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Original Article

Influence of pre-emptive versus preventive analgesia with oral acetaminophen on postoperative pain in painful ophthalmic surgeries: which one is better?

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Abstract

BACKGROUND: Patients undergoing certain ophthalmic operation are more likely to experience serious postoperative pain. This study was carried out to evaluate the effects of pre-emptive vs. preventive analgesia with oral acetaminophen on postoperative pain in painful ophthalmic surgeries.

METHODS: In a double blind clinical trial, 60 patients undergoing strabismus, retinal detachment or deep vitrectomy were randomized into three equal groups. The first group (G1) received oral acetaminophen one hour before induction of general anesthesia and placebo postoperatively. The second group received placebo before induction and acetaminophen after the operation (G2). The third group received placebo at both times (G3). Blood pressure, heart rate and occurrence of oculocardiac reflex (OCR) were recorded during the operation. Pain score (VAS: visual analog scale), the time of the first analgesic use (in hours), and total analgesic requirement (acetaminophen: mg) were determined until 24 hours postoperatively. Data was analyzed using ANOVA, Chi-2 and Kruskal-Wallis tests.

RESULTS: The mean pain score was lower in G1 compared with G2 at 2 and 24 hours after the operation (2.1 ± 0.6 vs. 2.7 ± 0.4, P = 0.001 and 1.1 ± 0.3 vs. 1.5 ± 0.5, P = 0, respectively). The pain score at 2, 6 and 24 hours after the operation was greater in G3 compared with G1 (2.8 ± 0.3 vs. 2.1 ± 0.6, P = 0, 2.3 ± 0.7 vs. 1.7 ± 0.5, P = 0 and 1.6 ± 0.4 vs. 1.1 ± 0.3, P = 0.001, respectively). There was no significant difference among the three groups with respect to the intraoperative hemodynamic changes, occurrence of OCR, the time of the first analgesic use and analgesic consumption.

CONCLUSIONS: The use of oral acetaminophen as pre-emptive analgesia one hour before painful ophthalmic surgeries may reduce postoperative pain intensity.

KEY WORDS: Ophthalmic surgery, postoperative pain, pre-emptive analgesia, preventive analgesia, acetaminophen.

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Clinical evidences demonstrate that surgical trauma may induce prolonged changes in both peripheral and central nervous systems that together amplify postoperative pain [1]. Preventing the establishment of altered central processing by analgesic treatment (defined as pre-emptive analgesia) may reduce acute postoperative pain [2]. Different agents and techniques have been used to study pre-emptive analgesia [3]. Patients undergoing some ophthalmic operations such as posterior segment, eye muscles or cornea were more likely to experience serious pain after surgery [4]. Previous studies have shown some pre-emptive analgesic effects in patients undergoing vitrectomy, retinal detachment and strabismus repair surgeries when general anesthesia was combined with regional anesthesia [5-8]. Hamilton has recently reviewed the complications of ophthalmic regional anesthesia in

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detail, including oculocardiac reflex, hemorrhage, brain stem anesthesia, globe perforation, myotoxicity, optic nerve damage and allergic responses [9].

Acetaminophen is frequently used for pre-emptive analgesia in surgeries associated with mild to moderate postoperative pain [10]. Peripherally, it is a weak inhibitor of cyclooxygenase, which accounts for the lack of any significant anti-inflammatory effects. Acetaminophen is thought to act as an inhibitor of the enzyme, scavenging hydroperoxides that seem to have an essential role in cyclooxygenase activity [11]. Acetaminophen also has a central site of action including inhibition of central cyclooxygenase activity and prostaglandin formation, and may interfere with various neurotransmitters and modulators controlling nociception [12]. Several studies have examined the prophylactic analgesic effect of acetaminophen in pediatric patients undergoing bilateral myringotomy and tonsillectomy [13-16]. No studies have been documented about the effect of oral acetaminophen as a pre-emptive analgesia on postoperative pain after painful ophthalmic procedures. It is suggested that further studies investigating pre-emptive or preventive analgesia should focus on patients undergoing these ophthalmic surgeries [4]. This clinical trial study was performed to assess the effects of pre-emptive vs. preventive analgesia with oral acetaminophen on postoperative pain in painful ophthalmic surgeries.

Methods

This double blind clinical trial study was approved by the Ethics Committee of our university and written consents were obtained from all patients or their parents. 60 patients ASA I , II with age of older than 10 who would be candidates for the strabismus surgery, the repairing of retinal detachment or deep vitrectomy under general anesthesia were studied in Feyz medical center of Isfahan, IRAN. Patients with history of opiate abuse or psychiatric disorders or usage of psychological and analgesic drugs were excluded from the study. Preoperative preparation was performed in all patients similarly. The NPO time was considered about 8 hours and during this period, patients received 0.3% saline in 3.33% dextrose solution 2 mg/kg/min. Anesthesia was induced with intravenous fentanyl 2 µ/kg, sodium thiopental 5 mg/kg and atracurium 0.6 mg/kg. After tracheal intubation, anesthesia was maintained using isoflurane (0.8%-1.2%) in O_2 (50%) and N_2O (50%). Propofol (100-150 µg/kg/min) with O_2 (50%) was used for patients who underwent retinal detachment repair or deep vitrectomy while N_2O (50%) was used for patients who underwent strabismus repair surgery. Intraoperative monitoring included electrocardiography, non-invasive blood pressure and pulse oximetry. Using a table of random numbers, patients were randomly allocated in three equal groups. In the first group (G1, n = 20) oral acetaminophen (Tylenol caplets: 500mg, Gitras inc. United States, New York) was administered one hour before operation and oral placebo at recovery room after full consciousness. Patients in the second group (G2, n = 20) received placebo before operation and acetaminophen postoperatively as the same time and dose as G1. In the third group (G3, n = 20), patients received placebo pre- and postoperatively. For blindness of the study, we used acetaminophen and placebo in preformed capsules. Patients with body weight of <25 kg, 26-50 kg, and >50 kg received 250 mg (0.5 caplets), 500 mg (1 caplets) and 750 mg (1.5 caplets) acetaminophen in preformed capsules, respectively. The anesthesiologist who provided the anesthesia and one of the investigators participating in the patients' evaluation were unaware of the type of medication administered.

Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial blood pressure (MAP) and heart rate (HR) were measured before the induction and during the surgery. After the induction the values were also recorded every 15 minutes until the completion of the operation. The occurrence of oculocardiac reflex (OCR), a vagal response manifested by cardiac arrhythmias and hypotension that elicited by pain, pressure, or manipulation

of the eyeball, were recorded during the operation [17]. Postoperative pain was assessed using an 11-point verbal analog pain score (VAS), with 0 corresponding to "no pain" and 10 to "the worst imaginable pain". The number of VAS equal to 1-3 was assumed as mild, 4-7 as moderate and 8-10 as severe pain. Pain scores were recorded at the recovery room after full consciousness of patients and at 1, 2, 6 and 24 hours_thereafter. One acetaminophen tablet was given to patients who requested an analgesic for postoperative pain. The time to first analgesic use as well as their 24 hour total requirement was recorded. Analgesic duration was defined as the time from completion of surgery until the first request for acetaminophen. Variables in two groups were compared using independent t-test for quantitative variables like age, operation time, SBP, DBP, MAP and HR before intervention. For comparison of quantitative variables between the two groups, ANOVA was used for repeated measurements, taking baseline values as covariate. Paired t-test was used to compare values in different times with baseline separately. Pain scores and amounts of postoperative analgesic were analyzed using Kruskal-Wallis test. Frequency distribution of patients' sex, type of operation, pain severity and occurrence of OCR were assessed by chi-square test. Values for quantitative variables were reported as mean ± standard deviation, and for qualitative variables as count and percent. For all tests statistical significance was assumed if $P<0.05$. SPSS version 12 was used for statistical analysis.

Results

There was no significant difference among the three study groups with respect to age, sex, type of surgery and operation time (table 1). SBP, DBP, MAP and HR did not differ among the three groups at any observation point. The occurrence of OCR during operation in G1, G2 and G3 groups was 2 (10%), 5 (25%) and 8 (40%) respectively ($P = 0.09$). The comparison of pain severity between the three groups is shown in table 2. There was no significant difference among the three groups with respect to pain score recorded at recovery time and at 1 hour after operation. The pain score was significantly different between the three groups at 2, 6 and 24 hours postoperatively (ANOVA). The pain score was lower in G1 compared with G2 at 2 and 24 hours after operation ($P = 0.001$ and 0 respectively, Tukey test). The pain intensity at 2, 6 and 24 hours after operation was greater in G3 compared with G1 ($P = 0$, $P = 0.006$ and $P = 0.001$, respectively, Tukey test). There was no significant difference between G2 and G3 in all the mentioned times. The occurrence of severe pain (VAS: 8-10) at recovery room, 1, 2 and 6 hours after operation is compared among the three groups in table 3. There was not any cases with complain of severe pain at 24 hours after operation in all the patients. There was no significant difference with respect to the time to first analgesic use among the three groups (G1: 2.6 ± 0.8, G2: 2.5 ± 0.7 and G3: 2.5 ± 0.6 hours).

Table 1. Patients demographic and operation characteristics

Characteristics		G1 (n = 20)	G2 (n = 20)	G3 (n = 20)
Age (year, mean ± SD)		34.8 ± 21.2	40.1 ± 23.2	35.4 ± 21.2
Sex (n, %)	Female	5 (25%)	6 (30%)	6 (30%)
	Male	15 (75%)	14 (70%)	14 (70%)
Type of surgery (n, %)	RD	6 (30%)	3 (15%)	3 (15%)
	ST	8 (40%)	11 (55%)	8 (40%)
	DV	6 (30%)	6 (30%)	9 (45%)
Operation time (min, mean ± SD)		101.2 ± 29.8	107.2 ± 29.7	117 ± 36.6

RD: retinal detachment repair, ST: strabismus repair, DV: deep vitrectomy.
No significant differences were seen among the groups.

Table 2. Comparison of pain scores among the three groups.

Times	Groups	Pain score (VAS: Mean ± SD)	P*
Recovery Room	1	2.8 ± 0.4	0.12
	2	3.0 ± 0	
	3	3.0 ± 0	
1 hour after operation	1	2.6 ± 0.5	0.19
	2	2.9 ± 0.2	
	3	2.9 ± 0.3	
2 hours after operation	1	2.1 ± 0.6	0.000
	2	2.7 ± 0.4	
	3	2.8 ± 0.3	
6 hours after operation	1	1.7 ± 0.5	0.009
	2	2.0 ± 0.6	
	3	2.3 ± 0.7	
24 hours after operation	1	1.1 ± 0.3	0.001
	2	1.5 ± 0.5	
	3	1.6 ± 0.4	

*ANOVA

Table 3. Comparison of severe pain (VAS: 8-10) occurrence among the three groups.

a.Groups	Recovery room	1 hour after operation	2 hours after operation	6 hours after operation
1	16 (80%)	13 (65%)	5 (25%)	1 (5%)
2	20 (100%)	19 (95%)	14 (70%)	4 (20%)
3	20 (100%)	18 (90%)	17 (85%)	10 (50%)
P*	0.014	0.095	0.001	0.012

*Pearson chi-square P value.

Although the mean consumption of postoperative oral acetaminophen was lower in G1 compared to G2 and G3 (325 ± 0.00, 425 ± 156 and 487 ± 165 mg respectively), but this difference was not statistically significant.

Discussion

Patients undergoing certain ophthalmic operation such as posterior segment, corneal and muscle surgery exhibit the highest postoperative pain intensity [4]. In present study, we compared pre-emptive vs. preventive analgesic effects of oral acetaminophen in patients who underwent painful ophthalmic surgeries. Data showed that there were not any_differences between pre-emptive (G1), preventive (G2) and placebo (G3) groups in regards of the postoperative pain intensity at recovery room and 1 hour after termination of surgeries. This fact may be related to remaining of analgesic effects of anesthetic and analgesic drugs used in general anesthesia. Pain scores were lower in pre-emptive and preventive groups compared with placebo group at 2, 6 and 24 hours after operation. These scores were not significantly lowered in pre-emptive compared with preventive group at 2 and 24 hours after operation. The frequency of severe pain was significantly lower in pre-emptive group compared with preventive and placebo groups at recovery room, 2, 6 and 24 hours after operation.

Mahfouz and Nabawi demonstrated that the use of sub-tenon block as pre-emptive analgesic before start of retinal detachment surgical repair under general anesthesia was effective in reducing postoperative pain [7]. Our results are compatible with findings of mentioned study, but were not similar to results of Ates and co-workers who reported that pre-emptive retrobulbar or subconjunctival blocks were not effective in reducing postoperative pain in strabismus surgery. This difference between our results and that of Ates study may be due to different pre-emptive analgesia technique, sample size (n: 20 vs. 10 in each group) and the duration of patients pain evaluation (24 vs. 6 hours) [8].

The effects of pre-emptive analgesia in postoperative pain relief in non-ophthalmic surgeries were showed in some studies [18-20]. The role of pre-emptive use of acetaminophen in reducing postoperative pain was shown in pediatric tonsillectomy patients [16] and pediatric patients undergoing bilateral myringotomy [13-15]. Our data are comparable with the results of these studies. The time until the first analgesic request was not significantly different among the three groups in our study. These findings are not similar to Reuben and co-workers study. This may be due to different operation and pre-emptive medication in both studies [18]. Total postoperative analgesic consumption was not significantly different among the three groups. This finding is similar to findings of some studies [16-21]. In this study, the occurrence of OCR was not different among the three groups. These results differ from findings of Mahfouz study in which the use of sub-tenon block as pre-emptive analgesia was effective in reducing intraoperative incidence of OCR [7]. This difference between the results of the two studies may be related to the different techniques of pre-emptive analgesia (oral acetaminophen vs. sub-tenon block). Development of central sensitization and hyperexcitability occurs after surgical incision and it results in the amplification of postoperative pain [1]. By preventing central sensitization, pre-emptive analgesia may reduce acute postoperative pain after surgery [2]. Acetaminophen by affecting central site including cyclooxygenase, prostaglandin and neurotransmitters activity may have an essential role in prevention of central sensitization. We concluded that the administration of oral acetaminophen (10mg/kg) as a pre-emptive analgesia one hour before painful ophthalmic surgeries under general anesthesia can reduce postoperative pain intensity.

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