

The Effectiveness of Parecoxib on Inflammatory Cytokines, Prostaglandin Levels, and Visual Analogue Scale Value among Preeclamptic Patients that Undergo Caesarean Section

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Abstract

Introduction: Preeclampsia is produced by the maternal immune system and trophoblast proinflammatory cytokines. Effective perioperative analgesics reduce surgery-related pain and inflammation. It explores how parecoxib affects IL-1, IL-6, prostaglandin and VAS in preeclampsia patients who had a spinal anesthesia cesarean. **Materials and methods:** This experiment uses a 2-group pretest and posttest. Samples were taken consecutively. The study group (n = 18) received parecoxib 40 mg IV bolus every 12 h 4 times and paracetamol 1,000 mg IV infusion every 8 h until 48 h postoperatively, while the control group (n = 18) received placebo NaCl 0.9 % IV bolus every 12 h 4 times and paracetamol 1,000 mg IV drip every 8 to 48 h. Participants' postoperative pain was assessed by VAS before, 12, 24 and 36 h after surgery. Statistical analysis was conducted on biomolecular examination data, including IL-1 β , IL-6, PGE2 and VAS values. **Results and discussion:** The study group had lower IL-1 β levels than the control group, although the difference was not significant ($p > 0.05$). In the study group, IL-6 levels were $4,782 \pm 5,673$ lower than in the control group ($6,147 \pm 5,957$). Study group IL-6 levels were higher than control group values, although not significantly ($p > 0.05$). The study group had lower PGE2 than the control group, but not significantly ($p > 0.05$). The study group's mean VAS value was 1.722 ± 1.994 , lower than the control group's 1.833 ± 2.007 and not significant ($p > 0.05$). The study group had considerably lower VAS values than the control group ($p < 0.05$). **Conclusions:** In preeclampsia patients who underwent caesarean delivery under spinal anesthesia, parecoxib administration influences IL-1 β levels after 24 h and VAS values after 12 h. It did not affect IL-6 or PGE2 levels in preeclamptic individuals who had spinal anesthesia caesarean sections.

Keywords: Preeclampsia, Parecoxib, Proinflammatory cytokines, IL-1 β , Visual analogue scale

Introduction

Hypertensive disorder of pregnancy (HDP) is a major cause of maternal and fetal morbidity and mortality [1]. During the 40-year period (1979 - 2018), there were 2.1 maternal deaths due to hypertension per 100,000 live births [2]. Preeclampsia affects 2 to 8 % of pregnancies worldwide [3]. In 2018, class B Arifin Ahmad Hospital in Pekanbaru, Riau Province, delivered 155 preeclampsia babies [4]. Pekanbaru's Grade C Bina Kasih Hospital delivered 102 preeclampsia infants in 2021. Severe inflammation and placental anti-angiogenesis dominate theories [5]. In preeclampsia, abnormal trophoblast cell invasion into the myometrial spiral arteries creates an uncontrolled, convoluted, cytokine-driven systemic inflammatory response [6]. IL-6 increases endothelial permeability and induces apoptosis of the trophoblastic cells [7,8]. IL-1 β also affects the maternal vascular endothelium and cause its dysfunction [9].

A caesarean section is associated with moderate to severe postoperative pain in the majority of women, which may affect postoperative recovery and patient satisfaction as well as successful breastfeeding and mother-child bonding. In addition, inadequate postoperative pain relief can lead to hyperalgesia and persistent postoperative pain [10]. NSAIDs reduce postoperative discomfort. Parecoxib

inhibits COX-2. To reduce neuroinflammation, this drug inhibits central and peripheral prostaglandin synthesis [11]. It eases surgery and analgesia. Parecoxib provides a safety profile for both surgical patients and breastfeeding mothers [12].

Previous meta-analysis studies showed that intravenous parecoxib was effective for reducing pain scores within 12 h at rest and between 12 and 24 h while sitting and reducing morphine consumption after hysterectomy, but had no apparent impact on initial analgesic requirements [13]. Meanwhile, a study conducted in 2016 on low-risk pregnant Thai women who were approved and scheduled for elective cesarean sections under spinal anesthesia did not find parecoxib to be effective in reducing cumulative meperidine consumption after cesarean section. However, administration of a single 40-mg dose of intravenous parecoxib after elective caesarean section demonstrated effectiveness in reducing pain scores, with a resulting increase in patient satisfaction [14].

Parecoxib is an analgesic, a powerful anti-inflammatory, and has minimal side effects on the health of the mother and baby. There has not been a single study evaluating how parecoxib impacts caesarean delivery perioperative stress response, especially in preeclampsia patients, so far. The aim of this study was to investigate the effects of perioperative parecoxib on IL-1 β , IL-6, prostaglandin levels and VAS values in preeclampsia patients undergoing spinal anesthesia caesarean sections.

Materials and methods

This is an experimental study with a 2-group pretest and posttest design. This study included preeclampsia patients who underwent spinal anesthesia caesarean section at RSUD Arifin Ahmad Riau Province and Bina Kasih Hospital Pekanbaru. Research began in April-November 2022. The inclusion criteria for the preeclamptic patients were hypertension (systolic BP > 140 mm-Hg and diastolic BP > 90 mm-Hg), proteinuria (> 0.3 g/d), and edema after 20th week of gestation [15]. The criteria for inclusion met the following criteria: Willingness to sign informed consent, single pregnancy, not having any history of pregnancy-related complications, diabetes, or any other chronic medical illness, vaginal bleeding throughout pregnancy, along with no evidence of congenital abnormalities, tuberculosis or smoking; age 20 - 45; and ASA physical status II and III. Eclampsia, HELLP syndrome, significant bleeding during surgery, repeat surgery and leukocytosis (leukocytes > 14,000 μ L) were exclusion criteria.

To determine sample size, a sampling formula is used to test the difference in the average of a group of paired data for an experimental pretest-posttest design. With the sample size formula used.

$$n_1 = n_2 = \left(\frac{(Z_\alpha + Z_\beta)S}{X_1 - X_2} \right)^2$$

where n_1 = Number of samples in the parecoxib group, n_2 = Number of samples in the control group, Z_α = Standard Deviat of alpha, Z_β = Standard deviation of beta, S = Standard deviation of the difference in scores between groups, $X_1 - X_2$ = The minimum difference between the averages that is considered meaningful.

For the minimum sample size related to clinical trials on numerical data with a 2-tail test, researchers set an alpha standard deviation of 5 % ($Z_\alpha = 1.96$) and a beta standard deviation of 5 % ($Z_\beta = 1.645$) [16]. Researchers determined the standard deviation of the minimum difference in means that is considered meaningful ($X_1 - X_2$) to be 2.02 and for the S value it was found to be 2.33 according to the standard deviation value from the literature [17]. Based on this formula, the minimum sample size was 18 for the research group and 18 for the control group. After consecutive sampling, samples were randomized into 2 groups.

The patient underwent spinal anesthesia by inserting 10 mg of bupivacaine and 25 μ g of fentanyl into the subarachnoid space. The study group received parecoxib 40 mg IV bolus per 12 h 4 times and paracetamol 1,000 mg IV infusion every 8 h until 48 h after surgery. The control group received a placebo NaCl 0.9 % IV bolus every 12 h 4 times and a paracetamol 1,000 mg IV infusion every 8 to 48 h after surgery. After surgery, researchers may administer extra analgesics such as ketorolac if both groups experience severe pain.

The patient's venous blood was sampled 4 times with a gap of 12 h before and after surgery. The samples will be centrifuged into serum at 1,000 rpm for 10 min at Arifin Ahmad Hospital, Riau Province, and Bina Kasih Hospital, Pekanbaru City. The serum will be transported to the Biomolecular Laboratory, Faculty of Medicine, Riau University, in a refrigerated box below -20°C . After preparation at Riau University's Biomolecular Laboratory, blood samples were transferred to Andalas University for IL-6, IL-1 β and PGE2 testing. Samples I-IV were analyzed for IL-1 β and IL-6. PGE2 was measured on samples 1

and IV. In addition to biomolecular examination, postoperative pain was measured and recorded using VAS several times: Postoperatively: 12, 24 and 36 h.

The results of biomolecular examination, including IL-1 β , IL-6 and PGE2 levels as well as VAS values, were examined with SPSS version 26.

Respondent characteristics

Patient age, education, and occupation are shown in **Table 1**. According to research, preeclampsia patients are on average 20 - 40 years old. In the US, women with incident preeclampsia were older at both index (aged 29.4 years; SD, 5.2 years versus aged 26.2 years; SD, 5.7 years) and subsequent pregnancies when compared to women who had never experienced preeclampsia [18]. This contradicts the Indonesian national health survey, which indicated 25 % of pregnancies had preeclampsia, with the highest rate in pregnancies over 35 [19]. According to 1998 - 2014 U.S. cohort research on preeclampsia, women aged 25 or older may experience serious morbidities. Women under 25 had a much higher rate of eclampsia. Acute cardiac failure and acute kidney injury were more common in women over 45 [20]. As the majority of mothers undergo pregnancy and childbirth during their reproductive years, preeclampsia is also more prevalent among this age group.

Table 1 Personal demographic data.

No	Description	Study group	Control group
		n (%)	n (%)
1	Age		
	17 - 25 years	2 (11.11 %)	5 (27.78 %)
	26 - 35 years	12 (66.67 %)	8 (44.44 %)
	36 - 45 years	4 (22.22 %)	5 (27.78 %)
2	Education		
	Elementary School	4 (22.22 %)	1 (11.11 %)
	Junior High School	4 (22.22 %)	7 (38.89 %)
	Senior High School	9 (50 %)	7 (38.89 %)
	Associate Degree	0 (0 %)	1 (11.11 %)
	Bachelor's Degree	1 (5.56 %)	2 (11.11 %)
3	Work		
	Work	1 (5.56 %)	2 (11.11 %)
	Not Working (housewife)	17 (94.44 %)	16 (88.89 %)

Effect of parecoxib administration on IL-1 β levels in preeclamptic patients who underwent cesarean section under spinal anesthesia

Pre-surgery IL-1 β levels were evaluated. **Table 2** shows IL-1 β levels in both groups. Tissue injury causes IL-1 β to produce COX-2 [9]. Surgery increases IL-6 and COX-2. IL-1 β and TNF- α , which are produced within hours of an injury, induce COX-2 transcription in the neural system and spinal cord neurons [21]. In 2019, Chinese researchers reported that intraperitoneal parecoxib injections on days 5 and 10 improved heat and mechanical hyperalgesia in bone cancer rats. Parecoxib reduced spinal cord IL-1 β , IL-6 and TNF- α [22]. These findings suggest that parecoxib sodium may inhibit pro-inflammatory factors and upregulate anti-inflammatory factors, reducing the inflammatory cascade in peripheral monocytes and the activation of microglia and astrocytes in the central nervous system, and reducing neuroinflammatory injury and oxidative stress pathway damage early on [23].

Lung maturation and decreased maternal progesterone boost SP-A and phospholipid release. Surfactant-A protein stimulates fetal amnion macrophages, which move to the uterine wall and generate IL-1 β , starting the inflammatory/prostaglandin cascade [24]. Preeclamptic patients may have had higher IL-1 β levels before surgery. In preeclampsia, all vascular inflammation components, including the

endothelium, are involved. Pregnant women with polymorphic cytokine genes that enhance cytokine production had an excessive reaction [9].

Table 2 Comparison of IL-1 β levels of the 2 groups.

Pick up time	Study group	Control group	<i>p</i> -value
Pre-surgery	1.625 $\pm$ 1.102	1.646 $\pm$ 0.660	0.391
12 h	1.065 $\pm$ 0.635	1.782 $\pm$ 1.469	0.066
24 h	1.001 $\pm$ 0.442	1.870 $\pm$ 1.432	0.019
36 h	1.150 $\pm$ 0.623	2.256 $\pm$ 1.804	0.023

Effect of parecoxib administration on IL-6 levels in preeclamptic patients who underwent cesarean section under spinal anesthesia

Pre-surgery IL-6 levels were assessed. **Table 3** shows IL-6 levels in both groups. Our study observed a significant increase in IL-6 after surgery, and IL-6 concentrations began to decrease 24 h after surgery, but there was no difference with the control group. In a meta-analysis study to evaluate the effect of parecoxib, there was no significant difference in IL-6 at 72 h after surgery [25]. Parecoxib has been used in intravenous and intramuscular injections with high safety and reliability. The inhibitory effect of parecoxib on COX-2 is 28,000 times stronger than its effect on COX-1, and can achieve strong anti-inflammatory and analgesic effects. IL-6 is the main proinflammatory cytokine in the acute stage of the inflammatory response [26].

Pro-inflammatory cytokines produce endothelial dysfunction and inflammation in preeclampsia [27]. Preeclampsia patients had increased placental IL-6, IL-8 and MCP-1. IL-6 and TNF- α levels increase considerably in preeclamptic placental tissue compared to normal pregnancies from 28 weeks of gestation until birth [8]. Preeclampsia patients had a significant increase in levels of IL-6 and TNF- α in pregnant females with preeclampsia compared to normal ones, with a *p*-value of 0.001 [28]. In the last trimester, myometrial leukocyte assault and migration also produce IL-6 [29].

In this study, parecoxib did not lower IL-6 levels, presumably because preeclamptic patients have higher IL-6 levels. IL-6 may increase trophoblast proliferation, invasion and oxidative stress in preeclampsia. An increased maternal inflammatory response leads to aberrant trophoblast invasion [28].

Table 3 Comparison of IL-6 levels of the two groups.

Pick up time	Study group	Control group	<i>p</i> -value
Pre-surgery	4.782 $\pm$ 5.673	6.147 $\pm$ 5.957	0.486
12 h	81.427 $\pm$ 127.251	60.247 $\pm$ 124.510	0.617
24 h	47,609 $\pm$ 67,297	43.055 $\pm$ 47.507	0.829
36 h	39.431 $\pm$ 43.705	49.212 $\pm$ 52.399	0.547

Effect of parecoxib administration on prostaglandin levels (PGE2) in preeclamptic patients who underwent cesarean section under spinal anesthesia

Pre-surgery and 36-h PGE2 levels were measured. **Table 4** shows PGE2 levels in both groups. Parecoxib decreases PGE2 levels, but not significantly. This data contradicts studies investigating the efficacy and safety of an analgesia regimen of intravenous parecoxib followed by oral celecoxib after total knee arthroplasty surgery, which provided positive evidence that sequential use of COX-2 selective NSAIDs after surgery reduces PGE2 levels in intraoperative intra-articular fluid, post-operative drainage surgery and knee circumference was also significantly reduced at 48 h postoperatively and 72 h in the parecoxib/celecoxib treatment group compared with the placebo group [30].

Increasing prostaglandins makes nociceptors more sensitive to bradykinin, histamine, serotonin, mechanical, chemical and temperature stimuli. Large peripheral prostaglandins affect gene expression in the central nervous system (CNS), causing hyperalgesia and allodynia [31]. This study found elevated preoperative and postoperative PGE2 levels. Painful stimuli in the periphery make cytokines called IL-1 and IL-6. These cytokines travel through the bloodstream to the CNS, where they turn on COX-2 enzymes in brain neurons, which raises PGE2 levels. PGE2 increases, causing discomfort.

Table 4 Comparison of PGE2 levels of the 2 groups.

Pick up time	Study group	Control group	<i>p</i> -value
Pre-surgery	730,538 ± 293,256	852.055 ± 357.641	0.809
36 h	886,166 ± 299,882	967.055 ± 405.886	0.501

Effect of parecoxib administration on Visual Analog Scale (VAS) values in preeclamptic patients who underwent cesarean section under spinal anesthesia

Serial VAS ratings assess pain. 12 - 36 h before surgery. **Table 5** provides measurements from both groups. A linear scale for immediate postoperative pain is the VAS. The VAS value measures pain severity better than other scales. Direct observation of the patient's non-verbal and verbal behavior can supplement subjective pain data [32]. In this study, we found that patients administered IV parecoxib had significantly decreased mean VAS scores. Parecoxib reduces pain by inhibiting spinal cord inflammatory factor production and activation of primary afferent neurons [22]. This is consistent with a systematic review of the effects of preemptive parecoxib: People with a joint replacement who received an intraoperative and preoperative preemptive injection of parecoxib compared to the placebo group experienced less pain at rest and during exercise after surgery, reduced opioid consumption, and no increase in adverse events [33].

Perioperative analgesics must be administered properly to relieve patient pain. Parecoxib reduces discomfort in gastrointestinal complications [34]. The anti-inflammatory and analgesic effects of parecoxib do not interfere with the function of the platelets, so there is less chance of excessive bleeding during surgery [35]. Parecoxib patients showed lower pain levels than placebo patients in the first postoperative days. Parecoxib improves body function (activity, mood, walking ability, relations with others and sleep) [36].

Table 5 Comparison of the VAS values of the 2 groups.

Pick up time	Study group	Control group	<i>p</i> -value
Pre-surgery	1.722 ± 1.994	1.833 ± 2.007	0.869
12 h	4.722 ± 1.017	5.500 ± 0.857	0.018
24 h	3.444 ± 0.921	4.944 ± 0.872	0.000
36 h	2.666 ± 0.766	4.166 ± 0.383	0.000

Limitations

The study had limitations, including being conducted during a pandemic, which hindered research activities, including the need for time to accommodate the sample size. This study only focuses on 2 inflammatory cytokines, IL-1 β and IL-6, in preeclamptic patients undergoing caesarean section. This study used only COX-2 inhibitors, specifically parecoxib, without combining them with other analgesics that may be more effective in inhibiting inflammatory factors. Additional investigation is required to explore the potential benefits of administering the parecoxib medicine in combination with other analgesics to lower inflammation. Furthermore, further research is needed to examine the use of other biomarkers, such as TNF- α and IL-10, as indicators of the inflammatory process

Conclusions

Based on the results obtained from this research, it can be concluded that administration of parecoxib has an effect on IL-1 β levels after 24 h in preeclamptic patients who underwent cesarean section under spinal anesthesia. Administration of parecoxib affects the VAS after 12 h in preeclampsia patients whose cesarean section was performed under spinal anesthesia. Administration of parecoxib has no effect on IL-6 levels or PGE2 levels in preeclamptic patients who underwent a caesarean section under spinal anesthesia.

Ethics declaration

This research involves humans as research subjects. Therefore, there is the possibility of ethical problems for research subjects in the form of discomfort in taking blood samples for IL-1 β , IL-6 and PGE2 testing as biomolecular markers for improvement. preeclampsia patients. For this reason, the patient's family and the patient are informed about this research. Participants that they can freely decide whether they want to participate in the research project and can withdraw at any time. The data obtained is kept confidential. Research results are presented as group data and not individual data. If participants were willing to participate in the study, they and their family caregivers signed research consent prior to the study. The Medical Faculty Andalas University, Indonesia, Research Ethics Committee approved the protocol (683/UN.16.2/KEP-FK/2022).

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