The Effect of Pre-Emptive Dose of Intravenous Ketamine on Oculocardiac Reflex in Pediatric Strabismus Surgery: A Randomized Clinical Trial

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Received: 04 Feb. 2019; Accepted: 16 Apr. 2019

Abstract- To evaluate the effect of pre-emptive dose of intravenous ketamine on Oculocardiac reflex (OCR) in pediatric strabismus surgery. 60 children with age between 2 to 8 years old candidate for strabismus surgery were randomly divided into two groups of 30 participants. After induction of anesthesia, in one group, pre-emptive dose of ketamine (0.15 mg/kg) was given intravenously (ketamine group), while the other group was given the same volume of normal saline (control group). During the surgery, OCR was recorded if the heart rate had decreased 20% or more from the baseline. In the recovery room, the incidence of nausea and vomiting, bronchospasm, laryngospasm, hallucination and recovery nurse satisfaction score were recorded. The incidence of OCR in total participants was 31 (51.7%). In control group 21 (70%) patients had OCR during surgery while this incidence was 10 (33.3%) in ketamine group which was significantly lower (*P*:0.004). the incidence of postoperative nausea and vomiting and the mean of recovery nurse satisfaction score in recovery room were not significantly different between two groups. The hallucination was not seen in any cases of two groups after surgery. The pre-emptive dose of ketamine (0.15 mg/kg) can reduce incidence of OCR in the pediatric strabismus surgery.

Acta Med Iran 2019;57(5):295-298.

Keywords: Oculocardiac reflex; Ketamine; Strabismus; Pediatric

Introduction

Oculocardiac reflex (OCR) which was first introduced by Aschner in 1908, is a trigeminovagal reflex (1). OCR is defined as 20% decrease in baseline heart rate after manipulation of globe. Although sinus bradycardia is a most common sign of OCR, other associated manifestations such as arrhythmia, decreasing arterial blood pressure, ventricular fibrillation, asystole and cardiac arrest were reported (2). It is stimulated by any manipulation of globe's structures including traction of extraocular muscles (EOM) particularly medial rectus, intra ocular injections and hematoma (3). Hence, strabismus surgery is considered as one of the most common interventions complicated by OCR reported in 14% to 90% of cases (4). There is no definite method for prevention of OCR, though, different managements including using anti cholinergic agents like atropine and glycopyrrolate, preventing hypoxemia and hypercapnia and sufficient depth of anesthesia were suggested in previous studies (5).

Ketamine is an anesthetic medication acting via blockage of N-methyl- D -aspartate (NMDA) receptors (6). In recent studies have been shown that ketamine may reduce incidence of OCR in strabismus surgeries by increasing sympathetic tone (3,6,7). Ketamine is used with different doses in anesthesiology. In this randomized clinical trial, we investigated the effect of pre-emptive dose of ketamine on the incidence of OCR in the pediatric strabismus surgery. To the best of our knowledge, there is no similar study for this dose of ketamine in the literature.

Materials and Methods

This double-blind, randomized clinical trial was done in strabismus ward surgery room of Farabi eye hospital in 2018. This study was approved in ethical committee of Tehran University of medical science and Farabi eye hospital. The principles of the declaration of

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Helsinki were considered in all steps of this study. Informed consent was obtained from all patients' parents before participating in the study. 60 pediatric patients with ASA class 1 and 2 aging between 2 to 8 years candidate for strabismus surgery, were included. The exclusion criteria were as follows: a history of hypersensitivity to drugs used in the study, psychiatric diseases, recent upper respiratory tract infections, taking tranquilizer medications, vasovagal reactions and taking medications disturbing cardiac conductive system and heart blocks.

The included patients were divided into two groups of 30 participants by block randomization, with a block size of four. In each group, patients were given oral midazolam (0.5 mg/kg) and atropine (0.1 mg/kg) diluted in 2 cc strawberry syrup 30 minutes before surgery. The similar anesthetic technique was performed in two groups. In the operating room after the setting of standard monitoring instruments, an intravenous route was secured, and 1 mg/kg fentanyl was given intravenously. The induction of anesthesia was done with sevoflurane 8% and oxygen 100%. After establishing the adequate depth of anesthesia, intratracheal intubation was performed. The anesthesia was continued with isoflurane 2.5% and spontaneous breathing with mapleson circuit (4 lit/min flow rate). After induction of anesthesia, in one group, a pre-emptive dose of ketamine (0.15 mg/kg) was given intravenously (ketamine group), while the other group was given the same volume of normal saline (control group). During the surgery, OCR was recorded if the heart rate had decreased 20% or more from the baseline. All surgeries were done by the same surgeon (MRA). Systolic and diastolic blood pressure and heart rate were measured again after surgery. In the recovery room, the incidence of nausea and vomiting, bronchospasm, laryngospasm, hallucination, and other complications were recorded, and the appropriate treatment was done. In addition, recovery nurse satisfaction score (Table 1) was given to each patient by the same nurse of recovery room.

Table 1. Recovery nurse satisfaction score

Recovery nurse satisfaction score	
Very dissatisfied	1
Some-What dissatisfied	2
Neutral	3
Satisfied	4
Very satisfied	5

Statistical analysis was performed with SPSS version 24 (SPSS Inc., Chicago, IL). We used independent t-test for comparing the mean of age, weight, systolic and diastolic blood pressure, heart rate, and recovery nurse satisfaction score between two groups. The frequencies of OCR, postoperative nausea and vomiting, and hallucination were compared by Chi-square analysis. Furthermore, paired t-test was used to compare heart rate, systolic and diastolic blood pressure before and after surgery in each group. *P* less than 0.05 were considered significant.

Results

A total number of 60 patients were included in this study. 24 (40%) of them were male. Their mean age was 5.5±1.85 years (range 2-8). They were randomly divided into two groups of 30 patients. As shown in table 2, there was no significant difference between two groups in gender, age, weight, systolic, and diastolic blood pressures and heart rate before surgery. The incidence of OCR in total participants was 31 (51.7%). In control group 21 (70%) patients had OCR during surgery while this incidence was 10 (33.3%) in ketamine group, which was significantly lower (*P*=0.004). the incidence of postoperative nausea and vomiting and the mean of recovery nurse satisfaction score in recovery room were not significantly different between two groups (Table 3). No hallucination was seen in any cases of two groups after surgery. The systolic and diastolic blood pressures and heart rate increased after surgery in both groups; however, their increase was not statistically significant (Table 4) except for heart rate in the ketamine group (*P*=0.003).

Table 2. Baseline variables

	Control group	Ketamine group	*P*
Age	5.57± 1.87	5.43±1.87	0.738
Gender	13 (54.17%)	11 (45.83%)	0.598
Weight	20.87± 7.41	19.63± 5.12	0.456
Systolic blood pressure	105.97± 8.58	105.7±7.64	0.899
Diastolic blood pressure	62.37± 9.95	59.7±9.14	0.284
Heart rate	114.43± 15.83	111.1± 18.63	0.458

Table 3. Incidence of recovery complications

	Control group	Ketamine group	*P*
Postoperative nosea, vomiting	7 (23.3%)	6 (20%)	0.754
Recovery nurse satisfaction score	4.43± 0.626	4.40± 0.814	0.859
Hallucination	0 (0%)	0 (0%)	
Brunchospasm and laryngospasm	0 (0%)	0 (0%)	

Table 4. Hemodynamic variables before and after surgery

		Before	After	*P*
Systolic blood pressure	**Control group**	105.97± 8.58	108.23± 7.14	0.215
	Ketamine group	105.7± 7.64	108.20± 6.72	0.204
Diastolic blood pressure	**Control group**	62.37± 9.95	67.07± 7.57	0.365
	Ketamine group	59.7± 9.14	60.47± 7.26	0.684
Heart rate	**Control group**	114.43± 15.83	121.50± 13.38	0.095
	Ketamine group	111.1± 18.63	124.87± 13.92	0.003

Discussion

The pre-emptive dose of ketamine (0.15 mg/kg) could reduce the incidence of OCR in pediatric strabismus surgery according to our findings in this randomized clinical trial. Since there was no significant statistical difference between two our groups in demographic and baseline variables, the confounding factors did not affect our results. Three phases have been described in the pathophysiology of OCR consisted of first, parasympathetic release resulted in decreasing heart rate following traction of EOM second, activation of sympathetic pathway and returning heart rate after maximal traction and third increasing heart rate in response to abrupt release of EOM (2). It was suggested that ketamine effect on reduction of OCR was applied by suppressing the first parasympathetic phase of OCR as a result of its sympathetic property. Ketamine can increase sympathetic tone via enhancing norepinephrine release (8-11). Different doses of ketamine are used in anesthesiology. Pre-emptive dose is a lowest dose of ketamine (0.15 mg/kg) used preoperatively to decrease postoperative pain by preventing formation of altered central processing of afferent input from injuries (12). To the best of our knowledge, there is no study in literature investigating the effect of this dose of ketamine on the incidence of OCR in the strabismus surgery.

In the study of Espahbodi et al on 90 patients undergoing strabismus surgery, the incidence of OCR was 20% in the group given ketamine 1.5 mg/kg versus 63% in the control group which was significantly lower (13). Hahnenkamp et al investigated 4 groups with different drugs for anesthesia induction and showed the incidence of OCR in the group received combination of ketamine (10-12 mg/kg) and midazolam (0.3 mg/kg) was 22%, significantly lower than other groups (7). Choi et al divided 120 patients undergoing strabismus surgery into 3 groups induced anesthesia with propofol, ketamine (1 mg/kg) and ketamine (2 mg/kg) respectively. The results of this study revealed the incidence of OCR during strabismus surgery was significantly lower in ketamine groups versus propofol, though, there was no significant difference between ketamine groups (3). Furthermore, Mizrak et al. concluded that infusion of 1-3 mg/kg ketamine for induction of anesthesia is more effective than propofol in reducing the incidence of OCR in children undergoing strabismus surgery (6). The results of all mentioned studies are consistent with our study, however in contrast to our findings Choi *et al*., in 2009 showed ketamine didn't influence the incidence of OCR in the pediatric strabismus surgery (8). In addition, in the study of Oh JN *et al.*, there wasn't significant difference between ketamine group (1 mg/kg) and group received midazolam (0.15 mg/kg) in occurring OCR during surgery (2). Postoperative vomiting occurs in 41-88% of pediatric strabismus surgery without prophylactic medications. Moreover, ketamine can induce postoperative nausea and vomiting in 7-26% of cases which was not dose dependent (14). The incidence of postoperative nausea and vomiting in ketamine group in our study was 20% which wasn't significantly different with control group. So it seems that the pre-emptive dose of ketamine (0.15 mg/kg) does not increase the incidence of postoperative nausea and vomiting.

Hallucination following use of ketamine has been reported in 0 to 10% of cases in previous studies (15). None of our cases had hallucination in the recovery room. It may be due to lower dose of ketamine in our study. Ketamine can increase blood pressure and heart rate via blocking the reabsorption of catecholamines

(16). In comparison of hemodynamic changes between two groups of our study, despite the increase of mean of blood pressure and heart rate, their difference wasn't statistically significant except for heart rate which was not clinically significant. Therefore, the pre-emptive dose of ketamine seems have no considerable effect on hemodynamic. The type of strabismus surgery and the relation between the incidence of OCR and type of EOM manipulated wasn't determined in this study. We suggest multi-centric larger sampled studies with consideration of type of strabismus surgery for future investigations. In conclusion, we showed pre-emptive dose of ketamine (0.15 mg/kg) can reduce incidence of OCR in the pediatric strabismus surgery.

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