

Effect of Intravenous Acetaminophen on Postoperative Pain in Vitrectomy: A Randomized, Double-Blind, Clinical Trial

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Abstract

Background: Nowadays, pain, nausea, and vomiting are regarded as important complications of anesthesia and surgery. The current study aimed at assessing the effect of preemptive intravenous acetaminophen on control of pain, nausea, vomiting, shivering, and drowsiness following the general anesthesia for retina and/or vitrectomy surgeries.

Methods: In a randomized, double-blind, clinical trial, 83 candidates for retina or vitrectomy eye surgery under general anesthesia were distributed into 3 groups: A) 41 patients in the control group who received 100 mL of normal saline just before the surgery and 100 mL of normal saline 20 minutes before the end of surgery; B) 21 patients in the preemptive group who received acetaminophen 15 mg/kg in 100 mL normal saline just before the surgery and 100 mL normal saline 20 minutes before the end of surgery; C) 21 patients in the preventive group who received 100 mL normal saline just before the surgery and acetaminophen 15 mg/kg in 100 mL normal saline 20 minutes before the end of surgery. Pain, nausea, vomiting, and shivering were assessed at the recovery and 2, 4, and 24 hours after the operation. Anesthesia emergence situation was assessed after arrival in the recovery room by the Richmond agitation-sedation scale (RASS) questionnaire. Blood pressure and heart rate were recorded before anesthesia induction, just after intubation, before extubation, and on discharge from the recovery room.

Results: Total intraoperative fentanyl, duration of operation, and duration of anesthesia were not different among the studied groups. Vital signs were not statistically different among the groups at before anesthesia induction, just after intubation, before extubation, and on discharge from the recovery room. Thirty-three patients in the control group (87.8%), 11 in preemptive (52.4%), and 14 in preventive groups (66.7%) needed acetaminophen in the first 24 hours after the surgery (P value = 0.008). Pain scores measured by visual rating scale (VRS) was lower in the preemptive and preventive groups, compared with those of the control group, in the recovery (P value = 0.006), 2 hours after the surgery (P value = 0.008), and 4 hours after the surgery (P value = 0.012), but not in 24 hours after the operation (P value = 0.1).

Conclusions: Intravenous acetaminophen administered as preemptive or preventive medication was effective and safe to control acute postoperative pain and analgesic request after the vitrectomy eye surgery.

Keywords: Intravenous Acetaminophen, Postoperative Pain, Vitrectomy

1. Background

Postoperative pain is a major complication in patients undergoing eye surgery (1, 2). As pain causes essential derangements in metabolism, it could affect the occurrence of other postoperative problems including respiratory complications, enhanced metabolism rate, salt and water retention, increased blood pressure, tachycardia, dysrhythmia, cardiac ischemia or infarcts, digestive tract problems, thromboembolic events, and anxiety and sleep disorders, which in turn may increase the overall costs of the hospital stay significantly. Proper application of anal-

gesics could be helpful to control such complications and results in overall quality of care and patients' satisfaction (3).

Preemptive analgesia is one of the known strategies to use analgesics, which could prevent pain and its central and peripheral hypersensitization before surgical tissue injury, to achieve a better result (4). Although opioids are used frequently in pain management, there are concerns about their possible complications (1, 5). Therefore, many studies focused on gabapentinoids (6-8), non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen or multimodal analgesia (9, 10), either as

preemptive, preventive, or as treatment of postoperative pain, and as substitute or additives for opioids (5, 9, 11, 12). Acetaminophen could be fascinating in this regard; it has no risk of nausea and vomiting, respiratory depression, urinary retention, and ileus of opioids (4, 5, 13), no platelet malfunction, gastric mucosal irritation, and renal toxicity of NSAIDs.

It is believed that acetaminophen prevents prostaglandin production in central nervous system (CNS) and inhibits pain impulses peripherally. Furthermore, it may block the central sensitization at spinal column. Acetaminophen passes the blood-brain barrier easily, to reach a high concentration level in cerebrospinal fluid (CSF) (11, 12). Intravenous acetaminophen metabolized in the liver by conjugation is excreted as glucuronide and sulfate forms from the kidney. However, less than 5% will excrete unchanged from kidney. Normally, its excretion half-life is 1 to 3 hours, which is increased in neonates and cirrhosis. Food and drug administration (FDA) approved intravenous acetaminophen to control mild to moderate pains alone and moderate to severe pains as additive for opioids (14).

Retina and vitrectomy surgeries are common worldwide, performed in high-risk patients with end-stage or poorly controlled systemic disorders. Under such circumstances, postoperative pain control could be of vital value.

2. Objectives

The current study aimed at assessing the effect of preemptive and preventive intravenous acetaminophen on the control of pain, nausea, vomiting, shivering, and drowsiness following general anesthesia in retina and/or vitrectomy surgeries.

3. Methods

A total of 83 patients undergoing retinal and/or vitrectomy surgery were enrolled in a randomized, double-blind clinical trial; the patients signed written consent, and were divided into 3 study groups.

Patients with significant pain syndromes, analgesic consumption in the last 48 hours, addiction or drug abuse history, end-stage renal or liver disease, and coronary, psychotic and neurologic diseases were not included in the study. Patients with any anesthetic or surgical complications that needed special care of reoperation in the next 24 hours, and the ones that denied or could not continue their cooperation, and delirious patients were excluded from the study.

All patients were educated to report pain based on verbal rating score (VRS) (0 to 10 scoring system, 0 = no pain, 10 = worst ever experienced pain) in their admission.

All patients were nil per os (NPO) for 8 hours before surgery and received 250 mL of normal saline (NS) before anesthesia induction. Following the administration of midazolam 0.01 mg/kg and fentanyl 2 μ g/kg, as premedication; intubation was performed after anesthesia induction by propofol 1 to 2 mg/kg and muscle relaxation by atracurium 0.5 mg/kg. Anesthesia maintenance was followed by propofol 100 to 150 μ g/kg/minute and remifentanyl 0.05 μ g/kg/minute. Anesthesia monitoring included pulse oximetry, non-invasive blood pressure (NIBP), and electrocardiogram. Based on a block randomization, patients were enrolled in 1 of the 3 study groups; A) 41 patients in the control group, who received 100 mL of NS before surgery and 100 mL of NS 20 minutes before the end of surgery; B) 21 patients in the preemptive acetaminophen group who received acetaminophen 15 mg/kg in 100 mL of NS before the surgery and 100 mL of NS 20 minutes before the end of surgery; and C) 21 patients in the preventive acetaminophen group who received 100 mL of NS before the surgery and acetaminophen 15 mg/kg in 100 mL of NS 20 minutes before the end of surgery.

Age, weight, height, and presence of concomitant medical problems; ie, diabetes mellitus, hypertension, thyroid diseases, etc. were recorded. The anesthesiologist and patients were blinded to the grouping. Another anesthesiologist was engaged in assessments before and after the surgery, and the nurses who assessed patients for pain scores, nausea, and vomiting in the recovery room, and 2, 4, and 24 hours after the surgery were also blinded to the surgery. Postanesthesia condition of each patient was evaluated and recorded based on the Richmond agitation-sedation scale (RASS) questionnaire, in 10 minutes after arrival in the recovery room. Pain control was provided by the intravenous doses of meperidine 0.5 mg/kg, every 2 hours if VRS scores were > 3. Total opioids or other analgesics in the first 24 hours after the surgery were recorded, as these medications were provided as needed, based on patient complaining from pain with VRS > 3. Blood pressure and heart rate values before anesthesia induction, 1 minute after intubation, before extubation, and before discharge from the recovery room were recorded.

3.1. Statistical Method

All variables were reported as means \pm standard deviation (SD) or the numbers of patients. Statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago IL, USA). Continuous data were compared by the one-way ANOVA, and the Bonferroni post hoc test was used to evaluate the differences between the 2 groups. To compare cate-

gorical data between the groups, Chi-square analysis or the Fisher exact test was performed appropriately. A P value < 0.05 was considered statistically significant.

4. Results

Eighty-three patients were enrolled in the study and none were excluded. Mean \pm SD age of the participants was 52.7 ± 15.2 years, ranged from 19 to 78; mean \pm SD body mass index (BMI) was 26.4 ± 4.4 kg/m² and male/female ratio was 44/39 (Table 1). There was no statistically significant difference among the groups in terms of age (P value = 0.87), weight (P value = 0.62), height (P value = 0.21), BMI (P value = 0.96), diabetes mellitus (P value = 0.56), hypertension (P value = 0.71), thyroid diseases (P value = 0.60), and fentanyl usage during the surgery (P value = 0.76) (Table 1). There was no statistically significant difference among the groups in terms of pain scores, based on ASA (American society of anesthesiologists) class (P value = 0.16) and RASS (P value = 0.22).

Blood pressure and heart rate recordings before anesthesia induction, 1 minute after intubation, before extubation, and before discharge from the recovery room were not statistically different (Table 2).

VRS pain scores were lower in the preventive and pre-emptive groups, compared with the control at recovery (P value = 0.006), 2 hours after the surgery (P value = 0.008), and 4 hours after the surgery (P value = 0.012), but not in 24 hours after the surgery (P value = 0.10) (Table 3). However, there was no statistically significant difference between the pre- and postoperation groups in this regard (P value = 0.99). Mean pain scores in the pre- and postoperation groups were lower in the recovery room, in comparison with other measurement times (P value < 0.001).

None of the patients in the postoperation group had nausea in the recovery room, but 7.3% of the patients in the control group and 4.8% in the preoperation group patients had nausea there. In 2 hours after the surgery, 34.1%, 23.8% and 33.3% of the patients had nausea in control, post- and preoperation groups, respectively. In 4 hours after the surgery, nausea occurred in 17.1%, 14.3%, and 14.3% of patients in the control, post- and preoperation groups, respectively. There were no statistically significant difference regarding the mentioned values (P values > 0.05).

Only 2 patients in the control group had vomiting in the recovery room, while there was no report on vomiting in other groups. In 2 hours after the surgery, vomiting occurred in 14.6%, 14.3%, and 9.5% of patients in the control, post- and preoperation groups, respectively. In 4 hours after the surgery, just 1 patient in the control group and 1 in the postoperation group had vomiting. In 24 hours after

the surgery, just 1 patient in the control group had vomiting. There was no statistically significant difference regarding the vomiting among the study groups (P value > 0.05).

In all studied cases, just 3 patients in the control group had shivering in the recovery room.

Postoperative administration of acetaminophen was reported in 36 (87.8%) patients in the control group, but in 14 (66.7%) patients in the postoperation group and 11 (52.4%) patients in the preoperation group (P value = 0.008).

5. Discussion

Based on the current study results, severity of pain based on VRS scores was lower in both acetaminophen groups, compared with the control group, while there was no statistically significant difference between the 2 acetaminophen groups. Furthermore, acetaminophen usage was more common in the control group, compared with 2 other groups. These results were in concordance with many other studies, which reported better pain control and lower analgesic usage following the intravenous administration of acetaminophen (5, 13). Khalili et al., used intravenous acetaminophen and found it effective on decrease of pain score and opioids use in 6 hours after the surgery in lower extremity surgeries, compared with the controls (15). Arici et al., reported similar results in the patients undergoing total abdominal hysterectomy; furthermore, they reported meaningful higher effectiveness of pre-operation intravenous acetaminophen compared with the postoperation group to control pain and decrease opioids use (16). Toygar et al., reported decrease of pain scores and morphine use in the first 24 hours after the discectomy, compared with the controls, while there was no obvious difference between the time of administration of acetaminophen either before or after the start of operation (17). Furthermore, Cakan et al., had the similar results with postoperative intravenous acetaminophen compared with NS in the control group regarding pain scores in the first 24 hours after surgery; they found no difference in opioids use in the patients undergoing lumbar discectomy and laminectomy (18).

However, there were some contradictories between the results of the current study and those of other studies (19). Vaideanu et al., found no difference in the pain scores and analgesic use between the intravenous acetaminophen and placebo groups in 60 patients undergoing panretinal photocoagulation surgery (19).

Differences in the results of intravenous acetaminophen could be the consequence of differences in the use of other coanalgesics, type of surgery, scheduling and education regarding pain score report, and other methodological variables.

Table 1. Demographic Variables of the Study Groups

	Control Group (n = 41)	Postoperation Group (n = 21)	Preoperation Group (n = 21)	P Value ^a
Age (year) mean (± SD)	50.2 (± 16.1)	52.3 (± 15.4)	51.6 (± 12.3)	0.25
Height (cm) mean (± SD)	165 (± 8.1)	164 (± 8.5)	168 (± 8.8)	0.21
Weight (kg) mean (± SD)	70.9 (± 14.2)	71.1 (± 12.1)	74.2 (± 12.2)	0.62
BMI (kg/m ²) (± SD)	26.3 (± 4.2)	26.7 (± 4.7)	26.4 (± 2.9)	0.96
Male, n (%)	23 (56.1%)	10 (47.6%)	11 (52.4%)	0.82
Diabetes mellitus, n (%)	12 (29.3%)	7 (33.3%)	9 (42.9%)	0.56
Hypertension, n (%)	16 (39%)	6 (28.6%)	7 (33.3%)	0.71
Thyroid diseases, n (%)	1 (2.4%)	0	2 (2.9%)	0.22
Intraoperative fentanyl (μg) mean (± SD)	79.2 (± 26.6)	76.2 (± 31.9)	82.6 (± 25.2)	0.76

Abbreviations: BMI, body mass index; Mean ± SD, mean (± standard deviation); n (%), number (percentage).

^aP value < 0.05.

Table 2. Vital Signs in Different Times During and After the Surgery^a

	Control Group (n = 41)	Postoperation Group (n = 21)	Preoperation Group (n = 21)	P Value ^b
SBP before induction (mmHg)	129 (± 21)	138 (± 25)	133 (± 21)	0.34
DBP before induction (mmHg)	84 (± 13)	85 (± 12)	84 (± 11)	0.97
HR before induction (pulse/min)	73 (± 14)	77 (± 13)	78 (± 18)	0.42
SBP 1 minute after intubation (mmHg)	117 (± 19.3)	120 (± 30)	116 (± 18)	0.81
DBP 1 minute after intubation (mmHg)	77 (± 13)	78 (± 16)	76 (± 13)	0.95
HR 1 minute after intubation (pulse/min)	73 (± 15)	77 (± 16)	77 (± 14)	0.43
SBP before extubation (mmHg)	125 (± 15)	133 (± 20)	129 (± 32)	0.35
DBP before extubation (mmHg)	80 (± 15)	84 (± 12)	86 (± 13)	0.21
HR before extubation (pulse/min)	73 (± 12)	78 (± 17)	74 (± 13)	0.41
SBP before discharge from the recovery room (mmHg)	125 (± 15)	130 (± 21)	131 (± 18)	0.49
DBP before discharge from the recovery room (mmHg)	77 (± 7)	78 (± 10)	96 (± 8)	0.85
HR before discharge from the recovery room (pulse/min)	74 (± 14)	72 (± 13)	71 (± 14.5)	0.91

Abbreviations: DPB, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

^aAll data are expressed as mean (± SD).

^bP value < 0.05.

In the current study, the pain scores and postoperative acetaminophen use had no statistically significant difference between the preoperation and postoperation acetaminophen groups; the increased efficacy of intravenous acetaminophen, when used as preoperative, was not approved by the current study results. It was consistent with the results of Toygar et al (17), but in contrast with the findings of Arici et al., who reported better pain control

and decreased opioids use in both acetaminophen groups (16).

Lower pain scores in the recovery room compared with the studied time in the preoperation and postoperation acetaminophen groups could be discussed by acetaminophen pharmacokinetic. Acetaminophen reaches to its peak plasma level in 45 minutes after oral administration, and 30 minutes higher than intravenous admin-

Table 3. Pain Scores in the Study Groups

	Control Group (n = 41)	Postoperation Group (n = 21)	Preoperation Group (n = 21)	P value ^a
VRS scores in the recovery room	3.2 (± 2.5)	1.5 (± 1.1)	1.6 (± 1.2)	0.008
VRS 2 hours after the surgery	5.3 (± 2.7)	3.4 (± 2.8)	3.2 (± 2.9)	0.008
VRS 4 hours after the surgery	3.7 (± 2.2)	1.9 (± 1.6)	2.2 (± 1.7)	0.012
VRS 24 hours after the surgery	1.6 (± 1.1)	0.86 (± 0.7)	1.2 (± 0.9)	0.193

Abbreviation: VRS, visual rating scale.

^aP value < 0.05.

istration. Acetaminophen half-life is 2 to 3 hours. The effect of intravenous acetaminophen is faster and longer than those of oral acetaminophen. The exact mechanism of analgesic effects of acetaminophen was not described, but there is evidence of central effect via prostaglandins production and serotonergic, opioids, nitric oxide, and cannabinoid pathways. Acetaminophen passes from blood brain barrier and increases serotonin in different parts of brain. It has peripheral anti-inflammatory effects, too (20).

In the current study, anesthesia complications including nausea, vomiting, and shivering were not different among the study groups, which confirmed the findings of Khalili et al., (15), however, it is in contrast with those of Cakan et al., (18) which showed the efficacy of acetaminophen to decrease postoperative nausea, vomiting, and shivering.

The current study found that, along with decrease of pain scores, intravenous acetaminophen did not deteriorate vital signs before induction, after intubation, before extubation, and in the recovery room, and there were no statistically significant difference in this regard.

Finally, based on the results of the current study, it could be concluded that preemptive and preventive use of intravenous acetaminophen could be effective and safe to control postoperative pain and analgesic use in the first 24 hours after surgery.

The current study had some limitations including low power of study, and a single-center study.

According to present study data, performing a greater multicenter or meta-analysis study could be encouraged.

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Footnotes

Conflict of Interest: Authors declared no conflict of interest.

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