ORIGINAL RESEARCH

Ketamine versus propofol for strabismus surgery in children

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Purpose: To compare the effects of intravenous infusion of ketamine and propofol anesthesia in children undergoing strabismus surgery.

Methods: Sixty pediatric patients aged 4–11 years were enrolled for the study. Patients in Group K were infused ketamine 1–3 mg/kg/hr (n = 30) and patients in Group P were infused with propofol 6–9 mg/kg/hr (n = 30). After giving fentanyl 1 μg/kg and rocuronium bromide 0.5 mg/kg, patients were intubated.

Results: The consumption of anesthetics ($P = 0.0001$) and antiemetics ($P = 0.004$), the incidence of oculocardiac reflex ($P = 0.02$) in Group K were significantly lower than in Group P. The recovery time ($P = 0.008$), postoperative agitation score ($P = 0.005$), Face Pain Scale ($P = 0.001$), Ramsay Sedation Score ($P = 0.01$) during awakening and at postoperative 30th min ($P = 0.02$) in Group K were significantly lower than in Group P. The postoperative agitation score during awakening was significantly lower than the preoperative values in Group K ($P = 0.0001$).

Conclusions: The infusion of ketamine is more advantageous than the infusion of propofol in children for use in strabismus surgery.

Keywords: ketamine, propofol, pediatrics, strabismus, surgery

Introductıon

Strabismus surgery may be associated with significant postoperative pain. Conjunctiva is the main source of this pain. Anxiety induces distress during the procedure, particularly for children who require repeated procedures.[2] Postoperative nausea and vomiting (PONV) for strabismus surgery[3] has an incidence of 20%–30%. As PONV causes distress for children, it is important to provide safe and effective analgesia. This pain may be treated with opioids, but PONV, which can be a major morbidity factor after strabismus surgery,[1] may limit their use. Various methods have been used together with antiemetics to diminish PONV.[4,5] However, there is no consensus on the choice of method.[6]

The incidence of the oculocardiac reflex (OCR) during strabismus has been variously reported as 14% to 90%, depending on the premedication, anesthetic agent, and the definition of OCR.[7] OCR occurs through the trigeminovagal reflex arc and can be triggered by mechanical stimulation such as pressure on the eye, intraorbital injections or hematomas and especially by traction on extraocular muscles.[8] 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 them has been found satisfactory.[9]

Propofol and ketamine are sedative and hypnotic anesthetic agents.[10,11] Propofol has a pharmacokinetic profile leading to rapid induction and recovery times with

minimal postoperative confusion.[10,12] Ketamine anesthesia is associated with the relatively rapid onset of action and fast recovery and least hemodynamic changes induced by OCR during strabismus surgery in pediatric patients.[11] As there are currently no published data comparing intravenous infusion of propofol and ketamine without using volatile agents, we aimed to compare propofol and ketamine with a special emphasis on the incidence of pain, agitation, sedation, OCR, PONV, hemodynamics and consumption of anesthetics during strabismus surgery in children.

Methods

The study was performed in accordance with the most recent version of the Helsinki Declaration. Following approval from the institutional review board, written informed consent was obtained from the patients' families. The study group comprised 60 patients (American Society of Anesthesiologists [ASA] physical status ≤ I) at the Medical Faculty Ethical Committee of Gaziantep University from February through August 2009. The patients were aged 5 to 11 years and were from the day-surgery hospital of the department of Anesthesiology and Reanimation of Gaziantep University School of Medicine.

Patients excluded include: those with ASA physical status greater than I; those who were younger than 5 years or older than 11 years; those who had hypertension, psychiatric disorders, drug allergy, cardiovascular and clotting disorders, or peptic ulcers; or those whose families did not approve inclusion. Each patients' family was informed about the application. Patients were assigned to 1 of 2 study groups using a computer-generated random number table: Group ketamine (Group K, n = 30) and group propofol (Group P, n = 30). Ketamine was prepared with isotonic saline solution in unlabeled, impermeable, red 50 mL syringe. Propofol 1% was prepared in unlabeled, impermeable, red 50 ml syringe by an assistant for intravenous infusion.

After the patients had been taken to the surgery room, standard monitors including electrocardiography, mean arterial pressure, end-tidal CO_2 and pulse oximetry were used. A 22-gauge cannula was inserted into a vein in the dorsum of the hand and saline was infused at a rate of 3 mL/kg/h. No patient was premedicated. After preoxygenation, with 6 L/min O_2, ketamine 1 mg/kg or propofol 3 mg/kg was given intravenously over 60 seconds by an anesthesiologist who was blind to the study. Both study solutions were prepared with isotonic saline solution in unlabeled, impermeable, red 50 mL-syringe. After administrating fentanyl 1 µg/kg (fentanyl citrate 5 ampoules, 0.05 mg/mL);

B. Braun Melsungen AG, Berlin, Germany, and rocuronium bromide ([10 mg/mL]; Esmeron, Organon, Oss Holland) 0.5 mg/kg the patients were intubated. Anesthesia was maintained with intravenous infusion of ketamine or propofol with 50% oxygen and 50% air at 6 L/min. Patients in Group K were infused with ketamine hydrochloride (Ketalar; flacon, 50 mg/mL, Ketalar®; Pfizer Ortakoy-Istanbul) at a rate of 1–3 mg/kg/hr. Patients in Group P were infused intravenous propofol 6–9 mg/kg/hr (propofol 1% fresenius, ampoules, 10 mg/mL). All procedures were performed by the same surgeon. Before the traction of extraocular muscle began, the anesthesiologist had atropine immediately available. During the traction, the minimal heart rate was recorded. If the heart rate decreased from the basal heart rate by 20% beats/min,[13] the anesthesiologist asked the surgeon to release the extraocular muscle. He injected 0.01 mg/kg of atropine intravenously if bradycardia did not improve. The hemodynamics were recorded at the measurement times such as intubation, incision, operation, extubation, and postextubation periods. Neuromuscular blockade was reversed.

Recovery time was recorded as the time from the cessation of anesthetic infusion to obtaining verbal communication. The duration of surgery was accepted as the time from incision to complete hemostazis. The duration of mental orientation was recorded as the time taken from the end of intravenous anesthetic administration until responding to two orientation questions correctly (Where are you, who am I). Intravenous anesthetics were stopped 5 minutes before ending the operation and extubation was performed. The number of OCR, the consumption (mg) of ketamine and propofol during surgery was recorded. Postoperative nausea and vomiting were evaluated via numeric rank score (NRS): 0 = no nausea; 1 = vomiting once; 2 = vomiting twice or more times.[1] The evaluation of postoperative pain was performed using Faces Pain Scale (FPS),[14] The FPS criteria used in this study were adapted from the FPS in order to make it possible to score on the widely accepted 0–10 metric.[14,15] Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so 0 = no pain and 10 = very much pain. In addition, Ramsay Sedation Score (RSS) was recorded on a numerical scale; 1 = anxiety and completely awake, 2 = completely awake, 3 = awake but drowsy, 4 = asleep but responsive to verbal commands, 5 = asleep but responsive to tactile stimulus, and 6 = asleep and not responsive to any stimulus. The preoperative and postoperative agitation (n, %) were evaluated using an emergence agitation (behavior score) score (1 = sleeping, 2 = awake and calm, 3 = irritable and crying, 4 = inconsolable crying, 5 = severe restlessness and

disorientation purposelessly wanting to get out of the bed).[16] As assessment of pain in younger children is difficult because of their limited understanding and verbal ablities, the evaluations of FPS, RSS, agitation score were performed with the help of children's parents during awakening. At the end of the operation, the satisfaction score of the surgeon was assessed according to the following numeric scale: 4 = excellent (no complaint from surgeon); 3 = good (minor complaint without any need for supplemental anesthetics); 2 = moderate (due to the small motion of ocular globe back, which required supplemental anesthetics); 1 = unsuccessful (continuous ocular motion bothering the surgeon).

Two observers performed the data collection. The first observer performed the study. The second observer who was blind to the study, evaluated and recorded the data. Nausea and vomiting were treated with trimetobenzamid HCl (Emedur®; 150 mg, Sanofi Synthelabo, ampoule). Nonopioid analgesic (metamizole) was given the patients who had FPS > 3 after operation. Patients were discharged from the hospital within the first 4 hours after surgery if: their motor–mental functions had returned completely; they had no bleeding, nausea, or vomiting; and they could be fed.

Statistical methods

The results of the study were evaluated using the SPSS (Version 15.0 for Windows; SPSS Inc., Chicago, IL) statistical analysis package. Among the groups, age, weight, recovery time, heart rate, mean arterial blood pressure, the consumption of anesthetics and antiemetics, anesthesia time were compared using independent sample *t*-test. The incidence of oculocardiac reflex, postoperative agitation score, FPS, RSS the incidence of OCR, were compared using the Kruskal–Wallis test. Data were presented as mean ± standard deviation (SD) or median (interquartile ranges) values or n (%). Statistical significance was reported when the *P* value was <0.05. After the power analysis according to the consumption of drug, we found the effect size 10 (alpha = 0.05, actual power = 0.98, delta = 4.0).

Results

The demographic characteristics (age, body mass index [BMI], gender), duration of surgery, duration of mental orientation, the number of the patients with agitation score < 4 were similar between the groups (Table 1).

Recovery times in Group K was significantly shorter than in Group P (*P* = 0.008, Table 1). The consumption of ketamine and propofol were 53.3 ± 19.3 mg in Group K and 180.8 ± 79.6 mg in Group P, respectively. The consumption

Table 1 Demographic data: recovery times; duration of surgery; mental orientation; agitation score; consumption of anesthetics and antiemetics

Demographic data	Group K (n = 30)	Group P (n = 30)	*P*
Age (yr)	7.7 ± 3.1	6.9 ± 3.0	0.2
Weight (kg)	27.5 ± 7.7	24.8 ± 7.0	0.1
Body mass index (kg/m²)	15.5 ± 1.2	15.3 ± 1.5	1.0
Gender (M/F)	11/19	12/18	0.2
Recovery times (min)	8.5 ± 4.1*	11.1 ± 3.0	0.008
Duration of surgery (min)	55.8 ± 19.3	54.6 ± 18.0	0.1
Duration of mental orientation (min)	38.8 ± 8.0	39.0 ± 9.6	0.9
The patients with agitation score <4 during postoperative 1-hour-period (n) (%)	14 (46)	11 (36)	0.3
The consumption of anesthetics (mg)	53.6 ± 19.6*	185.8 ± 78.6	0.0001
The consumption of antiemetic (Emedur, mg, amp)	5.0 ± 27.3*	20.0 ± 51.8	0.004

Notes: Data are presented as mean ± SD or n (%), n = 30, NS: variation is not significant, *P < 0.05 when compared with Group P

of anesthetic and antiemetic drugs (Emedur) in Group K were significantly lower than in Group P (*P* = 0.0001, *P* = 0.004, respectively; Table 1).

Nausea and vomiting was observed in 1 patient in Group K and in 4 patients in Group P. Postoperative NRS, sore throat, the number of patients required analgesic in postoperative 1-hour period, the satisfaction of surgeon during procedure were similar between the groups (Table 2).

The postoperative agitation score was significantly lower than the preoperative agitation score in Group K (*P* = 0.0001). The agitation score in Group K was significantly lower than in Group P during awakening (*P* = 0.005). The time of intraoperative OCR (*P* = 0.02) and FPS (*P* = 0.001) during awakening in Group K were significantly lower than in Group P. The RSS in Group K was significantly higher than in Group P during awakening (*P* = 0.01) and postoperative 60th minute (*P* = 0.02, Table 2).

The heart rate in Group K was significantly higher than in Group P during intubation, incision, extubation, and after extubation periods (*P* < 0.05, Figure 1). The mean arterial blood pressure in Group K was significantly higher than in Group P during intubation, incision, operation, extubation, and after extubation periods (*P* < 0.05, Figure 2). The increases in heart rate and mean arterial blood pressure disappeared in a few minutes without any treatment. Three patients in Group P were administered atropine 0.01 mg/kg to treat persistant bradycardia.

Table 2 Scores and analgesic requirements of the groups

	Group K	Group P	P
The time of oculocardiac reflex (OCR) (num)	9*	25	0.02
Preoperative agitation score	5.0000	5.500	0.4
Postoperative agitation score during awakening	1.0000*+	1.0000	0.005
Faces Pain Scale during awakening	2.0000*	5.0000	0.001
Ramsay Sedation Score during awakening	5.0000*	5.0000	0.01
Ramsay Sedation Score at postoperative 60th min	4.0000*	3.0000	0.02
Postoperative (numeric rank score) (50th median)	0.4000*	2.0000	0.002
Postoperative sore throat (n) (%)	8 (26.6)	12 (40)	0.2
The analgesic requirement during 1-hour postoperative period (n) (%)	6 (20)	9 (30)	0.3
The satisfaction score of surgeon during procedure	1.0000	1.0000	0.7

Notes: Data are presented as 50th (median) or num, n = 30, NS: variation is not significant, *$P < 0.05$ when compared with Group P, +$P < 0.05$ when compared with the postoperative agitation score with preoperative values

Discussion

The main findings of this paper indicate that infusion of ketamine is more effective than intravenous infusion of propofol, in decreasing the consumption of anesthetics, antiemetics, the incidence of OCR, FPS, agitation score, and shortening the recovery time of children undergoing strabismus surgery. Furthermore, ketamine infusion provides a higher grade of sedation.

In this study, surgical procedures, which were performed by the same surgeon, were similar regarding pain stimuli. The surgical procedures, the duration of surgery, the number of muscles operated were also similar between the groups.

Strabismus surgery is performed to restore binocular single vision and for cosmetic reasons (extensively in childhood). There are some undesired effects of the surgery such as postoperative pain,[3] anxiety, agitation,[17] PONV, and OCR.[13,18] These effects are the most frequent complications secondary to anesthesia, and leading causes for distress in patients recovering from general anesthesia.[19,20] PONV adds to the expense of care due to the cost of anti-emetic drugs and prolonged stay in the recovery room.[21]

Propofol is an intravenous sedative-hypnotic agent with amnestic properties that causes loss of consciousness reliably. It provides rapid onset of action and dose-dependent sedative effect and a smooth recovery without dysphoria. It also has antiemetic and amnestic properties. Propofol inhibits N-methyl-D-aspartate (NMDA)-receptors in hippocampal neurons and this may have contributed to the positive effects on the mood state after operation.[22] As there is a risk for accumulation in preterms and in the first two weeks of postnatal life, propofol clearance depends on postnatal age.[23] Propofol infusion syndrome has to be kept in mind if propofol is used for anesthesia at doses greater than 4 mg/kg/h of longer than 48 hours in especially pediatric patients.[24]

Ketamine, a recently launched S-isomer of ketamine, reportedly enhances analgesia greater than the racemic mixture.[25] Ketamine has intrinsic analgesic and amnestic properties and protects airway reflexes.[26,27] Ketamine activity has been suggested to be a result of the NMDA receptor
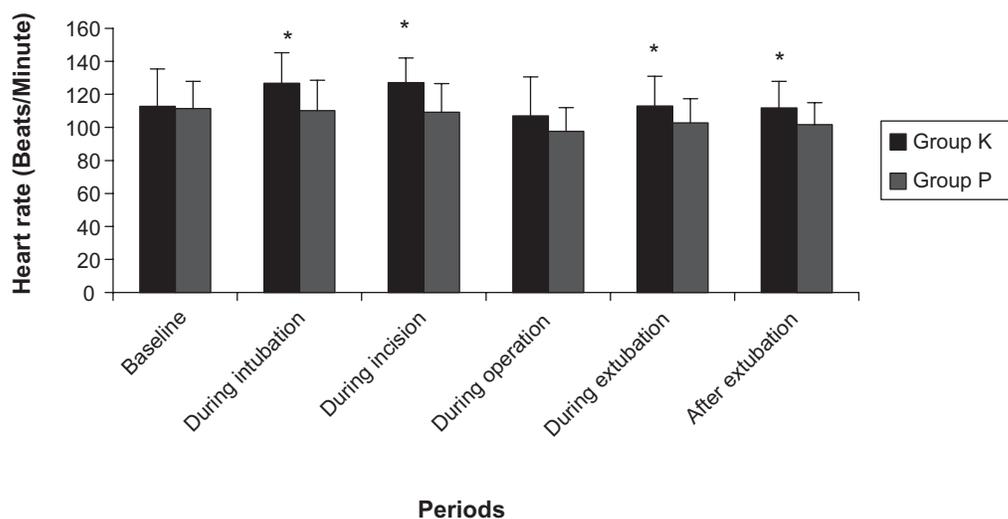
Figure 1 Heart rate of the groups.
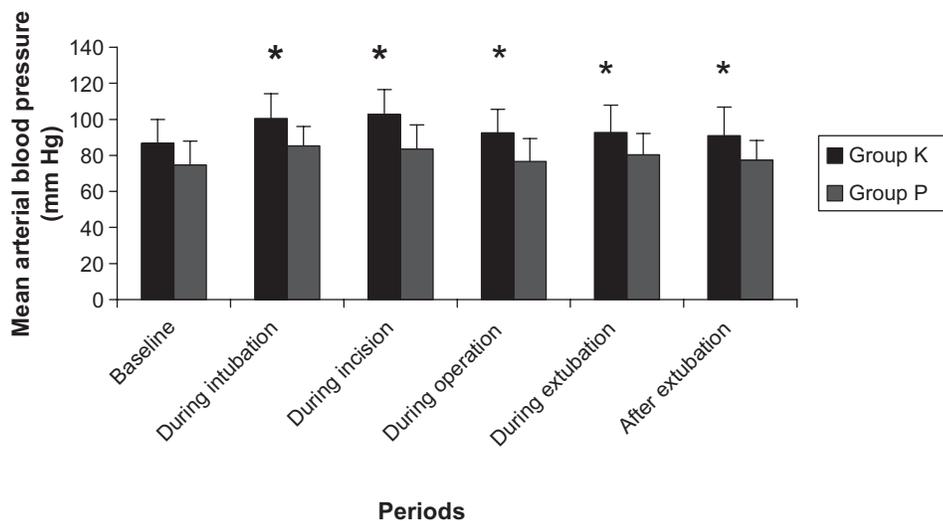**Notes:** n = 30,*p < 0.05, when Group K is compared with Group P.

Figure 2 Mean arterial blood pressure of the groups.
Notes: n = 30, $*P < 0.05$, when compared the Group K with Group P.

antagonist property,[28,29] furthermore, small-dose ketamine increases thalamic sensory output and arousal.[30] Therefore, the administration of intravenous ketamine appears to be a safe and useful technique for monitored anesthesia care in the ambulatory setting. Although, experiments demonstrated that ketamine is a potent trigger for pathologic neuronal apoptosis this was demonstrated as a antihyperalgesic and antiproinflammatory drug. Such benefits were investigated in the pediatric population.[31]

Both propofol and ketamine provided safe and effective sedation for the short, painful procedures performed.[32] Painful procedures necessary in the care of children are increasing.[2] Excessive pain can significantly lengthen the postoperative stay. Pain itself can also induce PONV.[33] The pain level during awakening affects the patient's agitation score. This adverse effect has a direct negative effect on patient satisfaction.[17] Although propofol produces dose-related sedation, amnesia, and anxiolysis, it is a poor analgesic and usually requires the use of an adjunctive analgesic agent.[34] Contrary to our study, McDowall et al[35] reported a decreased incidence of postanesthetic agitation with propofol, compared with sedation with ketamine or etomidate. This may be due to ketamine infusion in conjunction with low dose of fentanyl which could eliminate discomfort of children by increasing the sedation, decreasing the pain and thus agitation.

With titration of propofol or ketamine (without ocular motion, satisfactory muscle relaxation), the patients required a mean total dose of 185.8 ± 78.6 mg propofol and l53.6 $\pm$ 19.6 mg ketamine during procedure. Ketamine seems to be more cost effective. Some studies showed a significant

longer recovery or extubation time when ketamine was administered.[36,37] Moreover, it was reported that propofol has a pharmacokinetic profile leading to rapid induction and recovery times with minimal postoperative confusion.[34] However, in this study, recovery time in Group K was significantly shorter than in Group P.

In the present study, the incidence of PONV and the consumption of antiemetics in Group P are significantly higher than in Group K although propofol, which provides hypnosis and amnesia, is antiemetic.[38] When used solely as an induction drug, propofol has not been found to be beneficial in reducing the incidence of nausea or vomiting. The low consumption of ketamine may be the reason of low incidence of PONV as larger dosages of ketamine were associated with a clinically significant increase in PONV.[33] Thorp et al[39] reported that intravenous doses of ketamine-associated vomiting are not related to either the initial loading dose or the total dose but, the modest increase in receiving high cumulative doses (>7 mg/kg). Postoperative pain[40] and use of opioid analgesia in the perioperative period[41] may have contributed to this.

Three patients in Group P were administered atropine 0.01 mg/kg^{-1} to treat persistant bradycardia. The OCR was improved by releasing the traction first. Treatment with atropine (0.01 mg/kg) was only given in patients who had persistent OCR. In the current study, the patients administered with propofol seem to be more prone to develop pronounced OCR. Tramer et al[8] revealed that propofol, despite the use of anticholinergics, substantially increases the incidence of OCR. Propofol has the potency to increase the incidence of bradycardia by a central sympatholytic effect and vagal

stimulation. Ketamine seems to protect against the parasympathetic activation induced by OCR.[8] Choi et al[42] reported that 1–2 mg/kg of ketamine for anesthetic induction results in a lower incidence of OCR than propofol in children undergoing strabismus surgery.

The heart rate and mean arterial blood pressure in Group K were significantly higher than in Group P during intubation, incision, extubation, and after extubation periods. Similar to Badrinath et al,[43] heart rate and mean arterial blood pressure were within an acceptable range consequently no patient needed treatment.[43] As signs of emotional trauma may be less in children treated as day cases than in those hospitalized for one or more nights,[44] we discharged all patients during the four hours after surgery. The limitation of our study was the low number of subjects.

Conclusion

Our data suggests that intravenous infusion of ketamine as anesthetic with single dose of fentanyl as analgesic without volatiles may form a better combination of anesthesia than propofol in children undergoing strabismus surgery.

Disclosures

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