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ORIGINAL ARTICLE

Effect of intravenous preoperative versus postoperative paracetamol on postoperative nausea and vomiting in patients undergoing strabismus surgery: A prospective randomized study

Şaşılık cerrahisi uygulanan hastalarda preoperatif ve postoperatif uygulanan intravenöz parasetamolün postoperatif bulantı ve kusma üzerine etkisi: Bir prospektif randomize çalışma

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Summary

Objectives: This prospective randomized study aimed to compare the efficacy of preoperative versus postoperative paracetamol on postoperative nausea and vomiting (PONV) in children undergoing strabismus surgery.

Methods: Ninety-six patients were randomly divided into three equal groups (n=32). In the preoperative paracetamol group, patients received intravenous (IV) infusion of paracetamol [15 mg kg^{-1} (1.5 ml kg^{-1})] 1 h before surgery over 20 min and that of saline (1.5 ml kg^{-1}) in the recovery room. In the postoperative paracetamol group, patients received IV infusion of saline (1.5 ml kg^{-1}) 1 h before surgery over 20 min and that of paracetamol [15 mg kg^{-1} (1.5 ml kg^{-1})] in therecovery room. In the control group, patients received the IV infusion of saline (1.5 ml kg^{-1}) pre- and postoperatively. Postoperative pain condition was evaluated using the Faces Pain Scale. In the recovery room, an observer recorded the pain score, complaints of nausea and vomiting, the need for rescue analgesics, and the need for antiemetic drug during 24 h postoperatively.

Results: The incidence of nausea and vomiting during the first 0–6 h postoperatively was significantly lower in the preoperative paracetamol group than in the control and postoperative paracetamol groups (p<0.001). The number of patients requiring antiemetic administration during the first 0–6 and 6–12 h postoperatively was found to be higher in the control group than in the other groups (p<0.001, for all).

Conclusion: The preoperative administration of paracetamol reduces PONV incidence in children undergoing strabismus surgery.

Keywords: Strabismus surgery; paracetamol; postoperative nausea vomiting.

Özet

Amaç: Bu prospektif randomize çalışma, şaşılık cerrahisi uygulanan çocuklarda preoperatif ve postoperatif uygulanan intravinöz parasetamolün postoperatif bulantı ve kusma üzerine olan etkinliğini karşılaştırmayı amaçladı.

Gereç ve Yöntem: Doksan altı hasta randomize olarak 3 eşit gruba ayrıldı (n=32). Preoperatif parasetamol grubunda, ameliyattan bir saat önce 20 dakika sürecek şekilde 15 mg kg^{-1} parasetamol (1.5 ml kg^{-1}) intravenöz (IV) infüzyon ve iyileşme odasında ise serum fizyolojik IV infüzyonu (1.5 ml kg^{-1}) uygulandı. Postoperatif parasetamol grubunda ameliyattan bir saat önce 20 dakika boyunca serum fizyolojik (1.5 ml kg^{-1}) IV infüzyonu ve sonra iyileşme odasında 15 mg kg^{-1} parasetamol (1.5 ml kg^{-1}) verildi. Kontrol grubunda, hastalar preoperatif ve postoperatif dönemde serum fizyolojik (1.5 ml kg^{-1}) IV infüzyonu aldı. Postoperatif ağrı durumu ilk 24 saat boyunca Yüz Ağrı Ölçeği kullanılarak değerlendirildi. İyileştirme odasında bir gözlemci postoperatif 24 saat süresince ağrı skorunu, bulantı ve kusma şikayetlerini, analjezik ihtiyacını ve antiemetik ilaç ihtiyacını kaydetti.

Bulgular: Ameliyattan sonraki ilk 0-6 saatteki bulantı ve kusma insidansı preoperatif parasetamol grubunda kontrol grubuna (p<0.001) ve postoperatif parasetamol grubuna göre anlamlı olarak daha düşüktü (p=0.011). Ameliyattan sonraki ilk 0-6 ve 6-12 saatlerde antiemetik tedaviye gereksinim duyan hasta sayısının kontrol grubunda diğer gruplara göre daha yüksek olduğu bulundu (p<0.001, hepsi için).

Sonuç: Şaşılık ameliyatı geçiren çocuklarda preoperatif IV parasetamol uygulandığında, postoperatif bulantı ve kusma insidansını azaltmaktadır.

Anahtar sözcükler: Şaşılık cerrahisi; parasetamol; postoperatif bulantı kusma.

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Introduction

Strabismus surgery is a common ophthalmic surgical procedure in children. Postoperative nausea and vomiting (PONV) is an undesirable postoperative outcome, occurring in up to 88% of the patients undergoing strabismus surgery.[1] However, the mechanism for the high rate of PONV in these patients remains poorly defined; oculo-emetic reflex, an optokinetic imbalance, and a disturbance of visual axes have been considered responsible for the high incidence of PONV following strabismus surgery.[2, 3] PONV causes a delay in the oral intake and extends the duration of hospital stay.[4] Therefore, there have been attempts on using drugs having an antiemetic effect to reduce the incidence of PONV in children after strabismus surgery.[5, 6]

Paracetamol (acetaminophen; N-acetyl-p-aminophenol) has been well established as a safe and analgesic drug. It has been reported that intravenous (IV) paracetamol is effective and safe for postoperative analgesia in children.[7] However, the mechanism of the analgesic action of paracetamol remains unclear; it inhibits the cyclooxygenase enzyme and activates descending serotonergic inhibitory pathways.[8] Studies have also suggested that paracetamol reduces the incidence of PONV by affecting some serotonergic pathways in the central nervous system.[9, 10]

We hypothesized that preoperative IV paracetamol is useful in preventing PONV due to strabismus surgery in children. Therefore, we designed a prospective randomized study to compare the efficacy of preoperative versus postoperative paracetamol on PONV in children undergoing strabismus surgery. We also examined the effect of preoperative and postoperative paracetamol administrations on the total analgesic consumption after strabismus surgery.

Material and Methods

This prospective randomized study was approved by the Ethics Committee of Ataturk University, Medical Faculty, Erzurum, Turkey. This study was performed at the Anesthesiology Clinic of Ataturk University, Medical Faculty, Erzurum, Turkey. Ninety-six patients aged 2–14 years, with ASA (the classification of the American Society of Anesthesiologists) physical status I-II, who underwent elective strabismus surgery under general anesthesia were included. Written informed consent was obtained from the parents. Patients with a history of allergy to any of the study medications (general anesthetic agents or paracetamol); those with a history of previous PONV, hepatic, or renal disease; and those who used antiemetics, antihistaminics, analgesics, or corticosteroids 24 h prior to surgery were excluded.

Basic data including patients' age, weight, and height were recorded. All patients were pre-medicated with midazolam (0.5 mg kg^{-1}, orally) before anesthesia. Before transfer to the operating room, patients were randomly divided into three equal groups (n=32) using a computer generated random number table. In the preoperative paracetamol group (n=32), patients received the IV infusion of paracetamol [15 mg kg^{-1} (1.5 ml kg^{-1})] (Perfalgan®, Bristol-Myers Squibb, France) 1 h before surgery over 20 min and that of saline (1.5 ml kg^{-1}) in the recovery room after full consciousness.[9] Patients in the postoperative paracetamol group (n=32) received the IV infusion of saline (1.5 ml kg^{-1}) 1 h before surgery over 20 min and paracetamol [15 mg kg^{-1} (1.5 ml kg^{-1})] in the recovery room after full consciousness. In the control group (n=32), patients received the IV infusion of saline (1.5 ml kg^{-1}) pre- and postoperatively (Table 1).

A standardized general anesthesia regimen was provided to all patients. Standard monitoring, including non-invasive arterial pressure, electrocardiography, and pulse oximetry, was established in the operating room. Propofol (2–3 mg kg^{-1}) and lidocaine (0.1 mg kg^{-1}) were used for general anesthesia, and a laryngeal mask airway (LMA) was inserted. The maintenance of anesthesia was achieved using sevoflurane (2%–3%) and N2O/O2 (FiO_2, 50%). At the end of the surgery, LMA was removed and patients were transferred to the post-anesthesia recovery room.

Table 1. Study groups

	Preoperative paracetamol group	Postoperative paracetamol group	Control group
1 h before surgery	IV paracetamol (1.5 ml kg^{-1})	IV saline (1.5 ml kg^{-1})	IV saline (1.5 ml kg^{-1})
In the recovery room	IV saline (1.5 ml kg^{-1})	IV paracetamol (1.5 ml kg^{-1})	IV saline (1.5 ml kg^{-1})

Oculocardiac reflex (OCR) was defined as an acute decrease (≥30%) in the heart rate associated with traction on eye muscle. Atropine (0.01 mg/kg) was administered via IV in case the heart rate did not return to baseline following the release of muscle traction. The number of orbital muscles requiring surgery, duration of anesthesia, duration of surgery, and the number of patients who experienced OCR requiring treatment with atropine were recorded.

The primary outcome for this study was the incidence of nausea and vomiting during the first 24 h postoperatively, and the secondary outcome was the need for rescue analgesics and for antiemetic drug during 24 h postoperatively. In the recovery room, an independent observer blinded to the group assignment recorded the pain score, complaints of nausea and vomiting, the need for rescue analgesics, and the need for antiemetic drug during 24 h postoperatively. Nausea was defined as retching alone, and vomiting was defined as a forceful expulsion of gastric contents through the mouth or the nose.[9] Intravenous metoclopramide [0.15 mg kg^{-1}; maximum, 0.5 mg $kg^{-1}day^{-1}$] was administered in case of two or more vomiting episodes.

The postoperative pain condition was evaluated using the Faces Pain Scale every hour starting from when the patients were awake from arrival in the recovery room to 24 h postoperatively.[11] This scale includes six faces reflecting the severity of pain, and every facial expression has a numerical score. The selected face by children or their parents and the numerical score of selected face was recorded. In all groups, postoperative analgesia was provided with oral ibuprofen suspension (Ibufen®, Abbott, Istanbul, Turkey) [5 mg kg^{-1}; maximum, 40 mg $kg^{-1}day^{-1}$] for a Faces Pain Scale score of ≥3.

The primary endpoint of the study was the incidence of nausea and vomiting during the first 24 h postoperatively. The minimum sample size required for this study was calculated based on the Cok et al.'s study[9] using the Russ Lenth's Power and sample size calculation application.[12] Thirty patients in each group were needed to demonstrate a mean difference of 20% for the incidence of nausea between two study groups with a power of 80% and alpha 5%.

Data were analyzed using SPSS software 12.0 (SPSS Inc., Chicago, IL, USA) and calculated as mean ± standard deviation or number (%). $P<0.05$ was considered significant. Distribution of data was assessed using the Kolmogorov–Smirnov test. Comparisons among the groups were performed with one-way ANOVA test. Fisher's exact test was used to compare percentage values.

Results

Eligible patients for this study were analyzed in the CONSORT flow diagram (Fig. 1).[13] During the study period, 120 patients were eligible for this study and 110 met the inclusion criteria. Ninety-six children and their parents agreed to participate and were enrolled and randomly assigned into three groups (n=32 each). Six patients were excluded because they were discharged from the hospital within the first 12 h postoperatively. Eventually, the data from 90 patients were analyzed.

Baseline patients' characteristics are shown in Table 2. There were no statistically significant differences among the groups regarding sex, age, weight, height, ASA status, the number of patients who experienced OCR, the number of muscles operated, the duration of anesthesia, and the duration of surgery ($p>0.05$).

There were no statistically significant differences among the study groups with respect to the mean pain scores during the first 0–6, 6–12, and 12–24 h postoperatively (Table 3). As shown in Table 4, the incidence of nausea during the first 0–6 h postoperatively was significantly lower in the preoperative

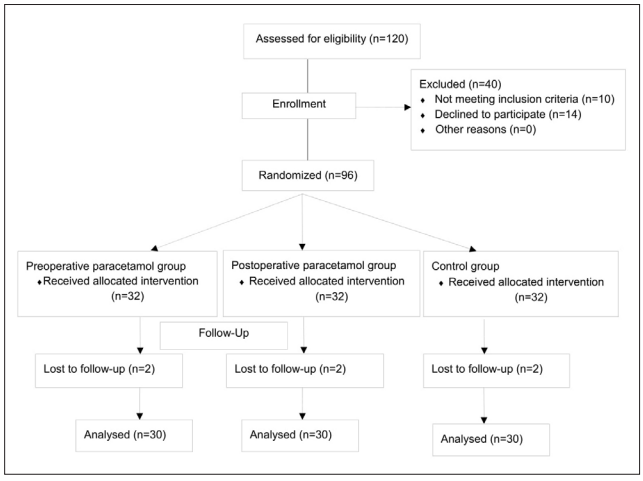

Figure 1. CONSORT flow diagram. The course of patients through this study was shown.

paracetamol group than in the control (p<0.001) and postoperative paracetamol (p=0.011) groups. Control group had a higher incidence of nausea during the first 6–12 h postoperatively than the preoperative and postoperative paracetamol groups (p<0.001, for both). Also, the incidence of postoperative vomiting during the first 0–6 h was significantly lower in the preoperative paracetamol group than in the control and postoperative paracetamol groups (p<0.001, for both groups) (Table 4). During the first 0–6 h postoperatively, 12 (40%) patients required oral ibuprofen administration in the control group, while six (20%) in the preoperative paracetamol group and four (13.3%) in the postoperative paracetamol group re-

Table 2. Demographic and operation characteristics of patients

	Preoperative paracetamol group (n=30)	Postoperative paracetamol group (n=30)	Control group (n=30)	p
Age (year)	9.13±4.24	7.66±3.56	9.13±3.57	0.233
Weight (kg)	30.50±13.12	25.00±10.71	28.43±13.41	0.232
Sex (male/female)	19/11	16/14	18/12	0.732
ASA I/II	25/5	26/4	23/7	0.756
Duration of surgery (min)	78.96±9.91	78.33±9.49	81.33±11.05	0.488
Number of muscles (1/2)	10/20	8/22	6/24	0.858
Patients who experienced OCR (n)	2	3	2	0.861

OCR: oculocardiac reflex.

Table 3. Mean pain scores of groups during 24 h postoperatively

	Preoperative paracetamol group (n=30)	Postoperative paracetamol group (n=30)	Control group (n=30)	p
0-6 h	2.43±1.04	2.73±0.94	2.70±0.91	0.424
6-12 h	1.30±0.79	1.20±0.66	1.53±0.73	0.200
12-24 h	0.66±0.66	0.26±0.58	0.53±0.81	0.082

Table 4. Incidence of nausea and vomiting in the groups

	Preoperative paracetamol group (n=30)	Postoperative paracetamol group (n=30)	Control group (n=30)
Nausea n (%)			
0-6 h	3 (10)	12 (40)*	16 (53)**
6-12 h	2(6.66)[a]	1(3.33)[a]	12(40)
12-24 h	3(10)	4(13.3)	3(10)
Vomiting n (%)			
0-6 h	2(6.6)[a]	8(26.6)	14(46.6)
6-12 h	3(10)	3(10)	5(16.6)
12-24 h	1(3.3)	2(6.6)	4(13.3)

*: p=0.011; **: p<0.001, compared with preoperative paracetamol group; [a]: p<0.001, compared with control group.

Table 5. Need for rescue analgesics and antiemetic drug in patients during 24 h postoperatively

	Preoperative paracetamol group (n=30)	Postoperative paracetamol group (n=30)	Control group (n=30)
Number of patients requiring rescue analgesia n (%)			
0-6 h	6 (20)*	4 (13.3)**	12 (40)
6-12 h	0	0	0
12-24 h	0	0	0
Number of patients requiring antiemetic n (%)			
0-6 h	3 (10)$^{\beta}$	11 (36)**,$^{\alpha}$	22 (73.3)
6-12 h	2 (6.6)$^{\beta}$	3 (10)$^{\beta}$	13 (43.3)
12-24 h	1 (3.3)	2 (6.6)	4 (13.3)

*p=0.008; **p=0.001; $^{\beta}$p<0.001; compared with control group. $^{\alpha}$p=0.017; compared with preoperative paracetamol group.

quired analgesic administration (p=0.008, p=0.001; respectively) (Table 5). None of the patients in any group required rescue analgesics during the first 6–12 and 12–24 h postoperatively. The number of patients requiring antiemetic administration during the first 0–6 and 6–12 h postoperatively was found to be higher in the control group than in the preoperative and postoperative paracetamol groups (p<0.001, for all). There are no differences among the groups in terms of antiemetic administration during 12–24 h postoperatively (Table 5).

Discussion

This prospective, randomized study was designed to evaluate the efficacy of IV preoperative and postoperative paracetamol administrations for the prevention of PONV in children undergoing strabismus surgery. The incidence of PONV during the first 6 h after surgery was significantly reduced in the preoperative paracetamol group than in the postoperative paracetamol and control groups. Also, the incidence of PONV was not significantly different in the preoperative and postoperative paracetamol groups during the first 6–12 and 12–24 h postoperatively.

Previous studies have demonstrated the effect of reducing postoperative pain following the use of preoperative paracetamol in different surgeries.[10, 14] Some studies have also revealed the antiemetic effect of IV paracetamol administration following surgery.[9, 10] However, our study is the first to compare the effect of preoperative and postoperative IV paracetamol administrations on PONV in children undergoing strabismus surgery.

The incidence of PONV has been reported to be approximately 40%–88% in patients undergoing strabismus surgery without antiemetic prophylaxis.[1, 5, 9] Researchers have suggested that the intraoperative tension on ocular muscles provokes a vagal response (oculocardiac reflex), which causes PONV.[2, 3] Also, the reduction in the incidence of nausea was found to be correlated with the reduction of pain.[15] Extreme retching or vomiting in the early postoperative period leads to prolonged recovery, an increased risk of bleeding, tension in surgical sutures, and an increased risk of pulmonary aspiration.[16] Drugs with antiemetic activity (e.g., metoclopramide and ondansetron), anesthesia techniques reducing postoperative pain (e.g., subtenon's or peribulbar blocks and topical NSAIDS), and analgesics (e.g., opioids, NSAIDS, and paracetamol) were recommended to reduce PONV in children undergoing strabismus surgery.[17, 18] In our study, the pain scores were similar among the three groups during the first 24 h following surgery; however, the incidence of nausea and vomiting during the first 0–6 h postoperatively was lower in patients in the preoperative and postoperative paracetamol groups than in those in the control group. Therefore, we suggested that sufficient an-

algesia was provided in the first 24 h in all groups. Thus, the reduction in the incidence of nausea and vomiting during the first 0–6 h postoperatively in the preoperative and postoperative paracetamol groups may be related to the antiemetic effect of paracetamol rather than pain reduction.

Studies in children have shown that IV paracetamol improves the quality of postoperative analgesia.[19, 20] A systematic meta-analysis has revealed that IV acetaminophen reduces nausea when prophylactically administered either before surgery or before arrival in the post-anesthesia care unit; but not when administered after the onset of pain.[15] Consistent with these results; the incidence of nausea and vomiting during the first 0–6 h postoperatively was found to be lower in patients who received preoperative paracetamol than in those who received postoperative paracetamol in our study. Chemoreceptor trigger zone includes dopamine, opioid, and serotonin 5-HT3 receptors and receptor antagonists (e.g., ondansetron and granisetron), which are used for the prevention and treatment of PONV.[21] Cok et al.[9] have reported that the intraoperative administration of IV paracetamol decreases the incidence of PONV during the first 24 h in children after strabismus surgery. Despite unclear mechanisms of analgesic and antiemetic actions of paracetamol, studies have shown that paracetamol inhibits the cyclooxygenase enzyme and affects some serotonergic pathways in the central nervous system.[8, 22] Serotonin is found in the brainstem vomiting center. AM404 (a metabolization product of paracetamol in the brain) inhibits the reuptake of anandamide.[23] Decreased anandamide levels were found to be associated with a high incidence of nausea and vomiting in humans.[24] This may be another explanation for the antiemetic effect of acetaminophen.

It is suggested that an altered visual perception and afferent impulses causing reflex are responsible for PONV after strabismus surgery. Also, the number of ocular muscles that are repaired was reported to be associated with an increased risk of PONV.[16] In our study, the groups were comparable with respect to patient characteristics including the number of patients who experienced OCR, the number of muscles operated, and the surgical procedure.

Limitations

The relatively small population is a limitation of this study. Studies with a larger sample are needed to evaluate the effect of preoperative paracetamol on the incidence of PONV.

Conclusion

The use of IV preoperative paracetamol reduces the incidence of PONV and postoperative antiemetic consumption during the first 6 h after strabismus surgery. Therefore, preoperative IV paracetamol reduces the incidence of PONV in children undergoing strabismus surgery. Further studies are necessary to prove the effectiveness of preoperative paracetamol in reducing the incidence of PONV among children after strabismus surgery.

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