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ORIGINAL RESEARCH **NEUROANESTHESIA**

Preventive efficacy of ibuprofen and dexamethasone combination for postoperative pain in posterior vertebral stabilization: a randomized controlled study

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ABSTRACT

Background: Posterior vertebral stabilization procedures often cause acute postoperative pain that can turn into chronic pain if not managed adequately. We compared the interleukin 6 (IL-6) level and pain intensity with preventive use of multimodal analgesia with different combinations of intravenous ibuprofen and dexamethasone in these patients.

Methodology: Thirty-nine eligible patients were randomized to receive intravenous ibuprofen 400 mg and dexamethasone 10 mg (Group A), ibuprofen 800 mg and dexamethasone 10 mg (Group B), and ibuprofen 800 mg alone (Group C). The study drugs were injected 30 min before surgical procedure followed by fentanyl 24 h postop in a single-blinded fashion. Serum levels of IL-6 were measured with ELISA. and pain intensity was measured using numeric rating scale (NRS) at preop, then at 2 h and 24 h postoperatively.

Results: There was a significant difference in the NRS scores between all treatment groups ($P < 0.005$) at all measurement times, where Group B had the lowest value. There was a significant difference between IL-6 levels between all treatment groups ($P < 0.005$) at all measurement times, where Group B had the lowest value at all measurement times. No side effects were observed in all treatment groups.

Conclusion: Preventive combination of ibuprofen and dexamethasone has efficacy and safety in managing acute postoperative pain in posterior vertebral stabilization procedures.

Abbreviations: COX – Cyclooxygenase; IL-6 - Interleukin 6; MAC - Minimum Alveolar Concentration; NRS - Numeric Rating Scale; NSAIDs - Non-Steroidal Anti-Inflammatory Drugs; PSA - Patient-Controlled Analgesia

Key words: Analgesia; Dexamethasone; Ibuprofen; Interleukin-6; Preventive Medicines; Spinal Surgery

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1. INTRODUCTION

Spinal cord injury is a neurological condition that weakens the socioeconomic status of the victim due to the cost of healthcare. According to the National Spinal Cord Injury Statistical Center in North America, there are 12,500 new cases each year, of which 90% are due to trauma. Meanwhile, 41% of spinal cord injuries occurred in Japan due to falls. Data from WHO in 2013 shows that there are more than 250,000 people who experience spinal cord trauma every year, and 90% are traumatic cases.

In 2018, this estimated prevalence doubled. Approximately 55% occur in the cervical region, 15% in the thoracic region, 15% in the thoracolumbar, and 15% in the lumbosacral region. Spinal surgery is the treatment of choice for spinal cord trauma; and it is is one of the orthopedic procedures that causes acute postoperative pain, which can turn into chronic pain if not managed properly.[1–3]

Surgical trauma will cause an inflammatory response. Interleukin 6 (IL-6) is one of the early inflammatory mediators in the acute postoperative phase. Cytokines are mediators that play a role in the inflammatory response if damage occurs, resulting in an increase in the morbidity and mortality of surgical patients.[4–6]

Preventive analgesia, which includes multimodal analgesic therapy before and after surgery, aims to reduce postoperative pain and reduce postoperative opioid consumption. In the recent years, many studies have been conducted on the preemptive administration of ibuprofen or dexamethasone for various types of surgery. Multicenter, randomized, double-blind, and placebo-controlled studies using ibuprofen 800 mg intravenously (IV) every 6 h have reduced pain intensity and the use of the opioid morphine in various surgical procedures.[7–9] Several studies have shown that a single dose of intravenous dexamethasone is effective in multimodal analgesia to reduce postoperative pain and total opioid requirements.[6,10] Different results were found by Nielsen et al., where the preemptive use of dexamethasone 16 mg IV in combination with paracetamol 1 g oral and ibuprofen 400 mg oral, did not significantly reduce the fixed visual analog scale and use of opioids.[11]

We aimed to analyze the efficacy of preemptive administration of ibuprofen 400 mg and dexamethasone 10 mg combination, ibuprofen 800 mg and dexamethasone 10 mg combination, and ibuprofen 800 mg based on pain intensity and IL-6 levels in postoperative decompression and posterior stabilization procedures.

2. METHODOLOGY

2.1. Study Design and Population

It is a single-blind randomized clinical trial. The study was conducted after obtaining an ethical clearance certificate from the Biomedical Research Ethics Commission, Faculty of Medicine, Universitas Hasanuddin (No. 481/UN4.6.4.5.31/PP36/2021). All patients who met the inclusion criteria were given a verbal explanation and signed consent forms obtained to participate in the study.

All patients scheduled to undergo decompression surgery and posterior stabilization under general anesthesia at our hospital from June to September 2021, were enrolled using the consecutive sampling method. The sample size was calculated using the Openepi with a power $1 - \beta = 0.8$, two-tail $\alpha = 0.05$, and a difference of 2.0 in the mean of pain intensity scores at the final follow-up period. The required sample size was 39 eligible patients (13 samples in each group).

Patients, aged 18-60 y, body mass index 18.5-29.9 kg/m^2, ASA-I or II, were included in this study. All participants had approval of the attending doctor to get involved in this study. Patients who were allergic to the drugs to be studied, suffered from liver or kidney dysfunction, cardiovascular disease and diabetes mellitus, long-term opioids use, and non-steroidal anti-inflammatory drugs (NSAIDs) users were excluded from this study. Drop out criteria included any surgical complication, resign from the study, and duration of surgery more than four hours.

2.2. Preventive Analgesia Procedure

Eligible patients were randomized into three groups using random generator application. Thirty minutes before surgery, Group A received ibuprofen 400 mg + dexamethasone 10 mg IV, Group B received ibuprofen 800 mg + dexamethasone 10 mg IV, and Group C received ibuprofen 800 mg + normal saline (0.9% NaCl) as placebo.

The patient was brought into the operating room and the monitoring devices were applied. Blood pressure, pulse rate, respiratory rate, and pulse oxygen saturation readings were recorded. After that, fentanyl 2 g/kg was given IV as premedication. Induction was done with propofol 2 mg/kg intravenous, atracurium 0.5 mg/kg and intubation done. Subsequently, anesthesia was maintained using the volatile anesthetic isoflurane 1-1.5 vol% in 60% oxygen. Fentanyl 1 g/kg /h was infused continuously via a syringe pump, atracurium 0.1 mg/kg every 30 min as intravenous bolus were used to maintain relaxation and controlled ventilation.

Table 1: Baseline characteristic of the study participant

Characteristic	Group A (n = 13)	Group B (n = 13)	Group C (n = 13)	P value
Age (y)	46.31 ± 12.71	46.15 ± 9.97	44.46 ± 11.86	0.846
BMI (Kg/m^2)	23.35 ± 3.05	23.13 ± 4.20	23.09 ± 2.61	0.828
Surgical duration (min)	188.08 ± 33.51	203.46 ± 40.07	203 ± 22.31	0.152
Bleeding volume (mL)	1038.46 ± 140.17	953.85 ± 187.6	1061.54 ± 91.64	0.396

*Data presented as mean ± SD; * P < 0.05 considered as significant*

Then mean arterial pressure (MAP) and heart rate (HR) were measured every 3 min. MAP was measured by a non-invasive method, and heart rate was recorded according to the electrocardiogram on the monitor. If hypotension occurred (MAP < 20% of the basal value), 5-10 mg of ephedrine bolus was given. Bradycardia (HR < 50 beats/min), was treated with atropine sulfate 0.5 mg IV with a maximum of 2 mg. After extubation, the patient was transferred to the recovery room. Analgesic fentanyl was given with PCA, with a demand dose of 0.3 µg/kg with lock-out intervals of 15 min, without background infusion and ibuprofen 400 mg/8 h IV for Group A and ibuprofen 800 mg/8h IV for Group B, and C.

2.3. Pain Intensity Measurement

Assessment of pain intensity using NRS done postoperatively, at 2, 6, 12, and 24 h, by doctors at the Acute Pain Service in the study period. The use of total fentanyl for 24 h postoperatively was recorded from the initial bolus dose given up to 24 h postoperatively.

2.4. Interleukin-6 Measurement

A blood sample was taken to measure the levels of IL-6 just before treatment. After that, IL-6 blood samples were taken 6 h after the first incision and 24 h after surgery. Measurement of IL-6 levels was performed at hospital laboratory using the Human IL-6 immunoassay quantikine HS serum (R&D system). The procedure used the Enzyme-Linked Immunosorbent Assay method and readings through the ELISA Reader Organon 680 (Biorad) with a 640 mm or 690 mm wavelength. The patient's blood was taken using a vacutainer set (needle, tourniquet, vacutainer tube). Interleukin 6 levels are expressed in pg/mL.

2.5. Data Collection

Other data collected included duration of surgery, age, body weight, height, and body mass index initially before surgery. Age was calculated based on the year of birth listed in the patient's status. Body weight was recorded in kg. Height was measured in cm.

2.6. Statistical Analysis

The data obtained were recorded and analyzed by SPSS 25 for Windows. Data are shown by means and frequencies of age, BMI, ASA PS, total opioid use, and side effects in each group. Normality test was performed using the Shapiro-Wilk test. Categorical variables are presented in frequency (n) and percentages tested by Mann-Whitney. Numerical variables are presented in the mean ± standard deviation (mean ± SD) and tested by one-way ANOVA (parametric test) if they met the requirements (normal distribution and homogenous); the Kruskal-Wallis test (non-parametric test) is used if it does not meet the requirements.

3. RESULTS

This study involved 39 patients who underwent elective decompression and posterior stabilization in the central operating room and met the inclusion criteria. The sample was divided into three groups, consisting of 13 patients each. The baseline characteristics of the study participant are shown in Table 1. There was no significant difference in age, weight, height, BMI, duration of surgery, and amount of bleeding (P > 0.05) between all decompression surgery and posterior stabilization groups. The results indicate the homogeneity of the data (Table 1).

3.1. Comparative effect on NRS

The results of the measurement of the NRS at rest and on movement in the three groups can be seen in Table 2. There was a significant difference in the NRS at rest at all measurement times between the three groups. Group B, which received a combination of ibuprofen 800 mg and dexamethasone 10 mg, always had the lowest significant value (P < 0.005) at rest as well as on movement at all measurement times (P < 0.005).

3.2. Effect on IL-6 levels

The measurement of IL-6 levels in the three groups at three time slots can be seen in Table 3. There was a statistically significant difference in the levels of IL-6 at 2 h postoperatively and 24 h postoperatively (P < 0.05). Group B, which received a combination of ibuprofen 800 mg and dexamethasone 10 mg, always had the lowest

Table 2: Comparison of NRS at rest and on movement in all group based on the time of measurement

NRS	Measurement Time	Group A (n = 13)	Group B (n = 13)	Group C (n = 13)	P value
Rest	2 h	2.85 ± 1.14	1.62 ± 0.87	1.85 ± 0.69	0.008*
	6 h	3.00 ± 1.08	1.31 ± 0.48	2.15 ± 0.90	0.000*
	12 h	2.31 ± 0.48	1.31 ± 0.63	1.69 ± 0.90	0.001*
	24 h	2.62 ± 0.56	1.15 ± 0.38	1.46 ± 0.52	0.000*
Motion	2 h	3.31 ± 1.03	1.46 ± 0.88	3.31 ± 1.11	0.000*
	6 h	3.92 ± 0.76	2.31 ± 0.60	3.23 ± 0.93	0.000*
	12 h	3.54 ± 0.66	2.23 ± 0.86	3.00 ± 1.08	0.003*
	24 h	2.77 ± 0.44	1.77 ± 0.93	2.31 ± 0.86	0.005*

*Data presented as mean ± SD; * P < 0.05 considered as significant*

Table 3: Comparative IL-6 levels (pg/ml) based on the time of measurement

Time to measure	Group A (n = 13)	Group B (n = 13)	Group C (n = 13)	p value
Preop	0.357 (0.308-0.398)	0.265 (0.220-0.358)	0.258 (0.236-0.281)	0.088
2 h postop	0.436 (0.411-0.494)	0.269 (0.304-0.460)	0.379 (0.254-0.842)	0.006*
24 h postop	0.286 (0.246-0.318)	0.175 (0.143-0.233)	0.179 (0.007-0.266)	0.044*

*Data presented as median (min-max); * P < 0.05 considered as significant*

Table 4: Comparison of changes in interleukin 6 levels between groups.

Time	Group	IL-6 level		P-value
		Mean ± SD	Range (min-max)	
Preop-2 h postop	A	0.07 ± 0.04	0.0154-0.1678	0.169
	B	0.09 ± 0.03	0.0522-0.1601	
	A	0.07 ± 0.04	0.0154-0.1678	0.287
	C	0.12 ± 0.15	0.0022-0.6065	
	B	0.09 ± 0.03	0.0522-0.1601	0.724
	C	0.12 ± 0.15	0.0022-0.6065	
Preop-24 h postop	A	0.071 ± 0.06	0.0615-0.0795	0.001*
	B	0.094 ± 0.014	0.0771-0.1253	
	A	0.071 ± 0.06	0.0615-0.0795	0.243
	C	0.083 ± 0.080	0.0047-0.2585	
	B	0.094 ± 0.014	0.0771-0.1253	0.054
	C	0.083 ± 0.080	0.0047-0.2585	
2 h postop-24 h postop	A	0.149 ± 0.043	0.0949-0.2330	0.014*
	B	0.19 ± 0.043	0.1439-0.2467	
	A	0.149 ± 0.043	0.0949-0.2330	0.88
	C	0.203 ± 0.161	0.0802-0.6675	
	B	0.19 ± 0.043	0.1439-0.2467	0.186
	C	0.203 ± 0.161	0.0802-0.6675	

*Data presented as mean ± SD, as well as Range (minimum-Maximum); * P < 0.05 considered as significant*

Table 5: Opioid requirements in all group

Opioid	Group A (n = 13)	Group B (n = 13)	Group C (n = 13)	P- value
Total opioids used (µg)	226.15 ± 59.52	48.46 ± 37.82	90.0 ± 24.64	0.000*

*Data presented as mean ± SD; * P < 0.05 considered as significant*

significant score compared to the other groups (all P < 0.05).

A comparison of changes in IL-6 levels between groups can be seen in Table 4. There are significant changes in IL-6 preoperative-24 h postoperative and IL-6 two h postoperative-24 h postoperative between the Group A and Group B (P < 0.05). It suggests that intravenous ibuprofen in combination with dexamethasone reduces IL-6 levels in postoperative decompression and spinal stabilization patients.

3.3. Effect on opioid use

The measurement results of opioid use in the three groups can be seen in Table 4. There were statistically significant differences in postoperative opioid use (P = 0.000). Group B patients, who received a combination of ibuprofen 800 mg and dexamethasone 10 mg, had the lowest value compared to the other groups (48.46 ± 37.82 µg).

No side effects, e.g., nausea, vomiting, allergies, pruritus, sedation, or respiratory depression, were noted in any group at any time.

4. DISCUSSION

This study revealed that the combination of ibuprofen 800 mg and dexamethasone 10 mg had significantly the lowest rest and on movement NRS values compared to other groups. Our results are comparable with previous studies that found that preemptive administration of 800 mg intravenous ibuprofen reduced postoperative NRS

values in elective orthopedic and abdominal surgery patients with general anesthesia compared with the control group. Previous studies by Gildasio et al., and Takdir M, found the administration of a single dose of dexamethasone more than 0.1 mg/kg IV was effective in multimodal analgesia strategies in reducing NRS values and postoperative opioid requirements. Different results were obtained by Nielsen et al., who showed that the preemptive use of dexamethasone 16 mg IV combined with paracetamol 1 g orally and ibuprofen 400 mg orally reduced the postoperative VAS scores on movement for 24 h significantly compared to placebo, but there was no significant effect on the resting value and morphine opioid use.[6,8–13]

Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs with the main mechanism of action by inhibiting the synthesis of prostanoids, which are produced by arachidonic acid by two cyclooxygenase enzymes, COX-1 and COX-2. Constitutive COX-1 and inducible COX-2 will catalyze the formation of prostanoid precursors, prostaglandin G2 (PGG2), and PGH2 from arachidonic acid. The cyclooxygenase enzyme exists in 2 isoforms called COX-1 and COX-2. These NSAIDs include non-selectively inhibiting the cyclooxygenase enzymes (COX-1 and COX-2), which trigger arachidonic acid to synthesize the pro-inflammatory PGE2 but have side effects due to the lack of prostaglandins in the stomach causing irritation and ulceration.[14–16]

Ibuprofen is a class of NSAIDs that is well known and has been used for a long time. The drug has analgesic, anti-inflammatory, and antipyretic effects. Intravenous ibuprofen works by inhibiting the COX-1 and COX-2 enzymes in converting arachidonic acid to prostaglandins, including thromboxane and prostacyclin. NSAIDs are divided into four groups in terms of their COX-1 and COX-2 inhibitory activities.[13,17,18]

Dexamethasone is a fluorinated derivative of prednisolone and is an isomer of betamethasone and acts on the glucocorticoid receptor. The drug has an anti-inflammatory potency of 25 times that of cortisol. The anti-inflammatory effect of 0.75 mg is equivalent to 20 mg of cortisol. Glucocorticoids inhibit the synthesis of cytokines and inflammatory mediators, which form a negative feedback. Glucocorticoids can inhibit prostaglandins through three mechanisms: induction and activation of annexin I, induction of MAPK (mitogen-activated protein kinase) phosphatase, and inhibition of cyclooxygenase 2. [3,6,10,19]

Preemptive analgesia is defined as the administration of antinociception to maintain the stability of the peripheral and central nervous systems so that no changes in central processes occur after receiving afferent input from the injured tissue. This is a definition revised by Kissin (2005). The initial definitions used in various clinical trials had limitations. In the past, preemptive analgesia was defined as 1) administration of antinociception initiated before surgery; or 2) administration of antinociception to prevent central sensitization. The administration of multimodal analgesia, in this case, provides a synergistic effect of the drug.[14,20,21]

This study also revealed that the combination of ibuprofen 800 mg and dexamethasone 10 mg was always

associated with significantly lower IL-6 levels than other groups. The results of this study were also stated by Andrew et al., in chronic spinal trauma. Ibuprofen decreased the IL-6 value by 3.2 pg/ml compared to 4.0 pg/ml in the control group. A study by James C et al., showed significant results for changes in IL-6 in sputum samples with an average decrease of 0.13 pg/mL ($P = 0.04$) for 28 days in patients suffering from cystic fibrosis.[22,23]

In the study of El Azab et al., IL 6 increased in both groups, with a lower value in Group 1 (administration of dexamethasone 100 mg) than in Group 2 as control ($P < 0.05$). Dexamethasone 100 mg before cardiac surgery alters circulating cytokines in an anti-inflammatory direction. Postoperative outcomes can be improved by inhibition of the systemic inflammatory response. In this study, it was explained that corticosteroids inhibit but do not abolish the IL 6 response because IL 6 production is influenced by the degree of surgical trauma and tissue damage and the effect of CPB.[5,10,17]

Interleukin-6 is one of the cytokines that appears early and is a mediator of induction and control of acute-phase protein synthesis released by hepatocytes during painful stimuli such as trauma, infection, surgery, burns. After trauma, plasma IL-6 concentrations can be detected within 60 min, peak between 4-6 h, and last up to 10 days. IL-6 is the most appropriate marker for the degree of tissue damage. The longer the plasma IL-6 level, the greater the postoperative morbidity.[4,10,19,24]

Several findings support the possibility that IL-6 has a modulating effect on nociception and pain in humans. Injury to tissue caused by trauma or surgery causes immediate and localized pain. This pain persists after the initial injury, implying that substances that prolong the pain are produced. IL-6 is produced in appreciable amounts at the surgical wound site. IL-6 enters the systemic circulation, where its concentration is related to the severity of the surgery and, therefore, to the severity of the tissue injury. At 24 to 36 h after surgery, plasma levels of IL-6 reach preoperative values because its production is reduced.[19,24,25]

Other results from this study found no side effects from giving ibuprofen 400 mg in combination with 10 mg dexamethasone, 800 mg ibuprofen in combination with 10 mg dexamethasone, or 800 mg for ibuprofen. These recent results are similar to the previous studies using a single dose dexamethasone for adult surgery. No side effects were observed and there was significantly decreased pain scores postoperatively. Erlangga ME et al. found that using dexamethasone 15 mg preoperatively as a single dose as an adjuvant analgesic effect in reducing NRS after modified radical mastectomy surgery, without any adverse side effects.[3,10,26]

5. LIMITATIONS

This study had several limitations. It used a relatively small sample and is only carried out at one center, so it is still possible to bias the results of treatment measurements. In addition, long-term monitoring was not carried out to monitor the impact of success in reducing pain intensity immediately after surgery.

6. CONCLUSION

The preemptive combination of ibuprofen and dexamethasone has efficacy in the management of acute postoperative pain in decompression surgery and posterior vertebral stabilization procedure through reduced numeric rating scale at the rest and on mavement, the IL-6 level, and the requirement for opioid use. This preemptive combination has no adverse effects on the patient.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

SG: Conceptualization, review, and supervision

SAD: Writing, conceptualization, editing, and original draft

AA: Conceptualization, review, and supervision

MR: Conceptualization, review, and supervision

TD: Review, and supervision

CW: Review, and supervision

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