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Comparison of Preventive Acetaminophen and Placebo in Pain Reduction After Cesarean Section; A Randomized Clinical Trial

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Abstract

Background: In subjects having a cesarean section, pain can increase hospital length of stay and postoperative complications. The preventive analgesia in the postoperative phase is known to be more effective than analgesic treatment in response to pain.
Objectives: In this study, the analgesic efficacy of preventive intravenous acetaminophen was compared with placebo in relieving postoperative pain after cesarean sections under spinal anesthesia.
Methods: In this double-blind randomized controlled study, 49 women undergoing elective cesarean section under spinal anesthesia were randomly allocated into two groups by block randomization in a referral hospital in Tehran in 2016. The intervention group received intravenous acetaminophen (Apotel®) (1 gram) and the placebo group received normal saline on arrival to the recovery room within 20 minutes. Then the total consumed doses of meperidine, visual analogue scale (VAS) score of pain, and the incidence of vomiting were determined and recorded for 24 hours postoperatively.
Results: Pain scores (VAS) were lower in the acetaminophen group throughout the study, but the difference was only significant at forth to eighth hours after the surgery ($P = 0.0001$). The total consumed doses of meperidine to treat the pain was significantly lower in the acetaminophen group at the fourth to the eighth hours after the surgery ($P = 0.0001$). The incidence of vomiting was the same between the groups ($P > 0.05$).
Conclusions: A single dose preventive intravenous acetaminophen has good efficacy in reduction of postoperative pain and reduces opioid use after cesarean sections under spinal anesthesia up to 8 hours after the administration.

Keywords: Analgesia, Postoperative Pain, Cesarean Section, Spinal Anesthesia, Acetaminophen

1. Background

Postoperative pain has many physiological, immunological, and psychological adverse effects, and development of chronic postsurgical pain is an unfortunate consequence of surgery that adversely impacts the patient's quality of life (1). There are several methods for postoperative pain management, including patient-controlled intravenous analgesia (PCIA), systemic analgesics, and regional methods.

To administer the systemic analgesics, preemptive and preventive analgesia methods are found to be more effective than the conventional method of postoperative analgesic use (2). In this regard, Nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen can be mentioned. Acetaminophen is a central cyclooxygenase (Cox3) inhibitor with less gastrointestinal side effects, antiplatelet aggregation effects, and is better tolerated (2). Owing to the side effect profile of opioids, such as respiratory depression, nausea, and vomiting, urinary retention, and constipation, a multi-modal approach of analgesia is the most common method of postoperative analgesia (3). The use of acetaminophen would decrease opioid consumption and prevent their side effects such as nausea and vomiting, hypotension, dizziness, prolonged bed rest, gastrointestinal problems.

In subjects having a cesarean section, pain can cause an increase in hospital length of stay and also could be a predisposing factor for other major complications such as constipation, atelectasis, and deep vein thrombosis (4). Analgesia after cesarean section is crucial to improve the

satisfaction rate in patients and decrease the complications. In postoperative pain management in subjects having a cesarean section, the neonatal concerns are also an important issue in the determination of the analgesic method. There are serious concerns about the adverse effects of postoperative mother's pain on the mother and neonate interactions and even long-term breastfeeding. Therefore, pain management after caesarian section needs special concern (5-7). The psychologic fragility of mother and the necessity of wellbeing to care the neonate elicit more concerns for pain management of obstetrics (8). There are several studies about the efficacy of preventive acetaminophen to reduce the postoperative opioid use, nausea and vomiting, and postoperative pain; however, there are few well-conducted randomized controlled trials regarding this issue (9, 10) .

2. Objectives

In this study, the preventive analgesic efficacy of intravenous acetaminophen is compared with placebo in relieving postoperative pain after cesarean sections under spinal anesthesia.

3. Methods

This is a double-blind randomized clinical trial study. After approval of the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1395.1119), forty-nine full-term women aged between 18 to 40 years were enrolled in this study who were candidates for elective cesarean section under spinal anesthesia in a referral hospital in Tehran, in 2016.

The inclusion criteria were as follows: term parturient, age range from 18 to 40 years, the American Society of Anesthesiologists (ASA) class 1 (healthy, non-smoking, no or minimal alcohol use) and 2 (mild disease only without substantive functional limitations), BMI < 40 who were candidates to undergo elective cesarean section under spinal anesthesia. The exclusion criteria were an operation duration of more than 3 hours, need for additional surgery, changing to general anesthesia or intraoperative opioid or anesthetic use, substance abuse, chronic pain syndromes, allergy to study medications, severe psychological disorders, hepatic, renal and cardiac diseases, preeclampsia, asthma, and an incision other than horizontal.

Helsinki declaration was applied to this study. All patients who fill the inclusion criteria and signed written informed consent form were included in the study and their demographic data were recorded. The patients were assigned to randomized permuted block method (each block with four patients) to receive either intravenous acetaminophen (1 gram in 100 mL normal saline) manufactured by UNIPHARMA company or placebo (100 mL normal saline) received normal saline on arrival to the recovery room within 20 minutes (50 mg/min). The primary outcome was total postoperative use of meperidine to treat the moderate or severe pains, visual analog scale (VAS) score and the second outcome was the incidence of emesis during the first 24 hours postoperatively. Before the surgery, the VAS was explained to the patients (0 as no pain and 10 as worst imaginable pain).

The study medications were prepared by an anesthesiologist who did not participate in the study. They were enveloped, sealed, and labeled with the patient's code. The envelopes were opened in the operating room before starting anesthesia by an anesthesiologist who was blinded to the patient study group and type of solution. On the day of the surgery, after arrival in the operating room, intravenous access was established and ECG, pulse oximeter, and non-invasive blood pressure monitoring were established. The anesthesia method was the same in all patients and spinal anesthesia was performed with a quincke 27-gauge needle with 12.5 mg bupivacaine 0.5% in the sitting position at the L3 - L4 or L4 - L5 interspaces. No sedative or dexamethasone was used during the surgery and all of the patients received 4 mg intravenous ondansetron after spinal anesthesia. The patients in the acetaminophen group received intravenous acetaminophen (Apotel®) (1 gram in 100 mL normal saline) and the patients in the placebo group received 100 mL normal saline in the recovery room. Postoperatively, all patients with VAS more than 3 received 100 mg diclofenac suppository and the patients with persistent VAS more than 3 received 25 mg intravenous meperidine up to maximum 200 mg within 24 hours. All of the data were recorded on a coded questionnaire, VAS, and opioid consumption was assessed at 0 (at arrival to recovery), 4, 8, 12, 24 hours postoperatively in the two groups. Also, the rate of vomiting was determined and compared across the groups at the same time. All of the data were collected by a nurse who was blinded to the patient group.

Data analysis was performed among 49 subjects, including 29 patients in the control group and 20 subjects in the intervention group by SPSS (version 23.0) software [Statistical Procedures for Social Sciences; Chicago, Illinois, USA]. Chi-square, Fisher's exact, and Independent sample *t*-test analyses were done and P values less than 0.05 were considered statistically significant.

4. Results

A total of 49 patients over a period of 6 months remained in the study after applying the exclusion criteria.

There was no difference between the two groups with regard to demographic characteristics (Table 1).

The meperidine usage was significantly lower in the acetaminophen group at 4 - 8 hours in comparison to the placebo group (P = 0.000) (Table 2).

As shown in Figure 1 and Table 3, there was a lower pain (VAS) in the acetaminophen group throughout the study, but the difference was only significant at forth to the eighth hours after the surgery (P = 0.000).

The incidence of vomiting was statistically similar between the groups and only one patient vomited in the control group (P = 1.000)

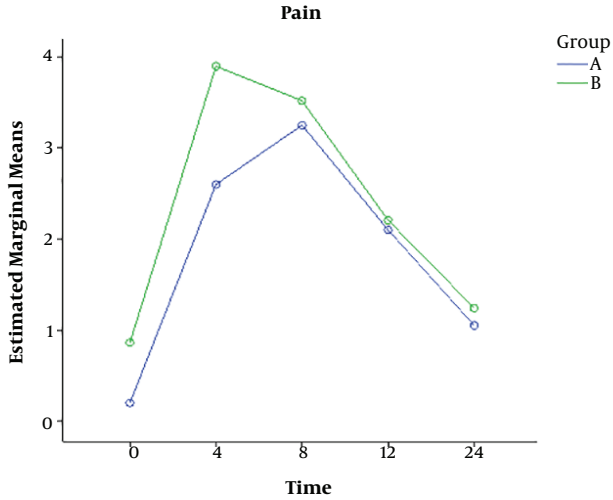

Figure 1. Pain is shown in the two groups during the study. A, acetaminophen group; B, normal saline group

5. Discussion

Cesarean section is a common surgical procedure ranging from 19 to 58 percent worldwide (10, 11). The indications to perform this method are comprised of repeated cesarean section, fetal distress, lack of labor progression, cephalopelvic disproportion (CPD), abnormal presentation, and hemorrhage (12). Despite the high safety of cesarean section, some adverse effects may be seen, which are more common in urgent procedures (12). Pain, bleeding, and infection are important concerns in cesarean section (10-13), which could decrease the satisfaction rate among the patients (14). Uncontrolled acute postoperative pain is associated with dissatisfaction and postoperative complications and is a strong risk factor for the development of chronic pain (15).

Preventive analgesia (analgesic before pain onset) has evolved from preemptive analgesia (analgesic before the surgical event), both have some advantages over the conventional treatment of pain (2). In this study, the preventive analgesic efficacy of intravenous acetaminophen was compared with placebo for postoperative analgesia in cesarean sections under spinal anesthesia.

Soltani et al. (16) reported that intravenous acetaminophen had higher efficacy for reduction of pain and opioid use in cesarean section in comparison to placebo and their results were similar to this study. Abu Omar and Awwad al Issa (17) assessed the efficacy of acetaminophen in cesarean section and it was seen that the use of this method led to lower opioid consumption as the results of this study showed. Ozmet et al. (18) reported the efficacy of preoperative use of single-dose intravenous 1 g paracetamol in decreasing the opioid consumption and the severity of pain in the first 24 hours in subjects having a cesarean section.

In a comparison of preemptive and preventive in-

Table 1. The Comparison of Independent Variables Between the Two Groups

	Acetaminophen	Control	P Value
Age, y	31.70 ± 1.5	32.24 ± 2	0.70
Gestational age, week	38.19 ± 1.5	38.41 ± 1.2	0.50
Height, cm	163.00 ± 4	164.20 ± 5	0.21
Duration of surgery, min	71.70 ± 11.5	70.05 ± 1.5	0.24

Table 2. Percentage and Number of Patients with Meperidine Injection Between the Study Groups

Time Intervals, h	Patient with Meperidine Injection[a]		P Value
	Acetaminophen	Control	
0 - 4	1 (5)	6 (20.7)	0.216
4 - 8	2 (10)	18 (62.1)	< 0.001
8 - 12	7 (35)	11 (37.9)	0.834
12 - 24	2 (10)	1 (3.4)	0.559

[a] Values are expressed as No. (%).

Table 3. The Comparison of Mean VAS Score Between Groups of the Study

Time Intervals, h	Mean VAS		P Value
	Acetaminophen	Control	
0 - 4	0.20	0.86	0.087
4 - 8	2.60	3.90	< 0.001
8 - 12	3.25	3.52	0.458
12 - 24	2.10	2.21	0.561

travenous paracetamol for pediatric dental surgeries, Kharouba et al. (19) indicated postoperative pain scores and opioid use were decreased in the preemptive IV paracetamol group in comparison to the preventive group. However, Imani et al. (20) in a study compared the effect of adding dexmedetomidine to paracetamol and ketorolac to control the postoperative pain in subjects having a cesarean section. They reported that the opioid use was slightly higher in the paracetamol group, and also the satisfaction was lower significantly in the paracetamol group.

Cattabriga et al. (21) assessed the efficacy of intravenous acetaminophen for cardiac surgery and it resulted in reducing the pain at 12, 18, and 24 hours after the operation. However, the opioid use was similar between the groups. Their results were generally consistent with the present study. Another study (22) reported lower pain after cesarean and lower tramadol use with the use of intravenous acetaminophen as we found in this study. Shimia et al. (23) assessed the efficacy of intravenous acetaminophen versus placebo for lumbar surgery and found that pain severity and analgesic use was lower in acetaminophen groups as we advocated in the current study. Jarineshin et al. (24) indicated that the meperidine decreased postoperative pain score and analgesic consumption more than paracetamol; however, it increased the vomiting score.

In the present study, we showed there were lower opioid consumption and VAS scores in the acetaminophen group, but the difference was only significant at forth to the eighth hours after the surgery. This time-limited efficacy could be matched with pharmacological properties of acetaminophen. On the other hand, vomiting was similar between the groups.

5.1. Limitations

This study used a single dose of acetaminophen and was held in one particular ethnic group in one medical center with particular medical protocols. Further studies with repeated doses in higher sample size to evaluate other secondary variables could enhance the utility of evidence-based outcomes.

5.2. Conclusion

We demonstrated preventive intravenous acetaminophen had better efficacy in the reduction of postoperative pain and opioid consumption after cesarean sections under spinal anesthesia in a limited time interval.

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Footnotes

Authors' Contribution: Study concept and design, analysis and interpretation of data, and statistical analysis: Ehsan Bastanhagh, Saghar Samimi Sadeh, and Somayeh Alsadat Moosavian; drafting of the manuscript: Saghar Samimi Sadeh and Ehsan Bastanhagh; critical revision of the manuscript for important intellectual content: Fardin Yousefshahi, Ehsan Bastanhagh, Saghar Samimi Sadeh, and Fatemeh Davari-Tanha.

Conflict of Interests: The authors declare that they have no conflict of interest regarding this study.

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