JARSS 2021;29(1):58-64
doi: 10.5222/jarss.2021.29484

Factors Affecting Oculocardiac Reflex Incidence in Pediatric Strabismus Surgery: Retrospective Study

Pediyatrik Şaşılık Cerrahisinde Okülokardiyak Refleks İnsidansını Etkileyen Faktörler: Retrospektif Çalışma

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ABSTRACT

Objective: *Oculocardiac reflex (OCR) activation is common during strabismus surgery. As a result of OCR, sinus bradycardia, atrioventricular block, ventricular fibrillation and even asystole may occur. Pediatric patients are also more vulnerable to the harmful effects of this reflex. The aim of this study was to determine the possible risk factors affecting the incidence of OCR in pediatric patients undergoing strabismus surgery.*
Method: *The medical records of the pediatric patients who underwent strabismus surgery between January 2015 and September 2018 were retrospectively reviewed. The operations performed by the same surgeon were included in the study. OCR was defined as a more than 20% reduction in HR induced by the extraocular muscle (EOM) manipulation. Demographic data, duration of surgery, history of any previous strabismus surgery and possible development of OCR, anesthesia management, neuromuscular blocker and anesthetic drugs used for anesthesia induction and maintenance as well as airway management, the number of operated eyes, and also the muscle types of the patients were all recorded. Risk factors for OCR were evaluated by logistic regression analysis.*
Results: *Out of 92 pediatric patients who were initially evaluated, six were excluded from the study because their files were missing. A total of 86 patients were included in the study. During surgery, OCR occurred in 29 (33.7%) patients. The absence of administering benzodiazepine for premedication (p=0.03) and nonuse of neuromuscular blocker after induction (p=0.046) in pediatric patients have been specified as independent risk factors. We found that the use of a neuromuscular blocker and benzodiazepine in premedication reduced the risk of OCR by 3.64 and 3.11 times, respectively.*
Conclusion: *The incidence of OCR may be reduced with preventive measures such as application of neuromuscular blocker, and premedication with benzodiazepine in strabismus surgeries.*

Keywords: *Pediatric patient, oculocardiac reflex, strabismus surgery*

ÖZ

Amaç: *Şaşılık cerrahisi sırasında okülokardiyak refleks (OKR) aktivasyonu yaygındır. OKR sinüs bradikardisi, atriyoventriküler blok, ventriküler fibrilasyon ve hatta asistol ile sonuçlanabilir. Pediyatrik hastalar bu refleksin zararlı etkilerine karşı daha savunmasızdır Bu çalışmada şaşılık cerrahisi geçiren pediyatrik hastalarda OKR insidansını etkileyen olası risk faktörlerini belirlemek amaçlandı.*
Yöntem: *Ocak 2015-Eylül 2018 tarihleri arasında şaşılık cerrahisi geçiren pediyatrik hastaların kayıtları retrospektif olarak incelendi. Sadece tek bir cerrah tarafından yapılan ameliyatlar dahil edildi. OKR; ekstraoküler kas (EOK) manipülasyonunun neden olduğu kalp hızında %20'den fazla azalma olarak tanımlandı. Hastaların demografik verileri, cerrahi süre, önceden geçirilmiş şaşılık cerrahisi öyküsü, OKR gelişip gelişmediği, anestezi yönetimi; indüksiyon ve idamede kullanılan kas gevşeticiler ve anestezik ilaçlarının yanı sıra hava yolu yönetimi , opere edilen göz sayısı ve kas tipi kaydedildi. OKR için risk faktörleri lojistik regresyon analizi ile değerlendirildi.*
Bulgular: *Başlangıçta değerlendirilen 92 pediyatrik hastadan, altısının dosyası eksik olduğu için çalışma dışı bırakıldı. Toplam 86 hasta çalışmaya dahil edildi. Ameliyat sırasında 29 hastada (%33.7) OKR görülmüştür. Pediyatrik hastalarda premedikasyonda benzodiyazepin (p=0.03) ve indüksiyon sonrası kas gevşetici uygulanmamış olması (p=0.046) bağımsız risk faktörleri olarak belirlenmiştir. Kas gevşetici kullanımının ve premedikasyonda benzodiyazepin uygulanmasının OKR riskini sırasıyla 3.64 ve 3.11 kat azalttığını bulduk.*
Sonuç: *Şaşılık cerrahilerinde OKR insidansı kas gevşetici uygulanması, benzodiyazepin ile premedikasyon gibi önleyici tedbirlerle azaltılabilir.*

Anahtar kelimeler: *Pediyatrik hasta, okülokardiyak refleks, şaşılık cerrahisi*

Received/Geliş: 29 May 2020
Accepted/Kabul: 08 October 2020
Publication date: 29 January 2021

Cite as: Aydın BG, Küçükosman G, Pişkin Ö, et al. Factors affecting oculocardiac reflex incidence in pediatric strabismus surgery: Retrospective study. JARSS 2021;29(1):58-64.

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INTRODUCTION

Activation of oculocardiac reflex (OCR) is common during strabismus surgery. OCR is known as the trigeminal-vagal reflex. This reflex is triggered when the ophthalmic branch of the trigeminal nerve is stimulated. It is transmitted to the medulla oblongata via the ciliary ganglion and the efferent pathway branches out to the heart. Vagal stimulation reduces both the heart rate and the contractions of the heart. Sinus bradycardia, atrioventricular block, ventricular fibrillation, and even asystole may occur [1].

In particular, pressure on the extraocular muscle (EOM), intraorbital injections, hematoma, mechanical stimulation, ocular manipulations, pain, and similar stimulations might trigger or deteriorate OCR [2].

It has been reported that the incidence of OCR in strabismus surgery reaches 90% and decreases with age. In other words, pediatric patients are at a higher risk. Pediatric patients are also more vulnerable to the harmful effects of this reflex, as cardiac output depends more on the heart rate , OCR is reported to have a lethal potential for this patient group [3,4].

Many factors play an active role in the occurrence of this reflex during surgery including preoperative anxiety, topical anesthesia, hypoxia, hypercarbia, acidosis, young age, medication affecting vagal tone and the anesthetic agents used in the surgery [5,6].

Unfortunately, there is no gold standard method to prevent OCR. It is worth noting that the only definitive treatment is stopping stimulation. The reflex is terminated once the pressure on the eyeball is released or the surrounding tissues are removed. However, in case of trauma, it may be difficult to stop stimulation and pharmacological treatment may be required with close cardiac monitoring [7].

On the other hand, studies demonstrate the use of some anesthetic drugs in the prevention of OCR or limitation of its incidence [8,9]. The aim of this study was to determine the possible risk factors affecting the incidence of OCR in pediatric patients undergoing strabismus surgery.

MATERIAL and METHOD

The study was approved by the Clinical Research Ethics Committee (2018-206-10/10). Then medical records of pediatric patients who had undergone elective strabismus surgery between January 2015 and September 2018 were reviewed. Operations performed by only one surgeon were included in the study, and actual tension on the muscle hook was not specifically measured for all patients. Patients diagnosed with cardiovascular disease, on cardiovascular medication and with missing or inaccessible medical records were excluded from the study. The documentations of 86 pediatric patients were investigated for the study.

Although premedication was not routinely applied, if needed midazolam (0.05-0.15 mg kg^{-1} IV) was preferred. In the operation room, all patients were monitored with electrocardiography, pulse oximetry, capnography and noninvasive blood pressure measurement. Intravenous induction was performed with propofol (2-2.5 mg kg^{-1} IV) and fentanyl (1 µg kg^{-1} IV) and a single dose of rocuronium bromide (0.3-0.4 mg kg^{-1} IV). Rocuronium was not given to all patients. After induction of anesthesia, Laryngeal Mask Airway (LMA) or intubation was applied for securing the airway according to the anesthesiologist's decision. Anesthesia was maintained with sevoflurane 2-3% in oxygen 50% and nitrous oxide or in oxygen 50% and air together with remifentanil infusion.

The routine practice at our clinic in the event of an OCR involves alerting the surgeon first to discontinue the operation (relief of traction). Then, if the disruption of transmission persists despite assuring a sufficient depth of anesthesia, ventilation and oxygenation, then atropine (10-20 µg kg^{-1}) is administered intravenously. This is stated in the intraoperative follow-up documents.

Demographic data, duration of surgery, history of any previous strabismus surgery and possible development of OCR, anesthesia management, muscle relaxants and anesthetic drugs used for anesthesia induction and maintenance as well as airway management, the number of operated eyes, and also the muscle types of the patients were all recorded.

Statistical method

The data obtained were analyzed using IBM SPSS V23. Shapiro- Wilk test was used to check whether the quantitative data were suitable for normal distribution. The categorical data were analyzed with Pearson's chi-squared test. Binary logistic regression analysis was used to determine the independent risk factors affecting OCR. The quantitative data were presented as mean ±standard deviation (SD), median (min-max) values, whereas the categorical data were presented as frequency (percentage). The level of significance was accepted as $p<0.05$.

RESULTS

Out of a total of 92 pediatric patients who were initially selected, 86 were included in the study, 6 patients with incomplete medical records were excluded from the study. The mean age of the patients included in the study was 7.32±4.82 years. Forty-six (53.5%) female and 40 (46.5%), male patients were included in the study. Of these children, 12 (14%) had a chronic illness. The diagnoses were cerebral palsy in 8, asthma in 3, and hypothyroidism in 1 patient. The mean duration of surgery was calculated as 57.55±21.81 minutes. Table I shows the types of the muscles operated. 39.5% of these patients received preoperative premedication before management of anesthesia. It was found that propofol and fentanyl were used as the induction agents in 100% and a neuromuscular blocker in 43% of the patients. Airway safety was secured by a laryngeal mask in 84 patients, and only 2 patients were intubated. For the maintenance of anesthesia, sevoflurane in oxygen 50% and nitrous oxide (88.37%) and sevoflurane in oxygen 50% and air with remifentanil infusion (11.62%) were administered.

Table I. The operated muscle types

	n	%
Lateral rectus	13	15.1
Medial rectus	38	44.2
İnferior oblique	6	6.97
Medial + Lateral rectus	16	18.6
Superior oblique + Medial + Lateral rectus	4	4.7
İnferior oblique + Medial + Lateral rectus	2	2.3
İnferior oblique + Medial rectus	7	8.13
Total		100

During the surgery, OCR occurred in 29 (33.7%) patients. The lowest pulse rate was between 40 and 50 bpm. All patients who developed OCR received atropine (0.02 mg kg^{-1} IV). The mean age was 8.78±5.61 years in the patients with OCR and 7.0±4.51 years in the patients without OCR. Female patients had (n=15: 53.6%), and had not (n=31:53.4%), OCR. There was no significant difference between patients with and without OCR in terms of age and sex. It was found that OCR was significantly higher in the children who were not given a neuromuscular blocker drug or any premedication (0.039 and 0.017, respectively) (Tables II and III).

Table II. Patient - and surgery-related factors leading to the development of oculocardiac reflex (OCR)

	OCR (+) (n=29)	OCR (-) (n=57)	p
Age (years)	8.78±5.61	7.0±4.51	0.059
Sex (F/M) (n)	15/14	31/26	0.815
Chronic disease +/-	8/20	6/52	0,058
Operation time (min)	56.84±19.09	57.76±22.65	0.707
ASA I/II (n)	21/8	50/7	0.077
Premedication +/- (n)	7/22	27/30	0.017
NMB +/- (n)	8/21	29/28	0.039
Anesthesia maintenance S+$N_2$0/S+R	25/2	51/8	0.495
Previous strabismus surgery +/- (n)	3/16	13/54	0.727
Extraocular muscle type H/C/H+C (n)	24/3/2	43/3/11	0.512
Single eye/double eye	10/19	25/32	0.403

F/M: Female/Male, min: minute, ASA: American Society of Anesthesiologists, NMB: Neuromuscular Blocker, S: Sevoflurane, $N_2$0: Nitrous oxide, R: Remifentanil, H: Horizontal muscles, C: Cyclovertical muscles H+ C: Horizontal+Cyclovertical muscles

Table III. Regression analysis for the occurrence of oculocardiac reflex (OCR)

	OR (95% CI)	p
Age	1.083 (0.969-1.209)	0,16
Sex	0.794 (0.271-2.325)	0.674
Chronic disease	0.460 (0.065-3.234)	0.435
Operation time (min)	0.992 (0.966-1.018)	0.549
ASA	1.005 (0.157-6.439)	0.996
Premedication with BDZ	3.642 (1.134-11.693)	0.032
NMB usage	3.114 (1.021-9.501)	0.046
Previous strabismus surgery	0.699 (0.175-2.787)	0.612
Extraocular muscle type	2.111 (0.554-8.048)	0.274
Number of eyes	0.711 (0.225-2.251)	0.562

ASA: American Society of Anesthesiologists OR: Odds Ratio, CI: Confidence Interval, BDZ: Benzodiazepine, NMB: Neuromuscular Blocker

Refraining from using benzodiazepine in premedication (p=0.03) and neuromuscular blocker after induc-

tion (p=0.046) in pediatric patients was specified as being among independent risk factors. It was found that the risk of developing OCR increased 3.64 times in the patients who were not administered muscle relaxants and 3.11 times in those who were not given any premedication. The variables of chronic disease, previous history of strabismus surgery, number of eyes operated, age, sex, ASA score, duration of surgery and muscle type were not identified as risk factors (Tables II and III).

It was observed that intraoperative oxygenation and ventilation were maintained without any problems in all patients. The oxygen saturation (SpO_2) was in the range of 97-100%, and the end tidal carbon dioxide ($EtCO_2$) was between 29 and 37 mmHg.

DISCUSSION

In our study, administration of benzodiazepine (midazolam) for anxiolytic purposes and neuromuscular blocker (rocuronium 0.3-0.4 mg kg^{-1} IV) for induction of anesthesia in children was identified as a mean to reduce OCR. While the risk of OCR was 3.64 times higher in the children who were not given the neuromuscular blocker, it was observed that not administering preoperative benzodiazepine increased this risk 3.11 times.

The oculocardiac reflex is defined as more than a 20% decrease in the heart rate or occurrence of a new arrhythmia during traction of EOM in strabismus surgery [7]. The incidence of oculocardiac reflex varies between 14% and 90%, depending on the identification and evaluation method of OCR, the type of anesthesia, premedication and surgery applied, and the anesthetic agents that are being used [1,4,10,11]. In a study that included children and adult patients undergoing squint surgery, Gilani et al. [12] stated that the incidence rates of OCR were 10%, and 70% in the groups that had and had not received atropine for premedication, respectively.

In a study analyzing 106 instances of pediatric ophthalmic surgery, the incidence of OCR during strabismus surgery was found to be 65% (34/52). The study reported nonuse of any medication or local/locoregional anesthesia to prevent the oculocardiac reflex [13].

In our study, OCR was defined as a 20% reduction in the heart rate in comparison to the basal heart rate. We determined an OCR incidence of 33.7% in the pediatric patients, which was in line with the literature.

Spectral analysis of HR variability showed that parasympathetic activity increased between the ages of 3 and 6 years and then decreased from 6 to 15 years of age in healthy children [14]. In our study, although there was no significant difference in the OCR incidence between the ages from 1 to 6 years and ages from 7 to 15 years, the OCR incidence was seen to be quantitatively higher in 1-6 years of age compared to 7-15 years of age (57.1% vs 42.9%). In our opinion, this situation was associated with increased parasympathetic activity in 1-6 years of age group.

In a study investigating the effects of 4 different neuromuscular blockers (alcuronium, vecuronium, pancuronium and tubocurarine) on OCR in children, it was found that the incidence of OCR and arrhythmia was lower in the group that was administered alcuronium, a blocker with a stronger tachycardia effect [15]. Karanovic et al. [16] conducted a study with a total of 161 children aged between 3 and 10 years who had undergone medial rectus muscle surgery. They found that the incidence of OCR was 29% in the patients who received rocuronium (0.4 mg kg^{-1} IV) before intubation, 53% in those receiving succinylcholine and 44% in the control group. In our study, rocuronium was administered at a dose of 0.3-0.4 mg kg^{-1} IV, and the risk of OCR was found to be 3.64 times higher in those who were not given muscle relaxants. We think that this was due to the fact that rocuronium has a mild vagolytic effect [17].

Preoperative anxiety is common in children. Nearly 60% of young children undergoing surgery and anesthesia are reported to experience anxiety on significant levels [18]. This situation further alleviates hemodynamic instability and causes more anesthetic consumption during anesthesia. Yi et al. [19], on the other hand, stated that the depth of anesthesia affected OCR and inhibited OCR when target Bispectral index (BIS) values were kept between 40 and 50 in children who received sevoflurane anesthesia.

In a study using desflurane and BIS monitoring, deeper anesthesia was shown to be a protective

effect against OCR, and the type of stretched EOM appeared not to be important in patients with BIS values of <50 in pediatric strabismus surgery [20]. In their study, Jeon et al. [21] reported lower entropy values following anesthesia in the group that received midazolam for premedication.

In our study, we found that OCR was 3.11 times higher in the children who did not receive premedication with midazolam, which we attributed to the role of premedication in achieving the desired anesthesia depth. Increased anesthesia depth, in turn, affects the subcortical areas and prevents development of OCR by suppressing the nociceptive and autonomic reflexes.

Many studies have reported an increased incidence of OCR with medial rectus traction, compared to other ocular muscles [22,23]. However, there are also studies reporting that no specific extraocular muscle is associated with an increase in OCR in comparison to other ocular muscles [24,25]. Aletaha et al. [26] found that the incidence of OCR in cyclovertical muscle operations was higher than that in horizontal muscle operations in an adult population which they attributed to the fact that cyclovertical muscles are more difficult to expose and might be subject to higher compression in the process. In another study examining the medial rectus, inferior oblique and lateral rectus muscles, it was stated that the tension threshold value of the medial rectus muscle (60 g) was smaller than that of the inferior oblique muscle (128 g). As for operations on the lateral rectus muscle, the decrease in the heart rate was significantly less than that observed in the surgeries of other two muscles [27]. In our study, in the operations where the surgical intervention involved the medial rectus muscle only, the rate of OCR was 44.7%. The incidence rates of OCR were 50%, and 23.07% when the interventions included only the inferior oblique muscle and only the lateral rectus muscle, respectively. However, since our study included patients who had more than one muscle intervention in the same session, the type of muscle operated could not be used as a predictive factor.

In a retrospective study, it was reported that the first operated muscle was a significant risk factor for OCR occurrence in pediatric patients with two muscle surgeries who received intravenous atropine (0.01 mg kg^{-1}) for premedication and rocuronium (0.6 mg kg^{-1} IV) for induction [28]. We did not conclude that this was an important risk factor for OCR, because this information was not included in the intraoperative anesthesia form.

It is important to know the appropriate anesthetic agent in order to reduce OCR occurrence, as the incidence may differ with each agent used. In a study investigating the effects of sevoflurane and desflurane on OCR incidence in pediatric strabismus surgery, no significant difference was found between their incidence rates of OCR (26% and 28%, respectively). Furthermore, it was reported that the incidence of OCR was lower in children aged 2-10 years as compared to the 6-10 years [9]. In our study, sevoflurane was used for maintenance in all children, as a result the effect of two gases on OCR was not identified.

Arnold et al. [29] reported that the use of fast-acting opioids (fentanyl, sufentanil and remifentanil) in induction or early maintenance increased the extent of bradycardia in OCR that occurred with extraocular muscle tension. Moreover, they stated that OCR most commonly increased with remifentanil (36%), followed by sufentanil (29%) and fentanyl (24%).

In two studies comparing Sub-Tenon's block and intravenous fentanyl use following induction in pediatric strabismus and cataract surgeries, the incidence of OCR was found to be significantly higher in the fentanyl group [30,31]. In our study, all pediatric cases were administered fentanyl (1 mcg kg^{-1} IV) during induction, and only 10 patients received additional remifentanil infusion with sevoflurane. Two (20%) out of these 10 patients developed OCR.

We were not able to demonstrate the superiority of a particular medication or technique in induction and maintenance of anesthesia in our study. In our study, we thought that, despite remifentanil infusion, the occurrence of the oculocardiac reflex at a lower incidence than reported in the literature may have occurred because sevoflurane neutralizes the direct negative coronotropic effect and parasympathetic activation of remifentanil by suppressing vagal activity.

Controlled ventilation with pulse oximetry and monitorization of $EtCO_2$ are both recommended to prevent hypoxemia and hypercarbia, which are factors contributing to OCR. Many authors believe that hypoventilation supports development of OCR. However, there are also opposite views in the literature [1,32]. In our study, $EtCO_2$ in all cases ranged between 29 and 37 mmHg, and SpO_2 between 97 and 100%.

This study had some limitations. Firstly, the design of this study was retrospective. Secondly, we did not know the depth of anesthesia because BIS monitoring was not performed for all patients. The occurrence of OCR could be affected by various pharmacologic agents. Based on this information, we believe that prospective, and more extensive studies may be planned regarding this issue.

CONCLUSION

Factors causing the activation of OCR and measures to prevent its development should be known. We believe that the incidence of OCR may be lowered with multiple preventive measures such as use of muscle relaxants, premedication with benzodiazepine in strabismus surgeries.

Ethics Committee Approval: Zonguldak Bülent Ecevit University, Clinical (2018-206-10/10)
Conflict of Interest: None
Funding: None
Informed Consent: Retrospective study

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