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AIM: *The issue of preemptive or preventive use of paracetamol still raises questions in terms of multimodal analgesia in cesarean delivery. A combination of paracetamol and opioid is commonly used for pain management after cesarean delivery. This study aims to compare postoperative pain level and analgesic consumption when using paracetamol at two different perioperative times in cesarean section.*
MATERIAL AND METHODS: *Sixty patients recruited for elective cesarean section under general anesthesia were included in this prospective study. Patients were randomly assigned to receive iv 1 g paracetamol 15 minutes before incision (Group PE) or after delivery of newborn (Group PV). Visual analog scale (VAS) values, 24-hour morphine consumption, additional analgesic requirement, side effects, and patient and surgeons' satisfaction were recorded.*
RESULTS: *Demographic data and hemodynamic values of the patients were similar in both groups. There was no differences between groups in terms of VAS scores at rest and during movement, additional analgesic requirement during the postoperative 1st hour, and 24-hour total morphine consumption. There was no difference in side effects, and patient and surgeon satisfaction scores postoperatively.*
CONCLUSIONS: *Preemptive and preventive use of paracetamol provides the same quality of analgesia and opioid sparing effect without increasing the frequency of adverse effects.*

KEY WORDS: Analgesia, Cesarean Section, General Anesthesia, Preemptive, Preventive

Introduction

Pain is one of the most frequent complaints after a cesarean section (CS) [1]. Postcesarean pain may impair the mother's ability to take care of and feed her baby in the immediate postoperative period. Early interaction between mother and newborn may also be negatively affected [2]. Furthermore, inadequate postoperative pain control is a crucial risk driver for the development of chronic pain and depression [3].

Paracetamol is a non-opioid drug whose mechanism of action is still not fully understood. It is thought to inhibit prostaglandin synthesis by inhibition of the cyclooxygenase (COX) enzyme in the central nervous system [3]. It is well known that other mechanisms such as serotonergic and opioidergic systems also contribute to its analgesic effect mechanism. The drug crosses the placenta but its safety in therapeutic doses for both mother and fetus has been established in the literature [4].

Preemptive analgesia is a treatment method that is initiated before the surgical procedure.

It is intended to prevent central sensitization caused by surgical incisional injury and other inflammatory responses to surgery. It is stated that it is more effective for postoperative pain control compared to the same treat-

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ment initiated after surgery [5]. Preventive analgesia is a broader concept. It is aimed to block the development of sustained pain. This definition includes any agent given at any time during the perioperative period that will be able to control pain-induced sensitization [5].
This study aims to compare the efficacy of preemptive and preventive use of paracetamol on postoperative pain scores, additional analgesic requirement, total morphine consumption, and patient and surgeon satisfaction scores in patients undergoing elective cesarean section under general anesthesia.

Material and Method

This study was approved by the Baskent University School of Medicine Ethics Committee (KA15/80) and was registered in ClinicalTrials.gov (NCT02714179). The study was completed within 6 months with the written informed consent of all patients. Sixty pregnant women who were planned for general anesthesia for elective cesarean delivery were included in this trial. Inclusion criteria entailed an elective single fetus pregnancy, a gestation period of over 37 weeks, and refusing regional anesthesia.
Exclusion criteria included cardiopulmonary or psychiatric diseases, allergy to the study drug, history of frequent analgesic use, intraoperative complication, and inability to use a patient-controlled analgesia (PCA) device. Detailed information and instructions about the use of PCA devices and visual analog scales (VAS) were given to the patients during the preoperative visit.
Patients were randomly allocated to one of the two study groups using computer-generated random number assignment (www.randomization.com).
Groups were designated as the Preemptive (PE) group and preventive (PV) group. Study participants, service nurses, and outcome evaluators were all blind to which group the patients were in (PE group or PV group). Fifteen minutes before the start of surgery patients in group PE (n=30) received iv 1 g of paracetamol (100 mL) and patients in group PV (n=30) received 100 mL of saline. To ensure the double-blind design the drugs were given by an anesthetist who was not one of the observers. All patients were informed 6 hours of preoperative fasting before surgery. No patient received premedication.
In the operation room, standard anesthesia monitoring was performed to all the patients. Anesthesia was initiated with lidocaine (0.5 mg kg^{-1}), propofol (2-3 mg kg^{-1}), and rocuronium bromide (0.6 mg kg^{-1}). Sevoflurane at 1-2% concentration in a 50% N_2O/O_2 mixture was used for maintenance.
Immediately after the delivery of the baby, morphine (0.1 mg kg^{-1}) was given to both groups. 100 mL normal saline was also given to group PE and 1 g paracetamol (100 ml) was given to group PV. Apgar scores were evaluated at the 1st and 5th minutes. Neuromuscular blockade was reversed by neostigmine and atropine combination at the end of the operation.
All patients were observed in the recovery room for one hour and evaluated in terms of hemodynamic variables and VAS (0=no pain, 10=the worst pain) scores at rest and during movement.
PCA with morphine was administered to all patients (0.015 mg kg^{-1} bolus dose, 15 min lockout, no background infusion, and 4h limit).
In addition to PCA therapy, 1 mg morphine was administered as an additional analgesic to the patients with VAS≥3. In the postoperative period, iv 1 g of paracetamol was given at 6-hour intervals to both groups for 24 hours by the service nurse who did not know the study. Postoperative 5th, 15th, 30th minute, 1st, 2nd and than followed by hours 4, 6, 12 and 24 hours the hemodynamic data, resting and movement VAS scores, additional analgesic requirement, total morphine usage in 24 hours, sedation levels, side effects (nausea, vomiting, constipation, allergic reaction, etc.), patients' and surgeons' satisfaction were recorded.
Sedation level was evaluated with the 6-point Ramsey Sedation Scale (1=awake, agitated patient, 2=awake, oriented patient, 3=patient responding only to orders, 4=sleeping patient who responds quickly by hitting the glabella, 5=sleeping, slow responding to stimuli, 6=patient unresponsive to a painful stimulus). Patient satisfaction was evaluated using a 4-point Likert scale (1=strongly pleased; 2=somewhat pleased; 3=somewhat not pleased; 4=strongly not pleased) and surgeon satisfaction was evaluated using a 4-point Surgeon Satisfaction Score (0 =bad, 1=fair, 2=moderate, 3=good, 4=perfect).
The primary outcome measure was the pain score which was evaluated by the visual analog scale. Secondary outcomes were an additional analgesic requirement, opioid use at 24 hours, patients' and surgeons' satisfaction.

Statistical analysis

In our study, the statistical parameters in the reference study[6] were taken into account in determining the sample size. Win-Epi 2.0 program was used for sample calculation. After sampling with a 95% confidence interval and 80% power, it was planned to enroll a total of 60 patients with 30 patients for each group in the study.
For statistical analysis of the data, SPSS 17.0 program was used. Categorical measurements were presented as numbers (percentages), and continuous measurements were expressed as Mean±SD, Median (Min-Max). Fisher's test was used to compare categorical variables. In the intergroup comparison of numerical variables, Student's t-tests were used when the assumptions were fulfilled, and Mann-Whitney U tests were used when the assumptions were not fulfilled. The statistical significance level was taken as 0.05 in all tests.

Results

Sixty-nine patients were initially assessed for the study but nine patients were excluded (did not meet the inclusion criteria [n=5] and refused to participate [n=4]). As a result, 60 patients were analyzed (Fig. 1).

Demographic variables were presented in (Table I) and no significant differences between the groups in terms of demographic variables were detected. Hemodynamic data also (SBP, DBP, HR, SpO_2) didn't differ among the groups during the preoperative and intraoperative periods (p>0.05). There was no statistically significant difference between the groups in terms of VAS scores at rest and during movement (Table II), additional analgesic requirement during the postoperative first hour (Table III), and 24-hour total morphine consumption (Table IV).

No significant difference was found between the two groups in terms of postoperative side effects (nausea, vomiting, constipation, allergic reaction, etc.), Apgar scores, patient and surgeon satisfaction scores (p>0.05), (Table I). The level of sedation during the postoperative period was similiar between the groups. Postoperative hemodynamic values (SBP, DBP, HR, SpO_2) remained stable for 24 hours and did not differ between the groups during the postoperative period (p>0.05).

Discussion

With this prospective study, we found that the use of preemptive and preventive iv paracetamol in the treatment of acute postoperative pain provided similar pain scores after cesarean section. In addition, we found that both implementations reduced the frequency of nausea and vomiting in the early postoperative period.

Providing optimal postoperative pain control is a determinant factor in the early and late success of surgical interventions. Poorly managed early postoperative pain is the most important risk factor for chronic pain that

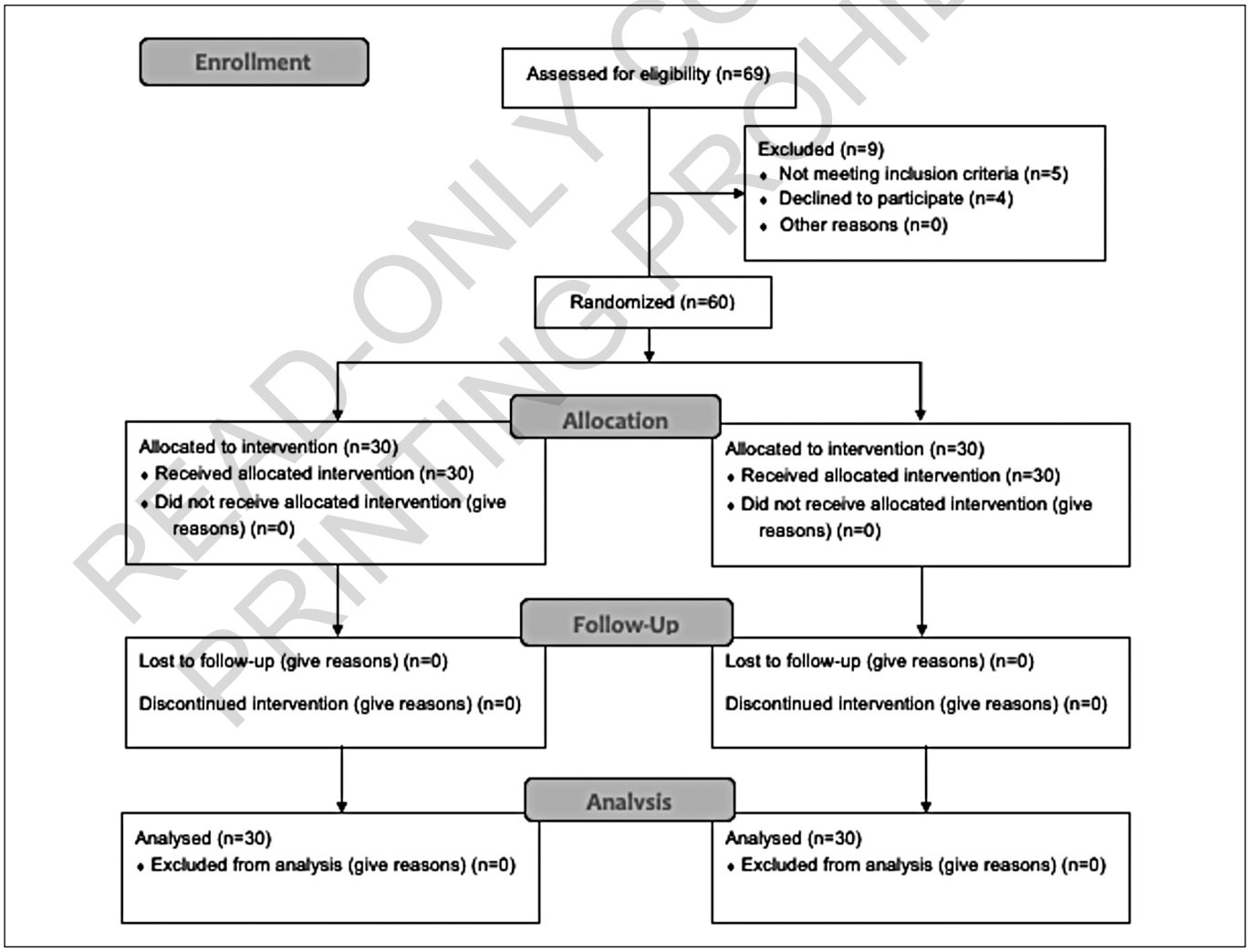

Fig. 1: Flow chart describing enrollment, allocation, follow-up and analysis of the study group.

develops after surgery [7]. This principle is more important in obstetric cases because, compared to the general surgery population, the mother must be mobilized early to feed and care for the baby after birth. In addition, uncontrolled postoperative pain will adversely affect breastfeeding and care of the newborn and it may lead to an increased risk of developing thrombotic events, chronic pain syndromes, and postpartum depression in the long term [1,2]. Even though there is improvement in pain management, postoperative pain control is often insufficient in this group of patients. This may be due to interindividual variabilities, poor understanding of mechanisms and dose restrictions due to side effects of analgesic drugs [4].

Paracetamol's analgesic efficacy, and safety have also been well demonstrated in various surgical procedures [8,9]. There are many trials in the literature that has investigated the effects of preemptive and preventive methods on postoperative pain scores following different surgical procedures and majority of the studies show the beneficial effects of preemptive analgesia [8,9,10].

To our knowledge, there is only one study comparing the preemptive and preventive use of paracetamol in cesarean delivery performed under general anesthesia [11]. In their study Group PE (n=30) received 1g of paracetamol 30 minutes before the surgery and patients in group PV (n=30) received it 30 minutes before the end of the operation. It was stated that VAS scores were significantly higher in the PE group at the first and 6th hours, and at the 4th and 8th hours in the PV group. In addition, it was found that the need for additional analgesia was higher in the PE group compared to the PV group but there was no difference between the groups

Table I - *Demographic and surgical characteristics.*

	Group PE (n=30)	Group PV (n=30)
Age (years)	31.63±5.36	31.66±4.81
Weight (kg)	81.56±9.52	79.00±9.14
Height (cm)	166.76±4.09	166.16±4.77
ASA II/III	30/0	30/0
Gravidity	2 (1-5)	2 (1-6)
Parity	1 (0-2)	1 (0-2)
Gestational age (wk)	38.36±0.69	38.57±0.74
Duration of surgery (min)	33.83±5.82	33.16±5.49
Birth weight (g)	3356.00±456.62	3326.00±467.83
Apgar score 1 min	9 (7-9)	9 (5-9)
5 min	10 (9-10)	10 (9-10)
Side effects	0	0
Patient satisfaction score	1 (1-2)	1 (1-2)
Surgeon satisfaction score	3 (3-3)	3 (3-3)

Data are shown as mean ± SD, median (min-max) or number of patients

Table II - *Postoperative VAS scores at rest and movement of the groups.*

VAS	Group PE(n=30)	Group PV(n=30)	p
5 min rest	2.90±0.99	3.03±0.92	0.61
5 min mov	3.80±1.21	4.03±0.92	0.56
15 min rest	2.96±0.92	3.13±0.77	0.52
15 min mov	3.90±1.09	4.13±0.77	0.51
30 min rest	2.10±0.66	2.33±0.60	0.17
30 min mov	3.10±0.66	3.33±0.60	0.17
1 h rest	1.76±0.50	1.90±0.71	0.68
1 h mov	2.76±0.50	2.90±0.71	0.68
2 h rest	1.73±0.52	1.70±0.59	0.74
2 h mov	2.70±0.53	2.66±0.66	0.87
4 h rest	1.46±0.57	1.66±0.71	0.27
4 h mov	2.43±0.56	2.66±0.71	0.18
6 h rest	1.40±0.49	1.63±0.55	0.10
6 h mov	2.36±0.49	2.63±0.55	0.06
12 h rest	1.26±0.44	1.43±0.50	0.18
12 h mov	2.20±0.55	2.30±0.59	0.46
24 h rest	1.23±0.43	1.30±0.46	0.56
24h mov	2.06±0.52	2.16±0.53	0.46

VAS: visual analogue scale, mov: movement, data are shown as mean ± SD

TABLE III - *Additional analgesic requirements of the patients in the first hour after surgery.*

Frequency	Group PE (n=30) n (%)	Group PV (n=30) n (%)	p
PO 5 min	0 (0%)	0 (0%)	
PO 15 min	14 (46,7%)	10 (33,3%)	0.43
PO 30 min	1 (3,3%)	0 (0%)	1.00
PO 1 hour	0 (0%)	0 (0%)	

PO: Postoperative, data are shown as number and percentage of patients n (%).

TABLE IV - *Postoperative PCA morphine consumption of the groups.*

Time	Group PE(n=30)	Group PV(n=30)	p
5 min	1.11±0.34	1.09±0.24	0,230
15 min	1.12±0.45	1.13±0.12	0,255
30 min	1.22±0.68	1.27±0.49	0,870
1 hr	1.53±1.17	1.45±0.54	0,890
2 hr	1.62±1.09	1.39±0.62	0,417
4 hr	1.63±0.94	1.62±0.51	0,789
6 hr	1.81±0.91	1.67±0.92	0,740
12 hr	1.72±1.26	1.85±0.84	0,910
24 hr	1.58±1.47	2.01±1.44	0,268
Total	13.07±2.39	13.19±2.19	0,875

PCA: Patient controlled analgesia, data are shown as mean ± SD or number of patients

in terms of 24-hour opioid consumption [11]. The administration period between the groups was 60 minutes. Considering the demographic data of the study, the mean operation time of the two groups was stated as 60 minutes, and the high VAS score in the PE group in the acute process may indicate that 30 minutes may be too early in terms of application time.

We presume that within a time frame of 90 minutes in total, the drug may have completed its peak effect and thus its efficacy may have decreased. In our study, the drug was administered to the PE group 15 minutes prior and the average operation time was 30 minutes. The similarity of acute postoperative pain with the PV group shows the importance of the time of paracetamol administration.

This difference can be explained by individual differences in pain sensation, and differences in gravida and parity counts. Also, routine administration of 1g iv paracetamol every 6 hours to all of our patients may be the reason for more effective analgesia and lower VAS scores at all postop hours. No significant difference was found between groups in terms of both resting and moving VAS scores at all hours.

Two previous studies have shown that preemptive 1g paracetamol had a significant effect on hemodynamic responses to tracheal intubation and provided better control of hemodynamic variables from intubation time to delivery of the newborn when compared with PV group [11,12].

Contrary to these studies, we did not find a positive effect on the hemodynamic response to tracheal intubation with the same dose. However, higher doses of paracetamol may exhibit stronger nonselective COX inhibitory activity and it may lower heart rate and blood pressure. In another study, it was stated that 1g of paracetamol did not affect blood pressure and heart rate but higher doses such as 2g can lower blood pressure as it exhibits strong nonselective COX inhibitory activity [13,14].

Another important issue is the effects of preoperative IV paracetamol use on the newborn. Studies have shown that preoperative IV paracetamol administration does not increase neonatal cord blood and has no adverse effects on the newborn [15,16]. In accordance with the literature, we found no significant difference in the 1st and 5th minute Apgar scores between groups [12,16].

Narcotic usage is a major risk factor for postoperative nausea and vomiting (PONV), and delayed mobilization. In our study, the incidence of nausea and vomiting was found to be low in both groups. This result supports the positive effect of paracetamol on PONV as shown in previous studies [17,18].

Patient and surgeon satisfaction scores were directly related to side effects and were found to be similarly high in both groups.

The success of postoperative pain management has a significant impact on patient satisfaction. However, caution should be taken when interpreting the results about satisfaction. Because the anxiety of the patients, pain threshold, and the behavior of the service nurses may also affect this score.

The limitation of this trial is the lack of an assessment of hospital discharge time. Although there is no significant difference in 24-hour morphine consumption, we think that this variable should be investigated in terms of how the two different methods affect the duration of discharge. The second limitation is that all of our patients were ASA II. We cannot make inferences about expectant mothers with more than one comorbidity or chronic pain disorder. Another major limitation was tissue handling by different surgeons. Because, whether the uterus was exteriorized or not, the type of incision, and whether the peritoneum was closed or not, could have had an affect on the pain scores.

It is already known that preemptive use of paracetamol provides more effective analgesia. The results of this study add to the literature as that these two techniques have similar efficacy in acute postop pain control. This study provides a reference framework for the impact of multimodal analgesia timing on postoperative pain in cesarean delivery.

Further research on the best timing for iv implementation should be the subject of future studies. These results must be checked and confirmed by more studies in the same surgical procedure. We also believe that our study and clinical experience may guide clinicians in this field.

Conclusions

The primary finding of this study is that preemptive and preventive paracetamol administration provides the same quality of analgesia and there is no superiority between them in acute postoperative pain control in patients who underwent cesarean section under general anesthesia.

Riassunto

La questione dell'uso preventivo o preventivo del paracetamolo solleva ancora interrogativi in termini di analgesia multimodale, e comunemente, si usa una combinazione di paracetamolo e oppioidi per la gestione del dolore dopo il parto cesareo. Questo studio mira a confrontare il livello di dolore postoperatorio e il consumo di analgesici quando si utilizza il paracetamolo in due diversi tempi perioperatori nel taglio cesareo.

Materiali e metodi: İn questo studio prospettico sono stati incluse sessanta pazienti reclutate per taglio cesareo elettivo in anestesia generale. Alle pazienti sono stati assegnati in modo casuale a ricevere 1g di paracetamolo 15 minuti prima dell'incisione (Gruppo PE) o dopo il parto del neonato (Gruppo PV). Sono stati registrati i valori della scala analogica visiva (VAS), il consumo di morfina nelle 24 ore, il fabbisogno di analgesici aggiuntivi, gli effetti collaterali e la soddisfazione del paziente e dei chirurghi.

Risultati: I dati demografici e i valori emodinamici delle pazienti erano simili in entrambi i gruppi. Non c'erano differenze tra i gruppi in termini di punteggi VAS a riposo e durante il movimento, ulteriore fabbisogno di analgesici durante la prima ora postoperatoria e consumo totale di morfina nelle 24 ore. Non c'era alcuna differenza negli effetti collaterali e nei punteggi di soddisfazione del paziente e del chirurgo dopo l'intervento.

Conclusioni: L'uso preventivo e preventivo del paracetamolo fornisce la stessa qualità di analgesia e l'effetto di risparmio di oppioidi senza aumentare la frequenza degli effetti avversi.

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