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The effect of intravenous paracetamol infusion on postoperative nausea-vomiting and pain following strabismus surgery in children- a randomised controlled trial

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Abstract

Strabismus surgery is associated with postoperative nausea-vomiting (PONV) and pain. In this prospective-randomized trial we aimed to investigate the effects of intra-operative paracetamol infusion on postoperative nausea-vomiting and pain following strabismus surgery in children. Following approval of ethical committee 50 pediatric patients aged between 3-12 physical status of ASA I-II (American Society of Anesthesiology) undergoing strabismus surgery are included in the study between 2012 and 2013 years. Patients were excluded from the study for these following reasons: known allergic history to paracetamol or other non-steroidal anti-inflammatory drugs (NSAID), morphine and other drugs used in the study; asthma; liver or kidney dysfunction and bleeding disorders. Patients were randomized into two following groups: intravenous paracetamol and IV morphine. Demographic data were similar among groups. Nausea, vomiting scales and anti-emetic requirement of the groups were compared at 0.min, 30.min, 2 hrs and 24 hrs. Analysis had shown that there is a significant difference at the 30th minute, there were no significant differences at other time periods. Wong-Baker faces pain rating scale were compared between groups at 0.min, 30.min, 2 hrs and 24 hrs and no significant differences were seen between group ($p > 0.05$). Analgesic requirement and sedation scores were compared between groups at 0 min, 30 min, 2 hrs and 24 hrs and no significant differences were seen between groups ($p < 0.05$). It can be concluded that intravenous paracetamol infusion can safely be used as a replacement to opioids in children undergoing strabismus surgery.

Keywords: Morphine, paracetamol, postoperative nausea-vomiting, pain scale, strabismus surgery

Introduction

Strabismus surgery, one of the most commonly performed surgeries on children, is associated with postoperative nausea-vomiting (PONV), pain, wound dehiscence and bleeding [1]. In this surgery, the oculoemetic reflex is stimulated by manipulation of the eye. With this stimulation, the release of neurotransmitters from the chemoreceptor trigger zone increases. Since emesis can lead to severe complications; nausea and vomiting must be treated during perioperative period. There is still no consensus in prevention and treatment of PONV. In strabismus surgery; emesis ratio, which has already been increased by the factors related to the surgery itself combined with the anesthesia and surgical stress, reaches to unacceptable levels of 88%. Various treatment protocols are being tested to reduce this ratio. Strabismus surgery in children is associated with both pain and vomiting. Analgesic agents used in strabismus surgery should not increase the PONV incidence; so the pain relief treatment is another problem encountered in strabismus surgery. It has been shown that preoperative and intraoperative use of opioids increase the PONV in pediatric patients undegoing strabismus surgery [2]. This has been associated with delayed gastric emptying, vestibular sensitization and the direct activation of the chemoreceptor trigger zone [3]. In some studies, the use of opioids that increase the incidence of vomiting are still recommended for postoperative analgesia but anti-inflammatory drugs are studied as an alternative for opioids with the hypothesis of maintaining analgesia and not increasing the nausea-vomiting incidence after strabismus surgery [4]. Also opioids have side effects like sedation, drowsiness, respiratory depression, myosis and hypothermia which are undesired in ambulatory basis.

Since paracetamol does not bind to the receptors that cause central side effects, it does not cause nausea, vomiting, sedation

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or respiratory distress [5]. On the other hand we know that opioids stimulate the chemoreceptor trigger zone and cause nausea and vomiting [6]. In this prospective-randomized trial we aimed to investigate the effects of intra-operative paracetamol infusion on postoperative nausea-vomiting and pain following strabismus surgery in children.

Materials and Methods

Ethics committee approval of our study was received from Hacettepe University Hospital with registration number LUT 09/56. Following approval of ethical committee 50 pediatric patients aged between 3-12 physical status of ASA I-II (American Society of Anesthesiology) undergoing strabismus surgery are included in the study. Patients were excluded from the study for these following reasons: known allergic history to paracetamol or other non-steroidal anti-inflammatory drugs (NSAID), morphine and other drugs used in the study; asthma; liver or kidney dysfunction and bleeding disorders. Between 2012 and 2013.

We planned this study considering that intra-operative paracetamol infusion can maintain analgesia during intra-operative period since its effect starts shortly after administration and lasts long enough to cover the post-operative period. This prospective, randomized and controlled study was carried out at Hacettepe hospital. This study was started in accordance with the Helsinki declaration and consort. Informed consent was obtained from the patients themselves or their legal guardians.

Patients were randomized by a blinded anesthesiologist using the closed envelope method. Patients were randomized into two following groups: intravenous (IV) paracetamol and IV morphine. In both groups standard anesthesia technique was applied. Drugs were prepared and labelled as group 1 and group 2. The drugs were administered by a blind anesthesiologist. All patients were premedicated with 0.7 mg kg-1 midazolam (Dormicum©, F. Hoffmann-La Roche Ltd. Basel Switzerland Cenexi SAS Fontenay, France) nasally 15-30 minutes prior to induction. Routine monitoring (ECG, saturation, tension) and iv cannula were installed. Anesthesia was induced with 2-3 mg kg-1 IV propofol. 0.5 mg kg-1 IV rocuronium bromide (Esmeron©, N.V. Organon, Oss, Netherlands, Glaxo Smith Kline) was administered before tracheal intubation. Anesthesia was maintained with infusion of 2% propofol (Propofol 2% Fresenius©), (6 mg kg-1 hr-1) and remifentanyl hydrocloride (Ultiva© Glaxo Smith Kline), (0.25 mcg kg-1 min-1) with 50% oxygen-air mix. As soon as the procedure was over neuromuscular block was reversed with 0.05 mg kg-1 IV neostigmine and 0.01 mg kg-1 atropine and patients were extubated within proper extubation criteria.

Paracetamol group received 15 mg kg-1 IV paracetamol infused in 30 minutes after the induction. Morphine group received 0.1 mg kg-1 IV morphine at the induction. We applied weight appropriate doses of both drugs that we commonly use in our clinic. 10 mg kg-1 hr-1 crystalloid solutions were used during the procedure.

Patients were transferred into the recovery unit after the surgery. Vital signs were monitored, nausea-vomiting, pain and sedation presence was assessed. These evaluations were made by the recovery unit doctor who did not take an active role in this study. After 2 hours of observation at the recovery unit patients were transferred to the ward.

PONV was assessed by a scale with 3 parameters which are 0-no nausea or vomiting, 1-nausea and retching, 2-vomiting.

Postoperative pain was evaluated using Wong-Baker faces pain rating scale. In this scale there are faces which represent the pain severity that gets higher from the left to the right and zero to five. According to this 0-no pain, 1-mild pain, 2-mild to moderate pain, 3-moderate pain, 4-moderate to severe pain, 5-severe pain. Our scoring were made over 10 points. Pain scores were evaluated hourly. Pain scoring in patients who had sedation score of 3 was made according to the responses to painful stimulus.

Sedation scoring was made over 4 parameters. 0-awake and anxious, 1-occasionally sleepy, easily awakened, 2-mostly sleepy, can be awakened, 3-continious sleep, hardly awakened.

During the 2 hours of observation at the recovery room, 0.1 mg kg-1 IV morphine was administered to the children who had pain score of ≥ 3. While the children were observed at the ward oral paracetamol suspension (Calpol©, Glaxo Smith Kline) were given to those who had pain score of ≥ 3. Rescue paracetamol dose was standard in all patients (15mg/kg-1). Maximum dose was 60mg/kg-1/day. No additional analgesics were used during the study.

IV Ondansetron (Zontron©, I.E. Ulagay) were given to the patients if nausea and vomiting was noted at the recovery room or at the ward. All possible side effects and complications were recorded during the observation period.

All data was analyzed with SPSS 15.0 (Chicago, IL, USA) program. Kolmogorov-Smirnov test was used to determine whether the variables differ from the normal distribution. To define the numerical data mean and standard deviation; to the numerical data that did not fit the normal distribution median, lowest-highest was presented. Categorical variables were defined as frequency and percentage and Chi-squared test was used in the group comparison. P-value < 0.05 was considered statistically significant.

Results

50 patients were examined in this study and patients were divided into 2 groups of 25 people each. Age, weight, duration of anesthesia, duration of surgery and recovery time of Group M (morphine) and Group P (paracetamol) are seen in [Table 1]. There were no significant differences between groups in terms of these variations ($p > 0.05$).

From the arrival at the recovery room, nausea and vomiting scales of the groups were compared at 0 min, 30 min, 2 hrs and 24 hrs. Analysis had shown that there is a significant difference at the 30th minute which is also seen in [Table 2] ($p < 0.05$). There were no significant differences at other time periods.

Anti-emetic requirement was compared at 0 min, 30 min, 2 hrs and 24 hrs. Analysis had shown that there is a significant difference at the 30th minute, also seen in [Table 3] ($p < 0.05$). There were no significant differences at other time periods.

Wong-Baker faces pain rating scale were compared between groups at 0 min, 30 min, 2 hrs and 24 hrs and no significant differences

were seen between groups, also seen in [Table 4] ($p > 0.05$).

Analgesic requirement and sedation scores were compared between groups at 0 min, 30 min, 2 hrs and 24 hrs and no significant differences were seen between groups, also seen in [Table 5] and [Table 6] ($p > 0.05$).

There was no significant difference between groups regarding the post-extubation complications ($p < 0.05$) [Table 7].

Table 1. Age of the patient,to be compared according to gender and clinical features (mean ± SS)

Demografic data	Group M (n=25)	Group P (n=25)	p
Age (year)	5.9 ± 3.3	6.2 ± 3.5	0.770
Weight (kg)	20.6 ± 9.3	23.0 ± 14.9	0.504
Duration of anesthesiae (minute)	71.8 ± 38.6	74.9 ± 30.6	0.753
*p < 0.05,T-Teste			

Table 2. Between-group comparison of postoperative nausea and vomiting value (n=the number of patients)

Nausea and vomiting		Group M n=25	Group P n=25	p
Arrival to the recovery unit	**0**	22 (%88)	24 (%96)	0.609
	1	0 (% 0)	0 (% 0)	
	2	3 (%12)	1 (%4)	
30. minute	**0**	19 (% 76)	25 (% 100)	*0.022
	1	0 (% 0)	0 (% 0)	
	2	6 (% 24)	0 (% 0)	
2. hours	**0**	22 (% 22)	24 (% 96)	0.235
	1	3 (% 12)	0 (% 0)	
	2	0 (% 0)	1 (% 4)	
24. hours	**0**	24 (% 96)	22 (% 88)	0.235
	1	1 (% 4)	0 (% 0)	
	2	0 (% 0)	22 (% 88)	
*p < 0.05, 0 = no availabe, 1 = nause-retching, 2 = vomiting, Ki-sguare teste				

Table 3. The comparison between groups of postoperative antiseptic drug needs (n=the number of patients)

Antiemetic drug consumption		Group M n=25	Group P n=25	p
Arrival to recovery unit	**Given**	1 (% 24)	1 (% 24)	1.000
	Not given	24 (% 96)	24 (% 96)	
30.minutes	**Given**	6 (% 24)	0 (% 0)	*0.009
	Not given	19 (%76)	25 (% 100)	
2. hours	**Given**	3 (% 12)	1 (% 4)	0.297
	Not given	22 (% 88)	24 (% 96)	
24. hours	**Given**	1 (% 4)	2 (% 8)	0.552
	Not given	24 (% 96)	23 (% 92)	
Total	**Given**	10 (%20)	4 (%8)	0.570
	Not given	15 (%30)	21 (%80)	
*p < 0.05, Ki-sguare teste				

Table 4. A comparison of intergroup face value scale

Face scale (0 – 10)	Group M (n=25)	Group P (n=25)	p
Arrival to recovery unit	0 (0-3)	0 (0-7)	0.835
30.minutes	0 (0-7)	0 (0-4)	0.908
2. hours	0 (0-4)	0 (0-6)	0.475
24. hours	0 (0-1)	0 (0-4)	0.934
median (smallest-the largest), Mann Whitney U teste			

Table 5. The comparison between groups of postoperative analgesia drug needs (n=the number of patients)

Analgesia reguirement		Group M n=25	Group P n=25	p
Arrival to recovery unit	**Necessary**	0 (% 0)	3 (% 12)	0.235
	Not required	25 (% 100)	22 (% 88)	
30.minutes	**Necessary**	6 (% 24)	3 (% 12)	0.463
	Not required	19 (% 76)	22 (% 88)	
2. hours	**Necessary**	2 (% 8)	2 (% 8)	1.000
	Not required	23 (% 92)	23 (% 92)	
24. hours	**Necessary**	1 (% 4)	2 (% 8)	1.000
	Not required	24 (% 96)	23 (% 92)	
Total	**Necessary**	8 (%16)	9 (%18)	1.000
	Not required	17 (%34)	16 (%32)	

Ki-sguare teste

Table 6. The comparison between groups of postoperative sedation needs (n=the number of patients)

Sedation (0 – 3)	Group M (n=25)	Group P (n=25)	p
Arrival to recovery unit	1 (0 – 3)	2 (0 – 3)	0.537
30.minutes	1 (0 – 3)	1 (0 – 3)	0.624
2. hours	0 (0 – 1)	0 (0 – 1)	0.234
24. hours	0 (0 – 1)	0 (0 – 1)	0.561

median (smallest-the largest), Mann Whitney U teste

Table 7. The comparison between groups of postoperative complications (n=the number of patients)

Complications	Grup M n=25	Grup P n=25	p
There were no complications	24 (% 96)	24 (% 96)	
Vomiting	1 (% 4)	0 (% 0)	1.000
Secretion	0 (% 0)	1 (% 4)	

Ki-sguare teste

Discussion

Strabismus surgery, one of the most commonly performed surgeries on children, is related to postoperative nausea, vomiting and pain. Pain is a contributing factor to vomiting so the good pain control decreased the incidence of postoperative vomiting [7]. Nausea incidence after strabismus surgery is 30–49% for adults [8]. The incidence of PONV in pediatric patients is often twice as high as in adults [9]. Nearly 65% of the patients experience pain following strabismus surgery in pediatric population [10]. Pain is typically mild and can be managed with acetaminophen or ibuprofen after strabismus surgery. In our study, we aimed to evaluate the effects of perioperative IV paracetamol infusion on postoperative nausea, vomiting, pain and recovery.

Acute post-operative pain treatment is mostly based on opioids. Opioids have side effects like respiratory depression, nausea, vomiting, hypotension, tachycardia, sweating and pruritus [11]. Mendel et al. related the use of opioids during pre-operative and intra-operative periods with increased PONV incidence in pediatric strabismus surgery [12]. They have shown that opioid dosage and therefore side effects can be reduced by using an anti-inflammatory agent. Also it has been shown that anti-inflammatory drug usage can reduce the opioid requirement in children [13]. Some authors suggested that following strabismus surgery, minimal pain is experienced and it can be treated effectively and safely with acetaminophen [14]. As in our study, opioid use significantly increased vomiting at 30 minutes.

The most limiting side effect of intra-operative opioid usage is the increased PONV incidence. PONV extends hospitalization time therefore increases institutional costs and also carries risks like dehydration, electrolyte imbalance and wound contamination [15]. Also; vomiting is considered as a life-threatening complication since it can cause tracheal aspiration in unconscious patients with no protective reflexes during recovery [16]. In strabismus surgery PONV is a serious concern since it can lead to various complications as described earlier and on top of all these unwanted complications retching itself can cause wound dehiscence and bleeding that leads to revision surgery [16].

Padda et al. compared rectal acetaminophen with IV fentanyl-droperidol and indicated that rectal acetaminophen group had less PONV incidence after strabismus surgery [17].

Munro et al. compared morphine with ketolorac, evaluating their post-operative emetic and analgesic effects in ambulatory strabismus surgery patients. They found that ketolorac use decreases post-operative vomiting thus intra-operative opioid usage can be avoided in strabismus surgery patients. They also suggested that routine morphine usage followed by routine antiemetic usage in all patient groups should be avoided [18].

Aksoy et al. examined the effects of paracetamol on PONV before

and after strabismus surgery. They stated that preoperative IV administration of paracetamol in children undergoing strabismus surgery reduces the incidence of postoperative nausea and vomiting [8].

Previous studies investigated pharmacological and non-pharmacological approaches and their effects on preventing PONV in pediatric strabismus surgery. Among the antiemetic group; droperidol, metoclopramide and ondansetron are shown to decrease PONV but it has also been demonstrated that they cause agitation, extended healing period, extra pyramidal symptoms and increased costs [19].

Cok et al. have reported that the intraoperative administration of IV paracetamol decreases the incidence of PONV during the first 24 h in children after strabismus surgery [20]. 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. Serotonin is found in the brainstem vomiting center. AM404 (a metabolization product of paracetamol in the brain) inhibits the reuptake of anandamide [21].

In our study we preferred IV paracetamol since it does not bind to the receptors that cause central side effects and it does not cause nausea, vomiting, sedation or respiratory depression [22]. We already know that opioids stimulate the CTZ causing nausea and vomiting, so we expected that IV paracetamol administration leads to less nausea and vomiting in post-operative period than morphine does. When we compared the nausea and vomiting scales between groups, we found that the nausea and vomiting incidence was significantly higher in morphine group at 30th min time period. In our study we planned to administrate ondansetron as an anti-emetic and based on this we compared the anti-emetic requirement of the patients. Analysis showed that increasing rates of nausea and vomiting is seen with increased anti-emetic need in morphine group. There was a significant difference at 30th minute time period in morphine group. Overall amounts of anti-emetics used in our patients showed that, in morphine group one patient requires two separate times of anti-emetic treatment but there was no significant difference between groups. We figured more patients should be studied to properly evaluate the anti-emetic requirement.

Padda et al. compared rectal acetaminophen with fentanyl - droperidol in strabismus surgery, they evaluated post-operative pain with Observer Pain Scale (OPS) and they found that analgesic efficiency of rectal acetaminophen was sufficient for this patient group [17].

Work of Van Aken H. et al. assessing analgesia in repeated administrations of paracetamol, morphine and placebo for removal of one or more bone-impacted third molars; studied patients suffering moderate postoperative pain at 3 groups of IV paracetamol, morphine and placebo. The number of patients requiring analgesia was significantly higher in placebo group than the morphine and IV paracetamol group in post-operative 5h period. Both groups showed no significant difference in total pain relief scores; statistical analysis was similar in terms of analgesic efficiency and stated that paracetamol provides post-operative analgesia equal to morphine [23].

Work of Hernandez-Palazon et al. reviewing the IV paracetamol administration effects on morphine consumption and side effect incidence after spinal fusion surgery showed that IV paracetamol administration reduces morphine use by 46% [24].

We evaluated post-operative pain and analgesic requirements for post-operative pain relief in our study using Wong-Baker faces pain rating scale (0-10). We applied additional analgesic treatment to patients who had 3 or higher scores. There was no significant difference in facial pain rating scales between morphine and IV paracetamol groups. Similarly, there was no significant difference between groups in terms of rescue analgesic requirement.

In the study of Padda et al. comparing rectal acetaminophen with fentanyl-droperdol in strabismus surgery, it was observed that patients received fentanyl-droperidol had longer recovery periods than patients received rectal acetaminophen. It was pointed out that fentanyl-droperidol combination extends recovery in prolonged surgical procedures and it was related to post-operative somnolence effects of droperidol [17].

When we review the post-operative sedation and recovery scales in our study, although statistically insignificant, in morphine group there was 1 patient who had sedation score of 1 until 24 hr period. We believe that a study with a larger number of patients should be conducted to determine a significant difference.

Total intravenous anesthesia (TIVA) is commonly used lately asserting it preserves cardiovascular stability better, provides complete and fast recovery and has low PONV incidence. It has been suggested an underlying myopathy can cause strabismus. For this reason in this patient group malign hyperthermia is more likely to be seen. The risk can be reduced by avoiding the drugs that cause malign hyperthermia. In our study we applied TIVA to all the patients of both groups in considering malign hyperthermia risk. For TIVA administration we preferred propofol as the hypnotic agent and remifentanyl as the analgesic agent. We also set the infusion rate of remifentanyl at 0.25 mcg kg-1 min-1 in our study ensuring fast recovery [25].

In the study of Padda et al. comparing rectal acetaminophen with fentanyl-droperdol in strabismus surgery, they also analyzed pharmacoeconomic cost-effectiveness. Results showed that prophylactic use of fentanyl-droperidol combination prolongs hospitalization and recovery periods and it was not superior to acetaminophen [17].

The fact that morphine causes nausea and vomiting like pain seems to be one of the important limitations of this study. In conclusion we observed that IV paracetamol infusion decreases PONV and anti-emetic need, it also has similar analgesic effects as morphine and IV paracetamol infusion can safely be used as a replacement to opioids in children undergoing strabismus surgery. We think that more patients should be studied in order to increase the accuracy of the results.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval

Ethics committee approval of our study was received from Hacettepe University Hospital with registration number LUT 09/56.

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