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Effect of different anesthetic agents on oculocardiac reflex in pediatric strabismus surgery

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Abstract
Purpose. The oculocardiac reflex (OCR) occurs frequently during pediatric strabismus surgery. The aim of this study was to assess the effects of various anesthetic regimens on the incidence of OCR during the surgery.
Methods. Two hundred and eighty children, 1 to 9 years old, undergoing elective strabismus surgery, were randomly assigned to eight groups; ketamine–sevoflurane (KS), ketamine–desflurane (KD), ketamine–propofol (KP), ketamine–remifentanil (KR), midazolam–sevoflurane (MS), midazolam–desflurane (MD), midazolam–propofol (MP), and midazolam–remifentanil (MR). No premedication was given. Anesthesia was induced using ketamine 1 $mg \cdot kg^{-1}$ or midazolam 0.15 $mg \cdot kg^{-1}$ with 66% N_2O in O_2. Laryngeal mask airways (LMAs) were placed with rocuronium 0.5 $mg \cdot kg^{-1}$. Anesthesia was maintained with sevoflurane 2–3 vol. %, desflurane 5–6 vol. %, propofol 7–8 $mg \cdot kg^{-1} \cdot h^{-1}$, or remifentanil 0.75 $\mu g \cdot kg^{-1}$ over 1 min, followed by a continuous infusion of remifentanil 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with 66% N_2O in O_2. Heart rate (HR) was recorded during extraocular muscle (EOM) manipulation. OCR was defined as a reduction in HR of more than 20% induced by the traction of an EOM.
Results. In patients given ketamine, OCR occurred more frequently in the KP (65.7%) and KR (62.9%) groups than in the KD (29.4%) and KS (37.1%) groups ($P < 0.05$). In patients given midazolam, OCR occurred more frequently in the MP (54.3%) and MR (60.6%) groups than in the MD (36.4%) and MS (31.4%) groups ($P < 0.05$).
Conclusion. Propofol or remifentanil anesthesia was associated with a higher incidence of OCR during pediatric strabismus surgery than sevoflurane and desflurane anesthesia, when either ketamine or midazolam was used as an induction agent.

Key words Oculocardiac reflex · Strabismus surgery · Anesthetics

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Introduction

The oculocardiac reflex (OCR) is frequently encountered during strabismus surgery [1]. It is triggered by pressure in the globe and by traction on the extraocular muscles (EOMs), as well as by pressure on the conjunctiva or the orbital structures [2]. The incidence of OCR during ophthalmic surgery ranges from 32% to 90%, depending on the intensity of observation and the definition of arrhythmias. Although the most common manifestation of the OCR is sinus bradycardia, various types of arrhythmia, even asystole, may occur [1].

As anesthetics influence the OCR, there have been many studies about the incidence of OCR with various anesthetics. Sevoflurane is associated with a lower incidence of OCR than halothane or propofol [3]. The incidences of OCR during strabismus surgery with sevoflurane and desflurane in children were similar [4]. Ketamine for anesthetic induction resulted in a lower incidence of OCR than propofol when combined with sevoflurane for maintenance in children undergoing strabismus surgery [5]. Remifentanil enhanced the degree of bradycardia due to OCR as compared with sevoflurane during the surgery [6].

We designed this study to assess the effects of various anesthetic regimens on the incidence of OCR during pediatric strabismus surgery.

Patients and methods

We obtained approval from our institutional ethics committee and informed consent from the parents of all the children. Two hundred and eighty children between the ages of 1 and 9 years, American Society of Anesthesiologists (ASA) physical status I or II, scheduled to undergo elective inpatient strabismus surgery, were enrolled in this study. The surgery was performed by the same surgeon. Solid food or milk products were

Table 1. Demographic data

	Age (years)	Sex (F/M)	Weight (kg)	Height (cm)
Ketamine				
D	4.7 ± 1.8	21/13	19.0 ± 5.5	107.2 ± 14.8
S	4.9 ± 2.1	21/14	19.8 ± 5.7	112.3 ± 13.2
P	4.9 ± 1.8	18/17	21.4 ± 5.1	108.9 ± 20.3
R	5.4 ± 2.0	18/17	21.9 ± 5.7	113.7 ± 13.9
Midazolam				
D	5.3 ± 1.8	12/21	21.4 ± 4.1	115.2 ± 9.5
S	5.2 ± 1.9	23/12	19.5 ± 4.5	111.1 ± 13.7
P	5.3 ± 1.7	17/18	21.0 ± 5.1	115.2 ± 10.1
R	4.6 ± 2.1	16/17	19.0 ± 7.0	106.9 ± 14.1

Values are means ± SD
D, desflurane; S, sevoflurane; P, propofol; R, remifentanil

allowed until 6 h before the surgery. Clear liquids were allowed until 3 h before the surgery. Peripheral intravenous cannulation was done in each patient's room, under topical anesthesia with EMLA cream (lignocaine-prilocaine; AstraZeneca, Karlskoga, Sweden). No premedication was given. The patients were randomly assigned to one of eight groups; ketamine–sevoflurane (KS), ketamine–desflurane (KD), ketamine–propofol (KP), ketamine–remifentanil (KR), midazolam–sevoflurane (MS), midazolam–desflurane (MD), midazolam–propofol (MP), and midazolam–remifentanil (MR) by parents picking one of 280 cards marked KS, KD, KP, KR, MS, MD, MP, or MR from a closed box.

On arriving in the operation room, all patients were monitored with electrocardiography, pulse oximetry, noninvasive blood pressure (BP), and capnography. Anesthesia was induced with ketamine 1 $mg \cdot kg^{-1}$ or midazolam 0.15 $mg \cdot kg^{-1}$ with 66% N_2O in O_2. Laryngeal mask airways (LMA) were placed with rocuronium 0.5 $mg \cdot kg^{-1}$. Anesthesia was maintained with sevoflurane 2–3 vol. %, desflurane 5–6 vol. %, propofol 7–8 $mg \cdot kg^{-1} \cdot h^{-1}$ or remifentanil 0.75 $\mu g \cdot kg^{-1}$ over 1 min, followed by a continuous infusion of remifentanil 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with 66% N_2O in O_2. Intermittent positive-pressure ventilation was used to maintain end-tidal carbon dioxide pressure (Et_{CO_2}) between 30 and 35 mmHg. Peripheral oxygen saturation (Sp_{O_2}) was maint ained above 98% with tidal volume set at 10 $ml \cdot kg^{-1}$ (Cato; Drägerwerk, Lübeck, Germany). The concentration and infusion rate of each anesthetic agent were adjusted according to the hemodynamic responses to surgery. Heart rate (HR) was recorded before EOM manipulation (pre-tension HR) and after EOM manipulation (tension HR). The OCR was defined as a more than 20% decrease in HR from pre-tension HR, or the appearance of arrhythmias. Treatment for OCR consisted of relief of traction. If HR did not return to baseline or if severe bradycardia (HR < 60 $beats \cdot min^{-1}$) developed, intravenous atropine 0.01 $mg \cdot kg^{-1}$ was given.

After the surgery was completed, neuromuscular blockade was antagonized with neostigmine 0.05 $mg \cdot kg^{-1}$ and glycopyrrolate 0.01 $mg \cdot kg^{-1}$ and all anesthetic drugs were discontinued. The LMA was removed when the patient breathed spontaneously. The children stayed in the recovery room for 1 h and were then discharged to the ward.

Statistical analysis was performed using SPSS for Windows version 12.0 (SPSS, Chicago, IL, USA). Data are expressed as means ± SD or as numbers (%). Differences in gender, type of manipulated EOM, and incidence of OCR were tested using Pearson's χ^2 test or Fisher's exact test. Statistical significance was considered to be $P < 0.05$.

Results

Data on 5 children were excluded from analysis because of protocol violations, so data on 275 children were analyzed. There were no differences in demographic data among the groups (Table 1). No problems with ventilation occurred during anesthesia, and Sp_{O_2} and Et_{CO_2} were well maintained. Severe hypotension or bradycardia requiring treatment did not occur during the anesthesia, except in the event of OCR due to EOM manipulation.

The overall incidence of OCR was 47.3% (130/275). The incidence of OCR in each group is shown in Table 2. In patients given ketamine, OCR occurred more frequently in the KP (65.7%) and KR (62.9%) groups than in the KD (29.4%) and KS (37.1%) groups ($P < 0.05$). In patients given midazolam, OCR occurred more frequently in the MP (54.3%) and MR (60.6%) groups than in the MD (36.4%) and MS (31.4%) groups ($P < 0.05$).

In most patients demonstrating OCR, HR returned to the baseline value after the release of the EOM. Atropine was given to three patients in the KP group, one patient in the KR group, one patient in the MP

group, and four patients in the MR group. There was one transient sinus arrest in a patient in the MR group, who recovered fully after the surgery.

The incidences of OCR were similar in patients administered ketamine or midazolam and did not differ significantly. And the incidence of OCR according to the type of manipulated EOM was not significantly different among the groups. Neither the patient's age nor their sex had an influence on the incidence of OCR, but the anesthesia maintenance agent did have a significant influence on this incidence (Table 3).

Discussion

The OCR is important as it may cause bradycardia, nodal rhythm, ectopic beats, ventricular fibrillation, or asystole. A variety of methods such as normoxia, normocapnia, premedication using atropine or glycopyrrolate, and adequate anesthetic depth have been used to prevent the OCR; however, none of these methods has been found to be consistently effective.

Anticholinergic premedication can decrease the incidence of OCR, but the practice remains controversial. It is suggested that the cardiac response may be attenuated by a timely prestimulus IV dose of anticholinergics [7]. Braun et al. [8] reported that anticholinergic agents for premedication did not decrease the incidence of OCR significantly. Misurya et al. [9] reported that atropine premedication and retrobulbar block with 2% lidocaine were highly effective for the prevention of OCR. Intravenous atropine may induce ventricular premature beats, bigeminy, and tachycardia that may outlast the OCR [1,10]. If atropine is given during vagal stimulation, there is the risk of converting sinus bradycardia into premature ventricular contractions and runs of bigeminy. Furthermore, if it is given during bradycardia, particularly in infants, the cardiac output is reduced and the drug takes longer to produce its cardioaccelerating effect [11]. In our hospital, anticholinergic premedication for pediatric patients has not been used in a routine manner.

In the present study, the incidence of OCR during anesthesia for pediatric strabismus surgery was greater with propofol or remifentanil than with sevoflurane or desflurane. Sevoflurane anesthesia led to less frequent OCR in pediatric strabismus surgery [3,4]. Sevoflurane depresses vagal activity, so it could, theoretically, lead to less pronounced bradycardia on EOM manipulation. This agent also led to fewer dysrhythmias in children undergoing strabismus surgery than halothane anesthesia [4].

Desflurane is the only agent that invariably increases sympathetic activity, so it contributes to raising the HR [12]. The most common manifestation of OCR is sinus bradycardia, which may be less likely to occur with increased sympathetic activity. But, in steady-state anesthesia with desflurane, vagal inhibition is a major factor for increasing HR rather than increasing sympathetic outflow [13]. The OCR occurs in the middle of the operation; it occurs at least 20 min after the induction of anesthesia when the surgeon manipulates an EOM. In the present study, the incidence of OCR was similar in patients administered sevoflurane or desflurane and did not differ significantly. These results match those reported in the study by Oh et al. [4].

There is an additional risk of bradycardic events during surgery with propofol anesthesia. Propofol is very likely to increase bradycardic events compared with other anesthetic regimens. It has the potency to increase the incidence of bradycardia by a central

Table 2. Incidence of the oculocardiac reflex (OCR) in each group

Ketamine	D (n = 34)	10 (29.4)
	S (n = 35)	13 (37.1)
	P (n = 35)	23 (65.7)*
	R (n = 35)	22 (62.9)*
Midazolam	D (n = 33)	12 (36.4)
	S (n = 35)	11 (31.4)
	P (n = 35)	19 (54.3)*
	R (n = 33)	20 (60.6)*
	275	130 (47.3)

*P < 0.05 compared with the corresponding sevoflurane group for patients administered ketamine or midazolam, respectively
Values are numbers (%)
D, desflurane; S, sevoflurane; P, propofol; R, remifentanil

Table 3. Factors related to incidence of the oculocardiac reflex (OCR)

	No OCR (n = 145)	OCR (n = 130)	P value
Age (years)	5.14 ± 1.97	4.94 ± 1.80	0.36
Sex (F/M; n)	77/68	69/61	1.00
I/L/M/S (n)	3/115/22/5	8/93/23/6	0.27
K/M (n)	71/74	68/62	0.63
D/S/P/R (n)	45/46/28/26	22/24/42/42	<0.01

Values are numbers (%)
I, inferior oblique; L, lateral rectus; M, medial rectus; S, superior oblique; K, ketamine; M, midazolam; D, desflurane; S, sevoflurane; P, propofol; R, remifentanil

sympathetic effect and vagal stimulation [14]. It increases the incidence of OCR in pediatric strabismus surgery [15]. Many investigators have used anticholinergic drugs such as atropine or glycopyrrolate to prevent the occurrence of bradycardic reactions due to the OCR during strabismus surgery with propofol anesthesia [16–19]. With or without atropine, propofol anesthesia led to a significantly greater incidence of OCR than isoflurane or sevoflurane anesthesia [3,17,18,20]. It led to a high incidence of OCR even after prophylactic high-dose atropine [17]. In the present study, the incidence of OCR during propofol anesthesia was much greater than that in the sevoflurane or desflurane groups.

Remifentanil is a potent synthetic opioid with an ultrashort duration of action, and a context-insensitive half life, and is used for pediatric anesthesia [6,21]; remifentanil itself can cause bradycardia [22]. In the present study, a bolus of remifentanil 0.75 $\mu g \cdot kg^{-1}$ given over 1 min, followed by a continuous infusion of remifentanil at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ provided hemodynamic stability during anesthesia. Dershwitz et al. [23] noted that the 50% effective dose (ED50) for remifentanil to abolish all surgical responses was 0.52 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (95% confidence interval of 0.16–0.88) in adults. Subsequent pharmacokinetic data for remifentanil in children (although preliminary) suggest that the drug's pharmacokinetic profile is, indeed, similar to that observed in adults [24]. Thus, our infusion rate of remifentanil is appropriate for the maintenance of anesthesia during pediatric strabismus surgery. In a study by Davis et al. [18], a bolus dose of remifentanil of 1 $\mu g \cdot kg^{-1}$ and a continuous infusion at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were well tolerated in children undergoing strabismus surgery, without significant changes in HR or BP. Davis et al. [18] used prophylactic atropine and found out that bradycardia due to OCR with remifentanil anesthesia was more frequent (12%) than that with alfentanil (0%), propofol (0%), and isoflurane (5%). In a study by Chung et al. [6], the incidence of OCR was more frequent with remifentanil anesthesia than with sevoflurane anesthesia, regardless of the induction agent used.

Ketamine seems to protect against the parasympathetic activation induced by the OCR [19, 20]. In view of the hypothesis that, as the OCR consists of an initial parasympathetic phase, followed by a sympathetic phase, ketamine anesthesia may, by increasing sympathetic tone, counteract vagal stimulation during the first phase of the OCR [8,20]. Choi et al. [19] reported that single-bolus IV ketamine for anesthetic induction was associated with a decreased incidence of OCR during pediatric strabismus surgery. Ketamine may reduce the incidence of OCR in combination with sevoflurane, which may have sympathomimetic effects and show inhibition of the parasympathetic reflex [25]. In the study by Choi et al. [19], the incidence of OCR after a single bolus of IV ketamine was much lower than that shown in our present study. This may have been the result of both the short duration of their surgery, which contributed to the lower likelihood of OCR, and the differences between their study and ours in the definitions and the methods used for measuring OCR. But in the present study, ketamine was not a factor that influenced the incidence of OCR (Table 3). Hahnenkamp et al. [20] reported that ketamine anesthesia was associated with the least hemodynamic changes induced by OCR during pediatric strabismus surgery. And they recommended that a combination of ketamine as an analgesic and a volatile anesthetic as a hypnotic agent may form a useful combination for strabismus surgery. In that study, a relatively high dose of ketamine (10–12 $mg \cdot kg^{-1} \cdot h^{-1}$) was administered for the induction and maintenance of anesthesia. Although such a relatively high dose of ketamine may reduce the incidence of OCR, it is very likely to result in many side effects, such as confusion, disorientation, or vivid dreams [26]. In the present study, ketamine had little effect on the incidence of OCR compared with midazolam. So we agree with Schaller's [27] opinion that ketamine cannot totally prevent the OCR. And we need more studies with ketamine and midazolam in pediatric strabismus surgery.

The limitation of the present study is that the doses of anesthetics used may not have been comparable. It was impossible to determine whether the anesthetic techniques resulted in equal depths of anesthesia during the stimulation. To assure that anesthetic depth was as similar as feasible, we considered using bispectral index (BIS) monitoring. But there have been many reports that the BIS value was not correlated with the anesthetic state in ketamine anesthesia [28]. In the present study, we adjusted the anesthetic doses based on the hemodynamic response to surgery. There were no additional problems with the maintenance of anesthesia, but the levels of anesthesia in the different groups might not have been equivalent.

In conclusion, we found that propofol or remifentanil anesthesia was associated with a higher incidence of the OCR than sevoflurane or desflurane anesthesia, and that ketamine had little effect on the OCR.

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References

1. Donlon JV, Doyle DJ, Feldman MA. Anesthesia for eye, ear, nose and throat surgery. In: Miller RD, editor. Miller's anesthesia. 6th ed. Philadelphia: Churchill Livingstone; 2006. p. 2527–55.
2. McGoldrick KE, Gayer S. Anesthesia and the eye. In: Barash PG, Cullen BF, Stoelting RK, editors. Clinical anesthesia. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 974–96.

3. Gürkan Y, Kiliçkan L, Toker K. Propofol-nitrous oxide versus sevoflurane-nitrous oxide for strabismus surgery in children. Paediatr Anaesth. 1999;9:495–9.
4. Oh AY, Yun MJ, Kim HJ, Kim HS. Comparison of desflurane with sevoflurane for the incidence of oculocardiac reflex in children undergoing strabismus surgery. Br J Anaesth. 2007;99: 262–5.
5. Gupta N, Kumar R, Kumar S, Sehgal R, Sharma KR. A prospective randomised double blind study to evaluate the effect of peribulbar block or topical application of local anaesthesia combined with general anaesthesia on intra-operative and postoperative complications during paediatric strabismus surgery. Anaesthesia. 2007;62:1110–3.
6. Chung CJ, Lee JM, Choi SR, Lee SC, Lee JH. Effect of remifentanil on oculocardiac reflex in paediatric strabismus surgery. Acta Anaesthesiol Scand. 2008;52:1273–7.
7. Gayer S, Tutiven J. Anesthesia for pediatric ocular surgery. Ophthalmol Clin North Am. 2006;19:269–78.
8. Braun U, Feise J, Mühlendyck H. Is there a cholinergic and an adrenergic phase of the oculocardiac reflex during strabismus surgery? Acta Anaesthesiol Scand. 1993;37:390–5.
9. Misurya VK, Singh SP, Kulshrestha VK. Prevention of oculocardiac reflex (O.C.R) during extraocular muscle surgery. Indian J Ophthalmol. 1990;38:85–7.
10. Mirakur RK, Jones CJ, Dundee JW, Archer DB. Intramuscular or intravenous atropine or glycopyrrolate for prevention of OCR in children during squint surgery. Br J Anaesth. 1982;54:1059–63.
11. Blanc VF. Atropine and succinylcholine: beliefs and controversies in paediatric anaesthesia. Can J Anaesth. 1995;42:1–7.
12. Ebert TJ, Perez F, Uhrich TD, Deshur MA. Desflurane-mediated sympathetic activation occurs in humans despite preventing hypotension and baroreceptor unloading. Anesthesiology. 1998;88: 1227–32.
13. Picker O, Schwarte LA, Schindler AW, Scheeren TW. Desflurane increases heart rate independent of sympathetic activity in dogs. Eur J Anaesthesiol. 2003;20:945–51.
14. Tramèr MR, Moore RA, McQuay HJ. Propofol and bradycardia: causation, frequency and severity. Br J Anaesth. 1997;78: 642–51.
15. Snellen FT, Vanacker B, Van Aken H. Propofol-nitrous oxide versus thiopental sodium-isoflurane-nitrous oxide for strabismus surgery in children. J Clin Anesth. 1993;5:37–41.
16. Watcha MF, Simeon RM, White PF, Stevens JL. Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. Anesthesiology. 1991;75:204–9.
17. Tramèr MR, Sansonetti A, Fuchs-Buder T, Rifat K. Oculocardiac reflex and postoperative vomiting in paediatric strabismus surgery. A randomised controlled trial comparing four anaesthetic techniques. Acta Anaesthesiol Scand. 1998;42:117–23.
18. Davis PJ, Lerman J, Suresh S, McGowan FX, Coté CJ, Landsman I, Henson LG. A randomized multicenter study of remifentanil compared with alfentanil, isoflurane, or propofol in anesthetized pediatric patients undergoing elective strabismus surgery. Anesth Analg. 1997;84:982–9.
19. Choi SH, Lee SJ, Kim SH, Kim JH, Kwon HH, Shin YS, Lee KY. Single bolus of intravenous ketamine for anesthetic induction decreases oculocardiac reflex in children undergoing strabismus surgery. Acta Anaesthesiol Scand. 2007;51:759–62.
20. Hahnenkamp K, Hönemann CW, Fischer LG, Durieux ME, Muehlendyck H, Braun U. Effect of different anaesthetic regimes on the oculocardiac reflex during paediatric strabismus surgery. Paediatr Anaesth. 2000;10:601–8.
21. Davis PJ, Cladis FP. The use of ultra-short-acting opioids in paediatric anaesthesia: the role of remifentanil. Clin Pharmacokinet. 2005;44:787–96.
22. Tirel O, Chanavaz C, Bansard JY, Carré F, Ecoffey C, Senhadji L, Wodey E. Effect of remifentanil with and without atropine on heart rate variability and RR interval in children. Anaesthesia. 2005;60:982–9.
23. Dershwitz M, Randel GI, Rosow CE, Fragen RJ, Connors PM, Librojo ES, Shaw DL, Peng AW, Jamerson BD. Initial clinical experience with remifentanil, a new opioid metabolized by esterases. Anesth Analg. 1995;81:619–23.
24. Davis PJ, Ross A, Stiller RL, Muir K, McGowan FX, Gupta SK, Margolis J, Greeley WJ. Pharmacokinetics of remifentanil in anesthetized children 2–12 years of age. Anesth Analg. 1995;80: S93.
25. Yamamura T, Kimura T, Furukawa K. Effects of halothane, thiamylal, and ketamine on central sympathetic and vagal tone. Anesth Analg. 1983;62:129–34.
26. White PF, Way WL, Trevor AJ. Ketamine: Its pharmacology and therapeutic uses. Anesthesiology. 1982;56:119–36.
27. Schaller BJ. Ketamine and decrease of oculocardiac reflex. Acta Anaesthesiol Scand. 2008;52:446.
28. Lee JY, Moon SH, Chung HS. Bispectral index changes during anesthesia induction with ketamine in children. Korean J Anesthesiol. 2005;49:663–6.