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The comparison of intraincisional bupivacaine infiltration and intravenous paracetamol administration for pain alleviation after cesarean section: a double-blinded randomized placebo controlled clinical trial

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Abstract. – OBJECTIVE: This study aimed to compare the analgesic effect of subcutaneous (SC) bupivacaine and intravenous (IV) paracetamol on postoperative pain and opioid requisites in patients undergoing cesarean delivery.

PATIENTS AND METHODS: One hundred and five women were allocated into 3 groups in this prospective, double-blind, placebo-controlled, randomized trial. Group 1 received SC bupivacaine, Group 2 received IV paracetamol following surgery and every 6 hours for 24 hours in the postoperative period, Group 3 received SC 0.9% saline and IV 0.9% saline at similar periods. Visual analogue scale (VAS) pain scores at rest and coughing, at 15 and 60 minutes, and 2, 6 and 12 hours, and total opioid necessity were measured.

RESULTS: VAS scores at rest were higher in placebo group than in bupivacaine and paracetamol groups at 15 minutes (p=0.047) and 2 hours (p=0.004). VAS scores at coughing were higher in placebo group than in bupivacaine and paracetamol groups at 2 hour (p=0.001) and 6 hours (p=0.018). Placebo group needed higher (p<0.001) doses of morphine than paracetamol or bupivacaine groups.

CONCLUSIONS: Intravenous paracetamol decreases pain scores similar to SC bupivacaine in the postoperative period compared to placebo. Patients taking bupivacaine or paracetamol need fewer opioid than placebo.

Key Words:
Opioid consumption, Pain score, Paracetamol, Bupivacaine.

Introduction

Cesarean section (CS) rates have been increasingly in various world regions[1,2]. Although effective analgesia has been shown to reduce postoperative complications[3,4], numerous studies[5-7] show that inadequate postoperative pain control is frequent in CS patients. Moreover, the most considerable concern of women undergoing CS is postoperative pain[8], which might hinder the bonding with the newborn and initiation of early breastfeeding[9]. On the other hand, insufficient pain relief would delay postoperative ambulation and, thus, increase the risk of thromboembolic events, which may increase postoperative maternal morbidity or mortality, give rise to prolonged hospital stay, and add up to the financial burden associated with CS. Acute pain following childbirth has also been demonstrated to impose an increased risk for persistent pain and postpartum depression[10]. Hence, any intervention that improves the postoperative pain alleviation would positively influence maternal and neonatal health as well as it would diminish the complications and costs.

The standard mainstay of pain relief in the postoperative period are opioids; however, they are known for their high-rate transfer into breastmilk and thus, sedative effects on the newborn in addition to decreased mentation and prolonged return of bowel function in mother[9]. To prevent the potential adverse effects of opioids, a variety of approaches, including local anesthetic agent wound infiltration, has been described for pain management after CS[11-14]. Cochrane Database systematic review[15] also indicated local analgesic infiltration to be of benefit in cesarean section. Intraincisional infiltration of bupivacaine is a commonly used postoperative analgesic regimen to alleviate post-cesarean pain[16]. Nevertheless,

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local anesthetic agents may present adverse effects, and even though in very small amounts, they are absorbed systemically and transferred to breastmilk[15]. Thus, the ideal postoperative analgesic regimen, which is expected to provide effective analgesia, be minimally invasive, not expensive and with minimal side-effects, is still being investigated[17].

On the other hand, paracetamol is often used after cesarean delivery, unless contraindicated, based on the knowledge that it does not present any risk to breast-fed infants, since it is expelled in breast milk in minor quantities[18]. However, evidence to support paracetamol use after caesarean delivery to control postoperative pain is limited. Thus, further investigation of paracetamol is required.

In this randomized, double blind, placebo-controlled study, we aimed to compare the effect of subcutaneous (SC) bupivacaine and intravenous (IV) paracetamol on postoperative pain and opioid requisites in patients undergoing cesarean delivery.

Patients and Methods

Study Design

A prospective, placebo-controlled, double-blind, randomized study was conducted between June 2014 and May 2015 in our Obstetrics and Gynecology Department, where approximately 7,200 women deliver each year. Institutional review board of local ethics committee approval was achieved before the beginning of the study. All patients signed an informed consent form and consented to the study. This study was registered to Clinical Trials (NCT02515422, available at: https://clinicaltrials.gov/).

Singleton pregnant women who had been scheduled for elective cesarean delivery were included in the study. Inclusion criteria included singleton term pregnancies between 38-41st weeks of gestation, age ≥ 18 years, ASA physical status I-II, and the lack of any important obstetrical problems. Exclusion criteria included multiple pregnancies, active labor, obstetric difficulties, intrauterine fetal deaths, unstable patients, clinically significant medical or surgical situations requiring special care or intraoperative complications that require extraordinary surgical procedures, special request for general anesthesia, known allergy or sensitivity to drugs used in the study, anxiety or depression throughout surgery, any systemic diseases (renal or hepatic insufficiency, thyroid diseases, chronic hypertension, epilepsy, psychiatric disorders, or intracranial hypertension) or medications which may alter the pain perception, history of opioid use, failure to understand VAS. Any participants received drugs that might change the perception of pain in the last seven days prior to cesarean section.

All participants were informed of the operation as usual, by the same physician who performed the cesarean operations. The participants completed a questionnaire evaluating sociodemographic characteristics and past medical history. The preoperative examinations involved anesthesia counseling and ultrasonic assessment. Afterwards, the pregnant women were randomly assigned into three groups using computer-aided random number chart with 35 patients in each group.

Patients, anesthetist, surgeon, and other staff were blinded to the contents of the medications. As shown in Figure 1, the Group 1 (Bupivacaine, n=35) received subcutaneous infiltration of 20 mL (100 mg) of bupivacaine 0.5% (Marcaine®, 20 mL inj. 5 mg bupivacaine hydrochloride/ml, AstraZeneca Drug Company, Istanbul, Turkey). The Group 2 (Paracetamol, n=35) received IV. paracetamol (Perfalgan®, 10 mg paracetamol/ml, 100 mL solution for infusion, Bristol-Myers Squibb, Rueil-Malmaison, France) 1 g (100 mL) after cesarean delivery and every 6 hours for 24 hours postoperatively. The Group 3 (Placebo, n=35) received SC 20 mL placebo (0.9% saline solution) plus IV. 0.9% saline administration (100 mL) at the same periods.

All procedures were carried out by the same experienced surgeon, using the consistent operation technique to exclude additional variables. The baseline arterial blood pressure, oxygen saturation electrocardiogram, and heart rate were monitored prior to anesthesia induction. Spinal anesthesia was managed at the L3-4 or L4-5 interspinous level by a 25G spinal needle. 8-10 mg bupivacaine 0.5% and 20 μg fentanyl were administrated intrathecally over 20 seconds to accomplish a T4 sensorial block, and then the surgery was consented to continue. There were three separate anesthesia trays for three different treatment groups labeled G1, G2 and G3 containing the bupivacaine, paracetamol, and normal saline solution. All subcutaneous medications were 20 mL in volume and identical syringes were used. All paracetamol and normal saline solutions were in an identical

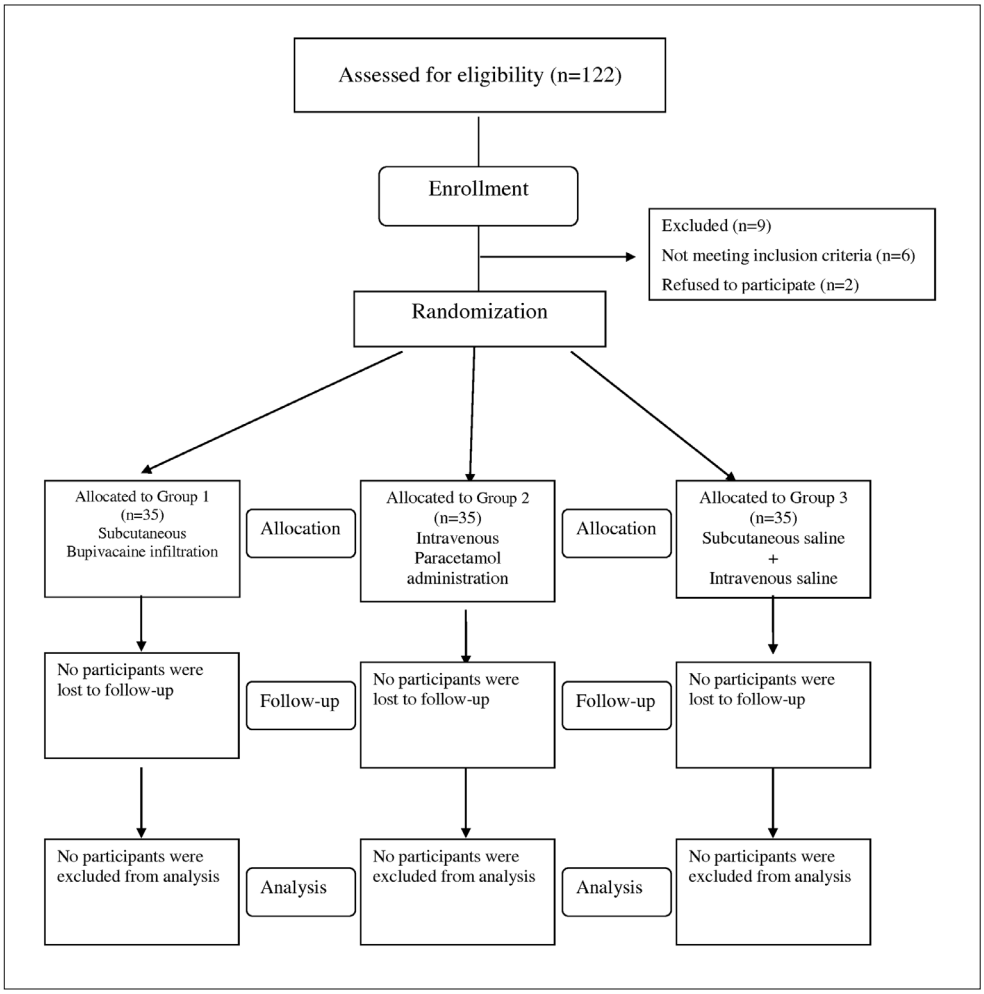

Figure 1. Flowchart diagram, the included and excluded patients. Values are presented as the mean ± standard deviation (SD).

bottle, not allowing identification of content to ensure blinding. Following the completion of operations, patients were transferred to the anesthesia recovery room, where they received routine postoperative care. Pain management after cesarean section was achieved through a patient-controlled IV analgesia device releasing morphine.

During the postoperative period, pain assessments were documented using a standard 10-cm VAS, throughout the postoperative 15th and 60th minutes, 2nd, 6th, and 12th hours, by the patients grading the pain from 0 (no pain at all) to 10 (worst pain) at rest and on coughing by an anesthetist blinded to study groups. If VAS score was ≥ 4, 75 mg diclofenac sodium (Dikloron®, Deva Drug Company, Istanbul, Turkey) was injected intramuscularly. The total diclofenac sodium dose did not surpass 150 mg in 24 hours. Total morphine consumption in PCA was also recorded.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v. 18 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using Shapiro-Wilk test. Variance homogeneity assumption was tested with Levene test. Parametric tests (Independent-samples *t*-test and post hoc Tukey test) were applied to data of normal distribution and non-parametric tests (Mann-Whiney U-test and Kruskal-Wallis Test) were applied to data of questionably normal distribution. Bonferroni post-hoc analysis was used for multiple comparison tests. The results for all items were expressed as mean±SD, assessed within a 95% reliance and at a level of $p<0.05$ significance. While determining sample size, reference values were received from the study by Honarmand et al[19] and found that minimum of 30 patients were needed in each group for significant difference between groups

Table I. Demographic and clinical characteristics of the groups.

	Group 1 (n = 35)	Group 2 (n = 35)	Group 3 (n = 35)	p
Age (mean ± SD)	29.74 ± 5.54	29.69 ± 6.45	29.51 ± 5.38	0.985*
BMI (mean ± SD)	29.06 ± 3.48	28.68 ± 4.28	28.98 ± 3.84	0.909*
Gravidity (median, range)	2 (2-3)	3 (2-3)	2 (2-3)	0.953**
Parity (median, range)	2 (2-3)	3 (2-3)	2 (2-3)	0.974**
Gestational age (median, range)	39 (39-40)	39 (39-40)	39 (39-40)	0.828**

*One Way ANOVA (with Bonferroni corrected). **Kruskal-Wallis Test (Mann-Whitney U test for post-hoc analysis).

for 80% power at type I error of 0.05. Analyses were performed by G-Power 3.1.7 (Kiel University, Kiel, Germany).

Results

A total of 105 singleton pregnant women were included. Each group consisted of 35 patients. As shown in Table I, the baseline characteristics of patients did not show significant difference among study groups.

Resting VAS scores at postoperative 60th minute, 6th hour and 12th hour time intervals were comparable, whereas they were significantly different at 15th minute (p=0.047) and 2nd hour (p=0.004) among the groups (Table II). At the 15th min time point, the statistically significance originated from the difference between paracetamol and bupivacaine groups. VAS scores at rest were significantly higher in paracetamol group than in bupivacaine group at 15 min. At the 2nd hour, mean resting VAS score was significantly higher in the placebo than in paracetamol and bupivacaine groups.

Coughing VAS scores at 15th, 60th min, and 12th hour intervals did not significantly differ (p=0.064, p=0.442, and p=0.225, respectively). However, at the 2nd and 6th hour controls, significant differences were present among study groups (p=0.001 and p=0.018, respectively). Placebo group had significantly increased VAS scores on coughing than those receiving bupivacaine or paracetamol at 2nd hour. At 6 hours, VAS score on coughing was higher in placebo group compared to the paracetamol group. Postoperative resting and coughing VAS scores are presented at Figures 2 and 3, respectively, with

Table II. Comparison of postoperative resting and coughing pain scores at different time intervals and postoperative opioid or analgesic requirements.

	Group 1 (n = 35) (mean ± SD)	Group 2 (n = 35) (mean ± SD)	Group 3 (n = 35) (mean ± SD)	p
Resting VAS scores				
15th min	0.08 ± 0.37*	0.89 ± 1.75	0.66 ± 1.57	0.047
60th min	1.09 ± 2.49	1.40 ± 1.59	1.51 ± 1.48	0.563
2nd hour	1.86 ± 1.59^{+}	1.89 ± 1.43^{+}	2.94 ± 1.47	0.004
6th hour	2.54 ± 1.65	1.94 ± 1.37	2.66 ± 1.66	0.128
12th hour	1.71 ± 1.74	1.40 ± 1.22	1.86 ± 1.59	0.446
Coughing VAS scores				
15th min.	0.23 ± 0.69	1.11 ± 1.92	0.86 ± 1.88	0.064
60th min.	1.63 ± 2.29	2.00 ± 1.97	2.26 ± 1.90	0.442
2nd hour	2.60 ± 1.80**	2.46 ± 1.74**	3.86 ± 1.46	0.001
6th hour	3.20 ± 1.59	2.26 ± 1.52^{++}	3.29 ± 1.84	0.018
12th hour	2.60 ± 1.82	1.97 ± 1.58	2.51 ± 1.50	0.225
Total VAS scores	8.77 ± 5.39	8.66 ± 4.57	11.20 ± 5.51	0.072
Total morphine consumption	11.01 ± 4.14§	10.64 ± 3.53§	16.04 ± 3.99	0.000
Additional analgesic requirement	0.54 ± 0.61	0.49 ± 0.56	0.77 ± 0.65	0.119

*p < 0.05 *vs.* Group 2; ^{+}p < 0.05 *vs.* Group 3; **p < 0.05 vs. Group 3; ^{++}p < 0.05 *vs.* Group 3 and Group 3; $^{§}p$ < 0.05 *vs.* Group 3. VAS: visual analog scale.

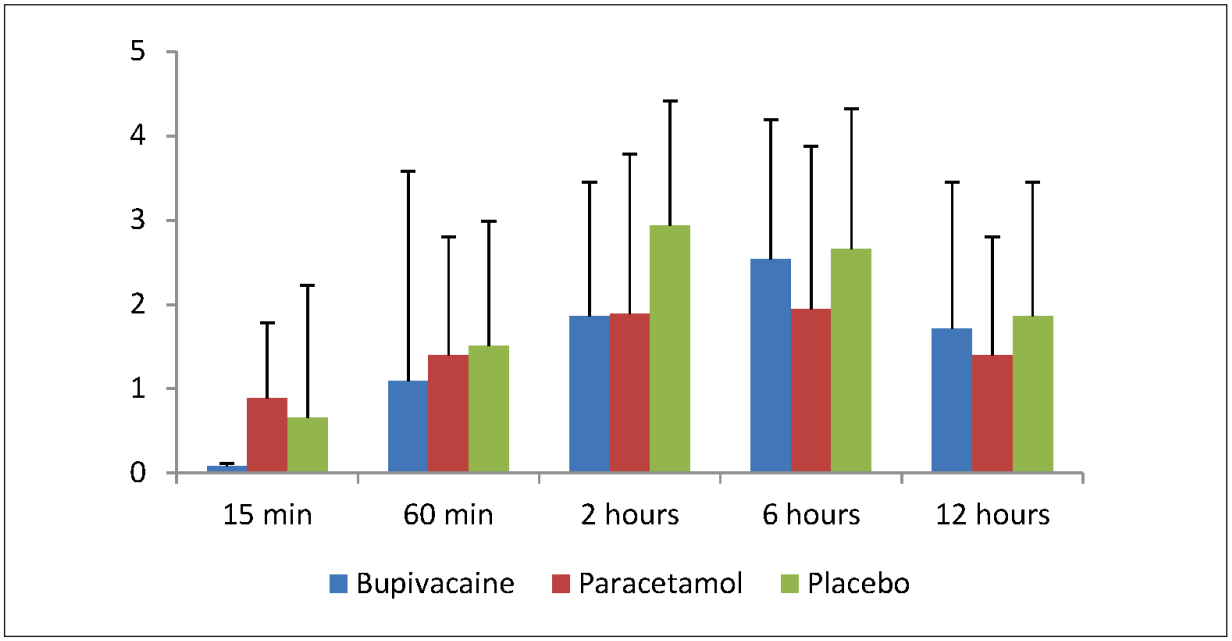

Figure 2. Postoperative resting visual analog scale (VAS) scores in the treatment groups. Values are presented as the mean ± standard deviation (SD).

the respective mean and standard deviation values. Additionally, total VAS scores did not differ significantly among the study groups (p=0.072).

Additional analgesic requirement was comparable among study groups (p=0.119). However, total morphine consumption was significantly different among the groups (p<0.001). Accordingly, placebo group needed higher doses of morphine than bupivacaine and paracetamol groups. Patients in paracetamol group required the lowest doses of morphine among the groups.

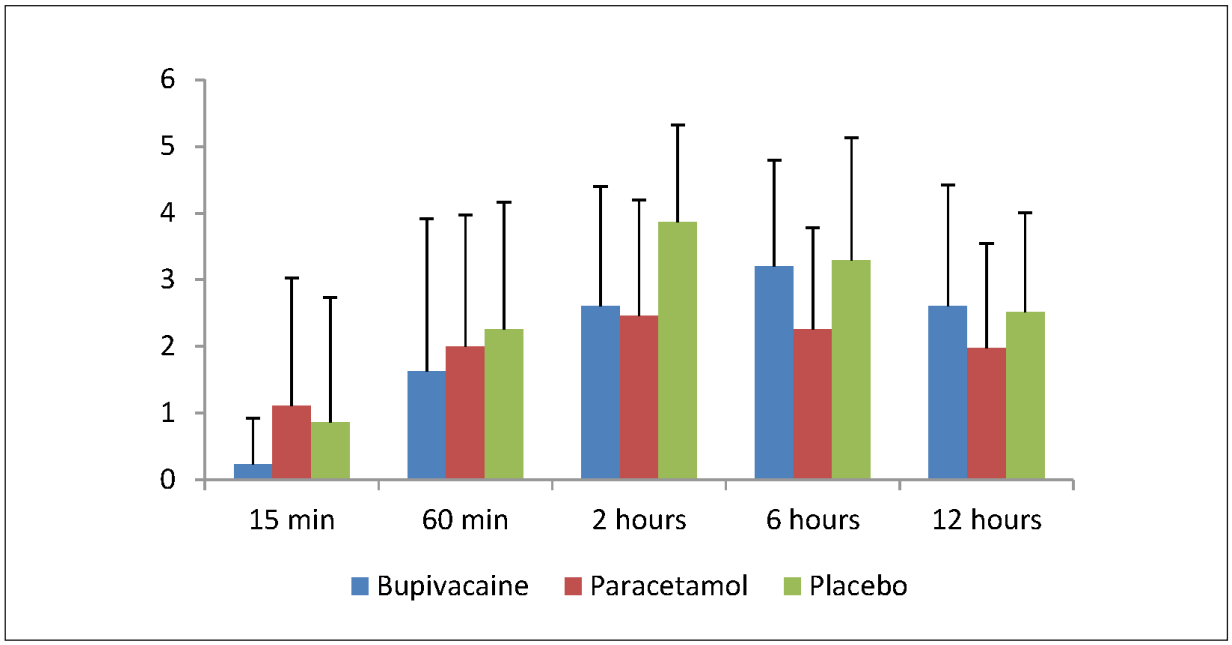

Figure 3. Postoperative coughing visual analog scale (VAS) scores in the treatment groups.

Discussion

In obstetrics practice, the most frequently used analgesic is paracetamol since it is known to be safe to use during pregnancy and human lactation. Paracetamol acts by central and peripheral NmethylDAspartate receptor and cyclooxygenase 2 (COX2) pain pathway inhibition[20].

Perioperative IV paracetamol administration for postoperative pain treatment has been appraised by systematic reviews[21] and was reported to be in association with lower pain scores and reduced postoperative opioid consumption. Moreover, single dose of IV paracetamol was reported to be efficient to alleviate postoperative pain[22-23].

Paracetamol has been compared with NSAIDs or COX inhibitors in women undergoing cesarean delivery in several studies[24-27]. Alhashemi et al[24] indicated that VAS scores and postoperative morphine consumptions did not significantly differ between patients receiving IV paracetamol and oral ibuprofen and concluded that IV paracetamol was a reasonable alternative to oral ibuprofen. Kiliçaslan et al[25] concluded that IV paracetamol significantly reduced the pain scores and tramadol consumption when compared to placebo. Mitra et al[26] compared IV paracetamol with tramadol in combination with rectal diclofenac in patients undergoing CS and reported that diclofenac-tramadol and diclofenac-acetaminophen combinations were comparable in achieving satisfactory pain control. Ayatollahi et al[27] assessed the preoperative single dose of IV paracetamol to control postoperative pain and suggested that patients given paracetamol had lower VAS scores and reduced analgesic dose in pain control.

Contrarily, Siddik et al[28] demonstrated higher morphine-sparing effect and better rest and on coughing VAS scores in diclofenac and diclofenac plus proparacetamol groups. Paech et al[29] reported no improvement in neither pethidine consumption nor in pain scores after the addition of IV and oral paracetamol to PCA epidural analgesia.

Local analgesic effect of bupivacaine has been investigated in several studies[8,11,16,30-32], and it is a commonly used local analgesic drug for intraincisional wound infiltration. Bupivacaine is considered to decrease opioid consumption and postoperative pain after cesarean delivery[16,32-35]. To the best of our knowledge, no study exists comparing the two very commonly used postcesarean analgesic regimens, IV paracetamol and intraincisional bupivacaine administrations, in a randomized controlled design. The present study investigated the postoperative pain and opioid requirement in after CS.

According to the results of our study, intraincisional bupivacaine infiltration and IV paracetamol administration significantly reduced postoperative opioid use and pain scores at rest and on coughing. Nevertheless, SC bupivacaine presented lower pain scores at rest than paracetamol in early postoperative period. Although the results of bupivacaine and paracetamol were similar, paracetamol might be a plausible alternative option in patients for which the local anesthetics are contraindicated or in those who wish to avoid the potential side effects of these agents. In the literature there are only two studies[33,34] comparing the effects of bupivacaine with IV paracetamol use on postoperative pain relief. Upadya et al[34] compared the efficacies of intraperitoneal bupivacaine and IV acetaminophen after cholecystectomy and reported that postoperative pain was greater in bupivacaine group than the paracetamol group at 8th, 12th and 24th hour time intervals and that IV paracetamol provided continued pain alleviation for 24 hours postoperatively. Rasooli et al[33] revealed that patients receiving intraperitoneal infiltration of bupivacaine and meperidine were compared to those receiving IV paracetamol infusion regarding postoperative pain and total morphine consumption after gynecologic laparoscopy and the authors reported better results for bupivacaine+meperidine group, only at postoperative 2nd, 4th, and 8th hours but not at 1st, 12th, and 24th hours. In contrast, our results revealed that at the postoperative 15th min at rest, pain scores were greater in paracetamol group compared to bupivacaine group. At the 2nd hour, pain scores in the bupivacaine and paracetamol groups were similar, but lower than the placebo group at rest. The groups did not differ with regard to pain scores at 6th and 12th hours at rest and at 12th hour on coughing.

One limitation of this study is the lack of the categorization of the patients according to the number of previous cesarean deliveries, since previous cesarean surgeries might have altered the pain perceptions. One bias of the study could be the fear of the parturient to receive analgesic agents and to avoid pushing PCA button due to the apprehension that these drugs may affect the baby.

Conclusions

In conclusion, IV paracetamol or subcutaneous bupivacaine administration reduces postoperative pain in the first 6 hours. In early postoperative period (15th min), intraincisional bupivacaine administration is superior to IV paracetamol in relieving pain, particularly at rest. Moreover, bupivacaine or paracetamol administration reduces postoperative morphine use compared to placebo.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

H. Aksoy and U. Aksoy designed the study, M. Ak and H. Aksoy collected the data, and M. Ak, G. Gokahmetoglu, and H. Aksoy analyzed the data and wrote the manuscript. M. Ak and H. Aksoy contributed to the study design and wrote the manuscript. All authors read and approved the final manuscript.

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Ethics Approval

All interventional procedures in this study were performed in accordance with both ethical and Helsinki Declaration standards. Ethics Committee approval was released from Erciyes University Medicine Faculty (2014/99).

Informed Consent

Informed consent was obtained from all participants.

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