85.3)	
Taking calcium-channel blocker	Yes	4 (5.3)	3 (4)	0.99
	No	71 (94.7)	72 (96)	
Hypertension	Yes	16 (21.3)	13 (17.3)	0.54
	No	59 (78.7)	62 (82.7)	
Taking antihypertensive	Yes	11 (14.7)	13 (17.3)	0.66
	No	64 (85.3)	62 (82.7)	

Values are mean±SD or number (%). SD=Standard deviation

group (9.3 percent) received ephedrine. On this basis, Chi-square test did not show any significant difference between the two groups.Monitoring the hemodynamic variables of patients

Table 2: Hemodynamic indexes for the two groups

Group/time	Mean arterial pressure		Diastolic blood pressure		Systolic blood pressure		Heart rate	
	Atropine	Xylocaine	Atropine	Xylocaine	Atropine	Xylocaine	Atropine	Xylocaine
Before of anesthesia	113.3 (21.2)	124.7 (25.9)	94.4 (16.2)	101.1 (20.5)	151 (21.7)	173.2 (39.7)	78.2 (16.1)	88.1 (16.1)
Onset of anesthesia	96.4 (19.9)	103.6 (21.3)	84.3 (17.1)	89.2 (19.4)	131.4 (27.5)	136 (28.5)	87 (14.1)	81.9 (15.3)
Onset of operation	92.7 (22.2)	91.2 (16.4)	81.4 (20.6)	78.5 (15.3)	122.4 (23.6)	118.2 (22)	83.3 (15.1)	69.7 (12)
15 min	97.2 (21.7)	100.5 (20.4)	85.6 (20.1)	86.6 (18.6)	130.2 (24.1)	134.5 (23.1)	81.1 (20.9)	70.9 (14.2)
30 min	96.2 (19.6)	97.3 (18.9)	79.6 (17.5)	82.2 (15.1)	126.6 (25.2)	127.6 (18.4)	83.4 (13.1)	71.7 (13)
60 min	94.4 (16.8)	90.6 (11)	79 (16.2)	78.3 (11.8)	122.9 (20)	119 (15.4)	78.8 (12.6)	73 (17.9)
120 min	96.7 (16.8)	98.4 (14.8)	82 (17.4)	84.1 (14.6)	127 (18.1)	131.5 (20.7)	79.9 (12.5)	72.6 (11.4)
P	0.22		0.38		0.11		0.003	

Values are mean±SD or number (%). Significant values $P<0.05$. SD=Standard deviation

Table 3: The frequency distribution of complications in xylocaine and atropine groups

Variable	Atropine	Xylocaine	Group level	*P*
Bradycardia	13 (17.3)	68 (90.7)	Yes	<0.001
	62 (82.7)	7 (9.3)	No	
Heart rate less than 60	10 (13.3)	30 (40)	Yes	<0.001
	65 (86.7)	45 (60)	No	
Hypotension	24 (32)	57 (76)	Yes	<0.001
	51 (68)	18 (24)	No	
Blood pressure less than 90 mmHg	6 (8)	21 (28)	Yes	0.001
	69 (92)	54 (72)	No	

Values are number (%). Significant values $P<0.05$

throughout the intervention showed that systolic, diastolic and mean arterial blood pressure did not have any significant differences between two groups during 120 min. However, heart rate changes had significant differences between two groups, so that the heart rate was higher in patients receiving IV atropine. As it was already explained, atropine is an anti-cholinergic drug which prevents bradycardia. In our study, the incidence of bradycardia in patients who received topical xylocaine was 90.7 percent and in patients who received atropine was 17.3 percent. Both groups showed a significant difference in this regard. In 40 percent of the patients who received xylocaine, heart rate dropped to less than 60 beats/min, whereas it only happened in 13.3 percent of patients who received atropine. The incidence of hypotension in patients who received atropine (68 percent) was significantly less than that of the patients who received xylocaine (24 percent). Particularly, severe dropping of blood pressure (dropping the blood pressure less than 90 mmHg), which can be problematic during anesthesia was lesser in the atropine group in compare with xylocaine (28 percent vs. 8 percent).

DISCUSSION

In this study, a total of 150 patients were allocated into 2 groups applying xylocaine and atropine. Two groups did not have any significant differences in respect of demographic and basic variables including age, sex, type of operation, duration of operation, taking beta blockers, taking calcium-blockers, history of high blood pressure and taking anti-hypertensive drugs. Hence, the confounding effect of these factors has been neutralized and differences are likely related to the type of medication that these patients take. Monitoring the hemodynamic variables of patients during the intervention showed that systolic, diastolic and mean arterial blood pressure did not have any significant differences between two groups from the onset to the min 120. However, heart rate changes had significant differences between two groups, so that the heart rate was higher in patients receiving IV atropine. As it was already explained, atropine is an anti-cholinergic drug which prevents bradycardia. In our study, the incidence of bradycardia in patients who received topical xylocaine was 90.7 percent and in patients who received atropine was 17.3 percent. Both groups showed a significant difference in this regard. In 40 percent of the patients who received xylocaine, heart rate dropped to less than 60 beats/minute, whereas, it only happened in 13.3percent of patients who received atropine. The incidence of hypotension

in patients who received atropine (68 percent) was significantly less than that of patients who received xylocaine (24 percent). Particularly, severe dropping of blood pressure (dropping the blood pressure less than 90 mmHg), which can be problematic during anesthesia was less in the group which received atropine (28percent in comparison with 8 percent). In a study done by Gilani *et al*. in 2005,[2] 60 patients undergoing strabismus surgeries under general anesthesia were investigated in two groups for the aim of comparing the effects of IV atropine before inducting anesthesia with placebo, similar results were obtained. In addition, in the placebo group who had received no premedication, dropping the mean of heart rate, incidence of junctional rhythm and the number of patients who needed atropine injection during the surgery were higher and the prevalence of this reflex was 70 percent in comparison with the experimental group which was 10 percent. Therefore, the mentioned study also showed that premedication by atropine in patients undergoing strabismus surgery prevents the occurrence of the reflex. In another study done by Ruta *et al*.[43] upon patients undergoing strabismus or retinal surgery, the effects of topical xylocaine was compared with placebo to prevent the reflex. The prevalence of the reflex in the placebo and topical xylocaine groups were 86.1percent and 37.1percent respectively. In addition, repeated episodes of severe bradycardia significantly reduced from 40 percent in the placebo group to 2.9 percent in xylocaine group. However, unlike our study that xylocaine was compared with atropine injection, in this study, xylocaine has been compared with placebo. In a study done by Misurya *et al*.[22] upon patients at the aged of 10-30 years undergoing strabismus surgery under general anesthesia, results similar to our study were obtained. In fact, the patients were assigned into four groups. Control group did not receive any premedication of atropine and retro bulbar Xylocaine. A group of patients received 0.6 mg of atropine sulfate before anesthesia and finally the reflex was seen just in 10 percent of patients, which did not have any significant difference with the control group. Another group of patients received 1 cc of 2 percent xylocaine for retro bulbar block and the reflex was seen in 20 percent of them, which did not show any significant differences with the control group. The third group of patients received both retrobulbar xylocaine and premedication of atropine, finally the reflex was seen in none of them and they had a significant difference with the control group. In fact, in the study, it was concluded that using a combination of both drugs in comparison with using each drug separately is more effective to prevent the reflex in strabismus surgeries. In another study done by Dehghani *et al*.[44] in Feiz Medical Center of Isfahan upon the patients undergoing scleral buckling surgery due to rhegmatogenous retinal detachment, the effects of topical xylocaine was compared with the placebo. Using xylocaine during the operation for the experimental group significantly reduced prevalence and severity of the reflex. In a study done by Snir *et al*.[49] upon the patients undergoing strabismus surgery under general anesthesia to investigate supplementary effects of topical anesthesia, sub-tenon anesthesia was done by injecting 3.4 cc of a combination of 2 percent xylocaine and 5 percent bupivacaine. According to the results, the incidence of episodes of reflex, arrhythmia and bradycardia was less than that of the control group. Although, the prevalence of bradycardia (dropping heart rate to more than 20 percent of basic) and blood pressure drop (more than 30 percent) in xylocaine group was higher than that of atropine group, the percentage of patients who needed medical intervention (six patients who were in xylocaine group, also received atropine to treat bradycardia. Likewise, six patients in xylocaine group and seven patients in atropine group also received ephederine) showed no statistically significant differences between these two groups. Although most of the ophthalmological patients have the history of cardiac diseases and hypertension and they might take medications for this purpose, but premedication by atropine showed no side-effects and it can be recommended. On the other hand, using topical xylocaine have largely reduced vagus reflex (bradycardia and hypotension). Therefore, due to this fact that topical xylocaine does not harm patients, applying this substance in ophthalmological surgeries prior to the onset of general anesthesia can be recommended. It should be noted that atropine and ephedrine can be used therapeutically, if it's needed. For the purpose of ethical considerations and study limitations, it should be noted that in this study usual drugs,

which are normally applied in ophthalmological surgeries have been used for patients; therefore, no ethical barrier or limitation has been determined.

CONCLUSIONS

According to this study, though we can recommend both topical xylocaine and IV atropine for prevention of oculocardiac reflex before beginning of surgery during general anesthesia, but the preventive impact of topical xylocaine on this reflex in ophthalmological surgeries such as retinal detachment and vitrectomy with scleral buckling has been less than the effect of IV atropine. Because IV atropine had no any side-effects in high risk patients in this study, therefore, IV atropine can be recommended for these patients who suffer from heart problems and hypertension with the history of taking anti-hypertensive drugs.

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