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Comparison of Pain Control and Inflammatory Profile in Cesarean Section Patients Treated with Multimodal Analgesia Utilizing Paracetamol and Ibuprofen

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Abstract

AIM: This single-blind study aimed to compare the combination of paracetamol with various doses of ibuprofen as multimodal analgesia in C-section surgery patients under spinal anesthesia. Levels of interleukin (IL)-6 and C-reactive protein (CRP) were analyzed as markers of inflammation.

METHODS: Treatment groups (20 patients each) were: Group A, 750 mg paracetamol and 400 mg ibuprofen; Group B, 750 mg paracetamol and 600 mg ibuprofen; and Group C, 750 mg paracetamol and 800 mg ibuprofen. Degree of pain (movement and rest), scored using the numeric rating scale (NRS) and levels of IL-6 and CRP were assessed at various time points within 24 h of surgery. Side effects and numbers of subjects requiring rescue fentanyl administration were also recorded.

RESULTS: Group C showed a rest NRS score of 1.00 ± 0.00 6 h postoperatively, compared with 2.00 ± 0.00 in Group B and 2.35 ± 0.87 in Group A. 4 h postoperatively, movement NRS scores were 1.00 ± 0.00 for Group C, compared to 3.00 ± 1.77 for Group B, and 4.85 ± 1.81 for Group A. At 12 h, IL-6 levels hours were 2.66 ± 0.04 pg/mL for Group A, 2.39 ± 0.02 pg/mL for Group B, and 2.05 ± 0.01 pg/mL for Group C. At 6 h, CRP levels were 1.18 ± 0.04 mg/L for Group A, 0.95 ± 0.01 mg/L for Group B, and 0.70 ± 0.02 mg/L for Group C. Overall, Group C showed the lowest values for all parameters analyzed, compared with other groups, and the differences were significant ($p < 0.05$). In addition, none of the patients in Group C required rescue fentanyl ($p < 0.05$), and no patients in any of the groups showed any side effects.

CONCLUSION: For pain management after C-section surgery, the combination of 750 mg paracetamol and 800 mg ibuprofen yielded the best results as assessed by NRS scores, levels of IL-6 and CRP, and fentanyl rescue.

Introduction

Cesarean section (C-section) is becoming more popular as a delivery method. C-section rates have risen worldwide from 4% in 1998 [1] to 21.1% in 2018 [2], while, in Indonesia, they have risen from 9.8% in 2013–18.5% in 2017 [3], [4]. With the increasing numbers of C-sections performed each year, proper anesthetic and post-operative pain management are critical for better results [2].

Post-operative pain in patients undergoing C-section is commonly moderate to severe [5]. If not treated properly, this can result in a prolonged recovery period as well as disturbances to daily activities, mother–infant relationship, maternal psychology, and the breastfeeding process. It may also result in hyperalgesia and persistent post-operative pain, with the risk of developing chronic pain [6], [7].

The inflammatory cytokine interleukin (IL)-6 can be used as a marker to indicate the degree of tissue damage [8], [9]. IL-6 is an inducer of acute-phase protein synthesis carried out by hepatocytes during pain stimuli. After trauma occurs, plasma IL-6 can be detected within 60 min, peaking between 4 and 6 h, and possibly persisting for as long as 10 days. C-reactive protein (CRP) is produced in the liver in response to IL-6, persisting in the blood for approximately 19 h, and can increase 1000-fold in infection or inflammation sites [8].

The multimodal approach to post-operative pain management involves the use of a combination of several analgesic drugs that differ in terms of their mechanism of action. This approach has several advantages, such as lowering the total dose of opioid requirement, improving pain control, and minimizing potential side effects associated with opioids, such as gastrointestinal and central nervous system disorders [10], [11], [12]. A randomized clinical study on total hip arthroplasty patients showed that the combination of paracetamol and ibuprofen resulted in a significant reduction in morphine consumption, compared with administration of paracetamol only. This indicated that paracetamol and ibuprofen could therefore be a feasible option for the early post-operative analgesia [12].

The aim of this study was to compare the efficacy and safety of the multimodal combination of intravenous (IV) paracetamol (750 mg) and various doses of ibuprofen (400 mg, 600 mg, and 800 mg) in the context of post-operative C-section patients who underwent spinal anesthesia.

Methods

Study design

This was a true experimental single-blind study conducted at Dr. Wahidin Sudirohusodo Central Hospital and its network hospitals in Makassar, Indonesia, starting from July 2021 and continuing until the required number of samples was reached.

Study population and subjects

The population included in this study were patients who were about to undergo C-section under spinal anesthesia. Subjects were selected randomly from all populations who met the inclusion and exclusion criteria and agreed to participate in this study.

Inclusion criteria in this study were as follows:

1. The patient was due to undergo C-section under spinal anesthesia
2. The American Society of Anesthesiologists physical status (ASA PS) = 2
3. Age of the patient was in the range 18–50 years
4. Body mass index (BMI) of the patient was 18.50–29.99 kg/cm^2
5. The patient agreed to participate in this study research and signed the informed consent form
6. Approval was obtained from the primary doctor who treated the patient.

Exclusion criteria in this study were as follows:

1. There was a history of allergies to the materials or drugs used in this study
2. Spinal anesthesia was contraindicated
3. The patient had received previous opioid therapy
4. There were existing uncontrolled medical conditions, such as impaired liver, kidney, coagulation, or cardiovascular function
5. The patient had a history of using narcotics, anticonvulsants, or corticosteroids, or non-steroidal anti-inflammatory drugs were used <24 h before the C-section
6. The patient was hemodynamically unstable.

Dropout criteria in this study were as follows:

1. The patient withdrew from this study
2. Severe complications (major hemorrhage, shock) occurred during surgery
3. There was conversion to general anesthesia during surgery.

Study consent and ethical eligibility

The study was approved by the Ethics Commission in Humans, Faculty of Medicine, Hasanuddin University (registration number: 482/UN4.6.4.5.31/PP36/2021). All patients who met the inclusion criteria were given a verbal explanation and signed the informed consent form to participate in this study voluntarily.

Spinal anesthesia procedure

Spinal anesthesia was performed in the left lateral decubitus position at the L3-L4 interspace [13]. All three groups underwent spinal anesthesia with Spinocan 25G spinal needle, 0.5% hyperbaric bupivacaine 8 mg without adjuvant at an injection rate of 3 s/cc. The patient was, then, positioned supine. Autonomic block height was confirmed by cold test, sensory block by pin prick test, and motor block by Bromage score [14].

Study procedure

Patients were randomly assigned to three groups, as follows: Group A (receiving IV paracetamol 750 mg + IV ibuprofen 400 mg), Group B (receiving IV paracetamol 750 mg + IV ibuprofen 600 mg), and Group C (receiving IV paracetamol 750 mg + IV ibuprofen 800 mg). All patients were asked to fast for 6 h before surgery; fluid requirements during fasting were met before surgery using lactated Ringer's solution. At the time of surgery, spinal anesthesia was performed on all patients. The patients were given different analgesics according to the group allocation before spinal anesthesia was administered; analgesics were continued every 6 h until 24 h after surgery. Blood samples were taken 1 h preoperatively and 6 and 12 h postoperatively for analysis of IL-6 and CRP levels. Assessment of pain intensity using the numerical rating scale (NRS) [15], [16] was carried out at 1-h before surgery (T0), intraoperative (T1), 2-h (T2), 4-h (T3), 6-h (T4), 12-h (T5), and 24-h (T6) post-surgery. We recorded NRS scores, IL-6 levels, and CRP levels during the observations.

Data processing and analysis

The obtained data were processed and the results were displayed in the form of text description, tables, or graphs, as means (with standard deviations), frequencies, and/or percentages, using SPSS 21 for Windows. For age, BMI, and ASA PS, the data

were presented as mean and frequency. Appropriate statistical test methods were chosen based on the type and form of data. The characteristics of Groups A, B, and C were tested using analysis of variance (ANOVA), and pain scores (NRS) were tested using repeated ANOVA. IL-6 and CRP levels were tested using a paired t-test. Side effects of ibuprofen and rescue fentanyl results were tested using the Chi-square test.

Results

Sample characteristics

A total of 60 patients were included in this study; homogeneity test results of the sample characteristics are presented in Table 1. Table 1 shows that there were no statistically significant differences in age, weight, height, or BMI between groups ($p > 0.05$). Hence, the three groups could be considered homogeneous based on these characteristics.

Table 1: Sample distribution

Characteristics	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	32.10 ± 6.30	30.25 ± 6.98	33.20 ± 4.78	0.310^{ns}
Body weight (kg)	67.45 ± 5.34	66.10 ± 6.66	67.45 ± 5.34	0.700^{ns}
Body height (cm)	157.50 ± 4.76	157.65 ± 5.18	157.50 ± 4.76	0.994^{ns}
BMI (kg/m2)	26.90 ± 2.22	25.97 ± 2.60	26.90 ± 2.22	0.364^{ns}
Surgical duration (minutes)	71.50 ± 2.35	71.50 ± 2.35	71.50 ± 2.35	1.000^{ns}
Bleeding volume (ml)	254.50 ± 10.99	256.00 ± 12.31	253.50 ± 9.33	0.769^{ns}

Sample distribution was tested by ANOVA; * $p < 0.05$ indicates significance, ^{ns}indicates non-significant result, BMI: Body mass index.

Pain scale (NRS)

The results of stationary pain NRS score comparisons between groups are presented in Table 2, and mobile pain score comparisons are presented in Table 3. For rest pain NRS scores, mean differences between Group A and Group C for the time ranges from T0–T1 to T0–T4, as well as T0–T6, were statistically significant ($p < 0.05$). Statistically significant differences in pain scores between Group B and Group C were also identified for the time ranges from T0–T2 to T0–T6 ($p < 0.05$) and between Group A and Group B for comparisons of pain at T0–T1 and T0–T6 ($p < 0.05$). Group C was more effective than Group B at relieving pain, and Group B was more effective than Group A at relieving pain.

For pain when mobile, mean differences in scores between Group A and Group C and between Group B and Group C for all time ranges were statistically significant ($p < 0.05$). Furthermore, statistically significant differences ($p < 0.05$) between Group A and Group B were identified for movement pain NRS scores at time ranges T0–T3, T0–T5, and T0–T6 (Table 3).

Table 2: NRS comparisons (at rest differences)

NRS at rest	Group	Mean ± SD	p
T0	A	0.00 ± 0.00	-
	B	0.00 ± 0.00	
	A	0.00 ± 0.00	-
	C	0.00 ± 0.00	
	B	0.00 ± 0.00	-
	C	0.00 ± 0.00	
T1	A	0.55 ± 0.51	0.001*
	B	0.00 ± 0.00	
	A	0.55 ± 0.51	0.001*
	C	0.00 ± 0.00	
	B	0.00 ± 0.00	0.001*
	C	0.00 ± 0.00	
T2	A	1.05 ± 0.51	0.963
	B	1.00 ± 0.00	
	A	1.05 ± 0.51	0.001*
	C	0.00 ± 0.00	
	B	1.00 ± 0.00	-
	C	0.00 ± 0.00	
T3	A	1.25 ± 0.78	0.431
	B	1.00 ± 0.00	
	A	1.25 ± 0.78	0.001*
	C	0.10 ± 0.30	
	B	1.00 ± 0.00	0.001*
	C	0.10 ± 0.30	
T4	A	2.35 ± 0.87	0.246
	B	2.00 ± 0.00	
	A	2.35 ± 0.87	0.001*
	C	1.00 ± 0.00	
	B	2.00 ± 0.00	-
	C	1.00 ± 0.00	
T5	A	1.20 ± 0.61	0.783
	B	1.35 ± 0.48	
	A	1.20 ± 0.61	0.413
	C	1.00 ± 0.00	
	B	1.35 ± 0.48	0.014*
	C	1.00 ± 0.00	
T6	A	2.10 ± 1.02	0.019*
	B	1.35 ± 0.48	
	A	2.10 ± 1.02	0.001*
	C	0.25 ± 0.44	
	B	1.35 ± 0.48	0.001*
	C	0.25 ± 0.44	
T1–T0	A	0.55 ± 0.51	0.001*
	B	0.00 ± 0.00	
	A	0.55 ± 0.51	0.001*
	C	0.00 ± 0.00	
	B	0.00 ± 0.00	0.121
	C	0.00 ± 0.00	
T2–T0	A	1.05 ± 0.51	0.963
	B	1.00 ± 0.00	
	A	1.05 ± 0.51	0.001*
	C	0.00 ± 0.00	
	B	1.00 ± 0.00	0.001*
	C	0.00 ± 0.00	
T3–T0	A	1.25 ± 0.78	0.431
	B	1.00 ± 0.00	
	A	1.25 ± 0.78	0.001*
	C	0.10 ± 0.30	
	B	1.00 ± 0.00	0.001*
	C	0.10 ± 0.30	
T4–T0	A	2.35 ± 0.87	0.246
	B	2.00 ± 0.00	
	A	2.35 ± 0.87	0.001*
	C	1.00 ± 0.00	
	B	2.00 ± 0.00	0.001*
	C	1.00 ± 0.00	
T5–T0	A	1.20 ± 0.61	0.783
	B	1.35 ± 0.48	
	A	1.20 ± 0.61	0.062
	C	1.00 ± 0.00	
	B	1.35 ± 0.48	0.001*
	C	1.00 ± 0.00	
T6–T0	A	2.10 ± 1.02	0.019*
	B	1.35 ± 0.48	
	A	2.10 ± 1.02	0.001*
	C	0.25 ± 0.44	
	B	1.35 ± 0.48	0.001*
	C	0.25 ± 0.44	

Comparisons of NRS differences between groups were tested using repeated ANOVA; *$p < 0.05$ indicates significance, NRS: Numeric rating scale.

Comparisons of IL-6 differences

Results of IL-6 measurements are illustrated in Figure 1, while comparisons of IL-6 levels between

Table 3: NRS comparisons (movement differences)

Movement NRS	Group	Mean ± SD	p
T0	A	0.00 ± 0.00	-
	B	0.00 ± 0.00	
	A	0.00 ± 0.00	-
	C	0.00 ± 0.00	
	B	0.00 ± 0.00	-
	C	0.00 ± 0.00	
T1	A	1.45 ± 0.68	0.259
	B	1.15 ± 0.36	
	A	1.45 ± 0.68	0.001*
	C	0.45 ± 0.51	
	B	1.15 ± 0.36	0.001*
	C	0.45 ± 0.51	
T2	A	2.05 ± 0.51	0.963
	B	2.00 ± 0.00	
	A	2.05 ± 0.51	0.001*
	C	1.00 ± 0.00	
	B	2.00 ± 0.00	-
	C	1.00 ± 0.00	
T3	A	4.85 ± 1.81	0.005*
	B	3.00 ± 1.77	
	A	4.85 ± 1.81	0.001*
	C	1.00 ± 0.00	
	B	3.00 ± 1.77	0.001*
	C	1.00 ± 0.00	
T4	A	3.75 ± 1.77	0.163
	B	2.60 ± 0.50	
	A	3.75 ± 1.77	0.001*
	C	2.00 ± 0.00	
	B	2.60 ± 0.50	0.001*
	C	2.00 ± 0.00	
T5	A	5.40 ± 1.46	0.001*
	B	2.75 ± 1.44	
	A	5.40 ± 1.46	0.001*
	C	2.00 ± 0.00	
	B	2.75 ± 1.44	0.147
	C	2.00 ± 0.00	
T6	A	2.80 ± 0.61	0.001*
	B	2.15 ± 0.36	
	A	2.80 ± 0.61	0.001*
	C	1.10 ± 0.30	
	B	2.15 ± 0.36	0.001*
	C	1.10 ± 0.30	
T1–T0	A	1.45 ± 0.68	0.259
	B	1.15 ± 0.36	
	A	1.45 ± 0.68	0.001*
	C	0.45 ± 0.51	
	B	1.15 ± 0.36	0.001*
	C	0.45 ± 0.51	
T2–T0	A	2.05 ± 0.51	0.963
	B	2.00 ± 0.00	
	A	2.05 ± 0.51	0.001*
	C	1.00 ± 0.00	
	B	2.00 ± 0.00	0.001*
	C	1.00 ± 0.00	
T3–T0	A	4.85 ± 1.81	0.005*
	B	3.00 ± 1.77	
	A	4.85 ± 1.81	0.001*
	C	1.00 ± 0.00	
	B	3.00 ± 1.77	0.001*
	C	1.00 ± 0.00	
T4–T0	A	3.75 ± 1.77	0.163
	B	2.60 ± 0.50	
	A	3.75 ± 1.77	0.001*
	C	2.00 ± 0.00	
	B	2.60 ± 0.50	0.001*
	C	2.00 ± 0.00	
T5–T0	A	5.40 ± 1.46	0.001*
	B	2.75 ± 1.44	
	A	5.40 ± 1.46	0.001*
	C	2.00 ± 0.00	
	B	2.75 ± 1.44	0.047
	C	2.00 ± 0.00	
T6–T0	A	2.80 ± 0.61	0.001*
	B	2.15 ± 0.36	
	A	2.80 ± 0.61	0.001*
	C	1.10 ± 0.30	
	B	2.15 ± 0.36	0.001*
	C	1.10 ± 0.30	

Comparisons of NRS differences between groups were tested using repeated ANOVA; *p < 0.05 indicates significance, NRS: Numeric rating scale.

groups are presented in Table 4. Mean differences in IL-6 levels were statistically significant (p < 0.05) for all group comparisons and both time ranges (T1–T0 and T2–T0).

Table 4: Comparisons of IL-6 differences between groups

IL-6 difference	Group	Mean ± SD	p
T1–T0	A	0.92 ± 0.05	0.001*
	B	0.71 ± 0.03	
	A	0.92 ± 0.05	0.001*
	C	0.51 ± 0.03	
	B	0.71 ± 0.03	0.001*
	C	0.51 ± 0.03	
T2–T0	A	0.74 ± 0.04	0.001*
	B	0.46 ± 0.04	
	A	0.74 ± 0.04	0.001*
	C	0.09 ± 0.03	
	B	0.46 ± 0.04	0.001*
	C	0.09 ± 0.03	
T0	A	1.91 ± 0.04	0.768
	B	1.92 ± 0.03	
	A	1.91 ± 0.04	0.762
	C	1.96 ± 0.02	
	B	1.92 ± 0.03	0.766
	C	1.96 ± 0.02	
T1	A	2.84 ± 0.04	0.001*
	B	2.64 ± 0.03	
	A	2.84 ± 0.04	0.001*
	C	2.48 ± 0.04	
	B	2.64 ± 0.03	0.001*
	C	2.48 ± 0.04	
T2	A	2.66 ± 0.02	0.001*
	B	2.39 ± 0.02	
	A	2.66 ± 0.02	0.001*
	C	2.05 ± 0.01	
	B	2.39 ± 0.02	0.001*
	C	2.05 ± 0.01	

Comparisons of IL-6 differences between groups were tested using repeated ANOVA; *p < 0.05 indicates significance, IL: Interleukin.

Comparisons of CRP differences

Figure 2 shows CRP measurements, while group comparisons of CRP levels are presented in Table 5.

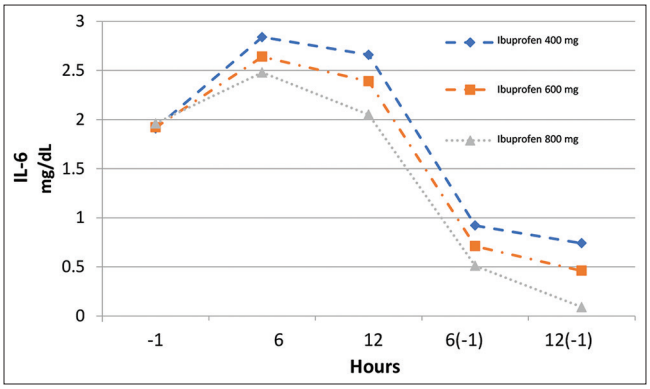

Figure 1: Interleukin-6 levels in all groups

Mean differences in levels of CRP were statistically significant (p < 0.05) for all group comparisons and all-time ranges examined (T1–T0 to T2–T0).

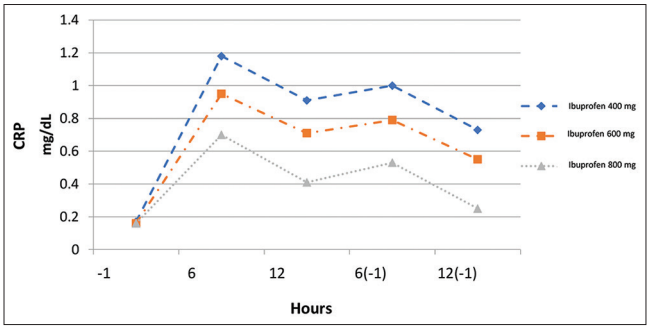

Figure 2: C-reactive protein levels in all groups

Table 5: Comparisons of CRP differences between groups

CRP differences	Group	Mean ± SD	p
T1–T0	A	1.00 ± 0.05	0.001*
	B	0.79 ± 0.02	
	A	1.00 ± 0.05	0.001*
	C	0.53 ± 0.02	
	B	0.79 ± 0.02	0.001*
	C	0.53 ± 0.02	
T2–T0	A	0.73 ± 0.02	0.001*
	B	0.55 ± 0.01	
	A	0.73 ± 0.02	0.001*
	C	0.25 ± 0.03	
	B	0.55 ± 0.01	0.001*
	C	0.25 ± 0.03	
T0	A	0.17 ± 0.00	0.237
	B	0.16 ± 0.01	
	A	0.17 ± 0.00	0.317
	C	0.16 ± 0.01	
	B	0.16 ± 0.01	0.277
	C	0.16 ± 0.01	
T1	A	1.18 ± 0.04	0.001*
	B	0.95 ± 0.01	
	A	1.18 ± 0.04	0.001*
	C	0.70 ± 0.02	
	B	0.95 ± 0.01	0.001*
	C	0.70 ± 0.02	
T2	A	0.91 ± 0.01	0.001*
	B	0.71 ± 0.01	
	A	0.91 ± 0.01	0.001*
	C	0.41 ± 0.03	
	B	0.71 ± 0.01	0.001*
	C	0.41 ± 0.03	

Comparisons of CRP differences between groups were tested using repeated ANOVA; *p < 0.05 indicates significance, CRP: C-reactive protein.

Fentanyl rescue and side effects

Fentanyl rescue results and comparisons of side effects of paracetamol and ibuprofen between groups are presented in Table 6. There were significant differences between groups regarding the requirement for fentanyl (p < 0.05); the lowest requirement was seen in Group C (0% of patients), followed by Group B (40%) and Group A (100%). However, there were no side effects (nausea, vomiting, allergy, pruritus, sedation, and respiratory depression) which were observed in any group (p > 0.05).

Table 6: Rescue fentanyl and side effects

Variable	Group			
	A (%)	B (%)	C (%)	p
Rescue Fentanyl				0.001*
No	0 (0)	12 (60)	20 (100)	
Yes	20 (100)	8 (40)	0 (0)	
Nausea				-
No	20 (100)	20 (100)	20 (100)	
Yes	0 (0)	0 (0)	0 (0)	
Vomiting				-
No	20 (100)	20 (100)	20 (100)	
Yes	0 (0)	0 (0)	0 (0)	
Allergy				-
No	20 (100)	20 (100)	20 (100)	
Yes	0 (0)	0 (0)	0 (0)	
Pruritus				-
No	20 (100)	20 (100)	20 (100)	
Yes	0 (0)	0 (0)	0 (0)	
Sedation				-
No	20 (100)	20 (100)	20 (100)	
Yes	0 (0)	0 (0)	0 (0)	
Respiratory depression				-
No	20 (100.0)	20 (100)	20 (100)	
Yes	0 (0)	0 (0)	0 (0)	

Comparisons between groups were tested using the Chi-square test; *p < 0.05 indicates statistical significance.

Discussion

Statistically significant differences in NRS scores (rest and movement) were observed for all time points in all groups. A previous study conducted by Southworth *et al*. examined the use of ibuprofen for post-operative pain management in elective orthopedic and abdominal surgeries. Their results showed that 800 mg ibuprofen was significantly more effective at reducing NRS scores (for both rest and movement pain) measured at three points over the course of 24 h, compared with 400 mg ibuprofen or a placebo [11].

Mean differences in IL-6 levels were found to be statistically significant for all group comparisons and both time ranges examined. A study on chronic spinal trauma treatment conducted by Park *et al*. showed that ibuprofen decreased IL-6 levels to 3.2 pg/ml in the treatment group, compared with 4.0 pg/ml in the control group [17]. IL-6 is one of the cytokines and a mediator of induction and control of acute phase protein synthesis released by hepatocytes during painful stimuli such as trauma, infection, surgery, and burns [18]. IL-6 is secreted by many cells, such as macrophages, monocytes, eosinophils, hepatocytes, and glial cells. IL-6 is the most appropriate marker for the degree of tissue damage [19]. The higher the plasma IL-6 level, the greater the post-operative morbidity [20]. Prostaglandins can also trigger IL-6 synthesis in some tissues. It is hypothesized that PGE2 induces the production of IL-6 through the prostaglandin receptor subtype, E prostanoid (EP), which activates NF-κβ [21]. IL-6 production is influenced by PG agonist receptors, by stimulating EP, there will be induction of an increase in IL-6, PGE2 stimulates IL-6 synthesis by mobilizing Ca from extracellular to intracellular through EP1, while EP2 and EP4 receptors are G-protein-coupled receptors that can activate cAMP levels which will then activate NF-κβ and will increase the synthesis of IL-6. By inhibiting the activity of cyclo-oxygenase I and II, ibuprofen results in decreased formation of prostaglandin and thromboxane precursors. This causes the synthesis of prostaglandins to decrease; hence, the production of IL-6 is reduced [22].

Similar to the IL-6 results, we found that the mean differences in CRP levels were significant for all group comparisons over the time ranges analyzed. In the study conducted by Park referred to above, ibuprofen reduced the CRP level to 2.3 mg/L, compared with 3.5 mg/L in the control group.[9] In a different study, subjects were divided into groups receiving tramadol (100 mg), ibuprofen (400 mg), or a combination of tramadol and ibuprofen (50 mg and 200 mg, respectively); results showed that CRP levels were significantly lower in the tramadol–ibuprofen group [23]. C-reactive protein (CRP) is produced in the liver in response to IL-6 [24], [25]. Products from activated monocytes in Hep 3B cells induce CRP production [26].

The present study identified significant differences between treatment groups relating to the need of study participants for the administration of rescue fentanyl. A multimodal analgesia study conducted by

Thybo *et al*. examined the need for rescue morphine in subjects receiving 1000 mg paracetamol and 400 mg ibuprofen, 1000 mg paracetamol and placebo, 400 mg ibuprofen and placebo, or 500 mg paracetamol and 200 mg ibuprofen; this revealed significant differences in the amount of rescue morphine required over a 24-h period in the different groups (20 mg, 38 mg, 26 mg, and 28 mg, respectively). The group with the lowest requirement for rescue morphine was the group receiving the highest dose of both paracetamol and ibuprofen. No significant differences in side effects were observed between groups [12].

In the present study, it was found that the decrease in IL-6 and CRP levels at 6- and 12-h post-surgery was not always followed by a decrease in NRS score. This could be explained by the subjective nature of the pain process, which is strongly influenced by various factors. Hence, interpretation of NRS scores and pain perceptions is different for each individual.

Conclusion

The combination of 750 mg IV paracetamol and 800 mg IV ibuprofen was found to be the most effective for post-operative pain management in C-section patients, as evidenced by pain scale, IL-6 and CRP levels, and minimal need for rescue fentanyl. We, therefore, recommend the use of paracetamol and ibuprofen as analgesia of choice in C-section. More studies are needed to determine the efficacy of paracetamol and ibuprofen in other types of surgery and through different drug delivery routes in the future.

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