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Effects of Pregabalin as Preemptive Analgesia for Pain Score, Sedation Score, and Cortisol Level after Caesarean Section Under Spinal Anesthesia

Muhammad Ramli Ahmad, Ardiansyah Siradjuddin, Syafruddin Gaus*, Syafri Kamsul Arif, Alamsyah Ambo Ala Husain, Andi Adil

Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Hasanuddin University-Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia

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***Correspondence:** Syafruddin Gaus, Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. E-mail: udhingaus@hotmail.com
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Abstract

INTRODUCTION: Cesarean section (C-section) is an increasingly common method of delivery, so optimal management of anesthesia and post-operative pain is essential for better outcomes. Preemptive analgesia is an effective method for preventing post-operative pain, with the benefits of pregabalin specifically being much studied and debated. This study aimed to determine the side effects and efficacy of different pregabalin doses for pain management and prevention of stress response in C-section patients under spinal anesthesia.

MATERIALS AND METHODS: This double-blind randomized trial study examined 30 patients who underwent elective C-section under spinal anesthesia with 0.5% hyperbaric bupivacaine 10 mg + adjuvant fentanyl 25 mcg, who were divided into three equal groups which received oral placebo or pregabalin (75 or 150 mg). Pain scores, sedation scores, and cortisol levels and changes were analyzed, the former two using Mann–Whitney tests, cortisol levels using one-way Analysis of variance (ANOVA) tests, and cortisol level changes using repeated-measures ANOVA tests on SPSS software version 20. Results were considered significant when $p < 0.05$.

RESULTS: There were significant differences in numerical rating scale between the placebo and pregabalin groups at rest and movement after surgery ($p < 0.05$), and in sedation scores between the placebo and 150 mg groups and between the 75 mg and 150 mg groups at 2 and 6-h post-surgery ($p < 0.05$), as well as cortisol level changes between all groups ($p < 0.05$).

CONCLUSIONS: Preemptive administration of pregabalin 75 mg is recommended for C-section surgery because it may reduce post-operative pain with minimal side effects.

Introduction

Preemptive analgesia is a method of administering preoperative analgesia/nociceptive stimuli to prevent central sensitization due to incision and inflammatory injury that occurs during and after surgery. It is an effective method for preventing post-operative pain [1]. One of the drugs that can be used as preemptive analgesia is pregabalin, for which there have been several studies regarding efficacy in reducing pain and post-operative opioid consumption. Pregabalin is a gamma-aminobutyric acid (GABA) analog, which is an inhibitory neurotransmitter but does not act directly on GABA receptors. Pregabalin binds the presynaptic $\alpha 2$-δ subunit of the calcium channel and modulates calcium entry through this channel, thereby reducing the release of excitatory neurotransmitters such as glutamate and substance P and resulting in inhibition of neuronal excitability and central sensitization [2], [3].

At present, caesarean section (C-section) is an increasingly common method of delivery. Worldwide, the C-section rate has increased from 4% in 1998 [4] to 21.1% in 2018 [5], while in Indonesia it has increased from 9.8% in 2013 to 18.5% in 2017 [6], [7]. With the increasing number of C-sections every year, optimal management of anesthesia and post-operative pain is essential for better outcomes [5].

In recent years, many studies have been conducted on the preemptive administration of pregabalin for various types of surgery with variable results [8], [9], [10], [11], [12], [13]. There has been substantial debate about the benefits of preemptive pregabalin for post-operative pain, so the need for further studies to determine the benefits of preemptive pregabalin administration in certain doses on various post-operative variables is clear. The objective of this study was to determine the effects of different pregabalin doses (75 and 150 mg) on pain score, sedation score, and cortisol level in C-section patients under spinal anesthesia.

Materials and Methods

Study design

This double-blind randomized trial study was conducted at the Educational Hospital Network in our institution at Makassar, Indonesia from March to April 2021.

Study population and sample

The population in this study consisted of patients who underwent an elective C-section surgical procedure in the central operating room of the Educational Hospital Network in our institution. Samples were selected consecutively from all patients that met inclusion criteria and agreed to participate in this study. Inclusion criteria in this study were as follows: Aged 20–45 years, body weight 50–80 kg, body height 150–170 cm, body mass index (BMI) 18.5–29.9 kg/m^2, and American Society of Anesthesiologists Physical Status II. Exclusion criteria in this study were as follows: Spinal anesthesia was contraindicated, patients with a history of asthma, hypertension, heart and cardiovascular disease, epilepsy or antiepileptic drugs use, psychiatric disorders, chronic pain, diabetes mellitus, impaired kidney or liver function, allergy to study materials, alcohol use, received opioid therapy, neuropathic analgesic drugs, anti-inflammatory drugs, and chemotherapy. Drop-out criteria in this study were as follows: Anesthesia or surgery complications occurred, conversion to general anesthesia during surgery, and patient withdrawal from the study.

Study permit and ethical clearance

Ethical clearance was obtained from the Ethical Committee for Biomedical Study on Humans, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia (no. 60/UN4.6.4.5.31/PP36/2021). All participants who participated in this study were given verbal explanations and signed consent forms.

Study procedure

Patients were allocated to one of three groups, P0 (receiving placebo/oral 1 h before surgery), P75 (receiving pregabalin [Lyrica®, Pfizer, Indonesia] 75 mg/oral 1 h before surgery), and P150 (receiving pregabalin [Lyrica®, Pfizer, Indonesia] 150 mg/oral 1 h before surgery) before undergoing an elective C-section surgery preparation procedure under spinal anesthesia with 0.5% hyperbaric bupivacaine (Regivell®, Novell, Indonesia) 10 mg + adjuvant fentanyl (Etanyl®, Kimia Farma, Indonesia) 25 mcg. Measurement of cortisol level (K0) was conducted 2 h before C-section. After the anesthetic agent was administered, the height of the autonomic block was assessed with a cold test, and the sensory block was assessed with a pinprick test, and the motoric block was assessed with a Bromage score [14]. After the surgery was completed, cortisol level (K1) was measured and the patient was transferred to the post anesthesia care unit. Cortisol levels were also measured 6 h (K2) after surgery. Pain scores were assessed using numerical rating scale (NRS) [15] and sedation scores were assessed using Ramsay sedation scale (RSS) at 2, 6, 12, and 24 h after surgery [16].

Data processing and analysis

Normality was tested using the Shapiro–Wilk test. Variables are presented as mean ± standard deviation (mean ± SD) and were tested by one-way analysis of variance (ANOVA) and repeated-measures ANOVA (parametric tests) if they qualified (normal distribution and same variance). If they did not qualify, Kruskal–Wallis and Mann–Whitney tests (non-parametric tests) were used. All analyses were performed on SPSS software version 20.

Results

Sample characteristics

The sample characteristics of the three groups are shown in Table 1. There were no significant differences in age, body weight, body height, BMI, and duration of surgery between the groups. Based on this result, the data could be characterized as homogeneous.

Pain score (NRS)

Table 2 outlines the comparison of NRS in each group. There were significant differences in NRS at rest and movement between the P0 and P75 groups and between the P0 and P150 groups. However, there were

Table 1: Sample characteristics

Characteristics	P0 group (n: 10)	P75 group (n: 10)	P150 group (n: 10)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)*	28.00 ± 6.70	28.90 ± 6.03	31.20 ± 5.43	0.488^{ns}
Body weight (kg)*	63.10 ± 6.93	65.20 ± 6.17	62.60 ± 5.95	0.630^{ns}
Body height (cm)#	154.30 ± 0.04	155.90 ± 0.04	154.30 ± 0.03	0.488^{ns}
BMI (m/kg^2)*	26.45 ± 2.12	26.91 ± 3.17	26.27 ± 1.88	0.832^{ns}
Duration of surgery (minutes)#	61.70 ± 25.16	59.00 ± 14.49	68.50 ± 31.00	0.883^{ns}

*Data were analyzed with one-way ANOVA test. #Data were analyzed with Kruskal–Wallis test. nsnot significant.

Table 2: Comparison of NRS in each group

NRS	Post-operative measurement Time	Group	Mean ± SD	p
Rest	2 h	P0	2.60 ± 0.51	0.004*
		P75	1.90 ± 0.31	
		P0	2.60 ± 0.51	0.003*
		P150	1.80 ± 0.42	
		P75	1.90 ± 0.31	0.542^{ns}
		P150	1.80 ± 0.42	
	6 h	P0	3.30 ± 0.82	0.007*
		P75	1.80 ± 1.13	
		P0	3.30 ± 0.82	0.000*
		P150	1.10 ± 0.31	
		P75	1.80 ± 1.13	0.101^{ns}
		P150	1.10 ± 0.31	
	12 h	P0	2.60 ± 0.69	0.035*
		P75	1.70 ± 0.94	
		P0	2.60 ± 0.69	0.000*
		P150	1.10 ± 0.31	
		P75	1.70 ± 0.94	0.100^{ns}
		P150	1.10 ± 0.31	
	24 h	P0	1.50 ± 0.52	0.374^{ns}
		P75	1.30 ± 0.48	
		P0	1.50 ± 0.52	0.057^{ns}
		P150	1.10 ± 0.31	
		P75	1.30 ± 0.48	0.276^{ns}
		P150	1.10 ± 0.31	
Movement	2 h	P0	3.70 ± 0.48	0.001*
		P75	2.90 ± 0.31	
		P0	3.70 ± 0.48	0.006*
		P150	2.90 ± 0.56	
		P75	2.90 ± 0.31	0.957^{ns}
		P150	2.90 ± 0.56	
	6 h	P0	4.40 ± 0.84	0.010*
		P75	2.90 ± 1.37	
		P0	4.40 ± 0.84	0.000*
		P150	2.20 ± 0.63	
		P75	2.90 ± 1.37	0.135^{ns}
		P150	2.20 ± 0.63	
	12 h	P0	3.60 ± 0.69	0.035*
		P75	2.70 ± 0.94	
		P0	3.60 ± 0.69	0.001*
		P150	2.00 ± 0.81	
		P75	2.70 ± 0.94	0.067^{ns}
		P150	2.00 ± 0.81	
	24 h	P0	2.60 ± 0.51	0.018*
		P75	1.60 ± 0.96	
		P0	2.60 ± 0.51	0.002*
		P150	1.40 ± 0.96	
		P75	1.60 ± 0.96	0.618^{ns}
		P150	1.40 ± 0.96	

Data were analyzed with Mann–Whitney test. *: Significant, ^{ns}Not significant.

no significant differences in NRS at rest and movement between P75 and P150 groups.

Sedation score (RSS)

Table 3 outlines the comparison of sedation scores in each group. Significant differences were found in the sedation scores between the P0 and P150 groups at 2 and 6 h after surgery, and between the P75 and P150 groups at 2 and 6 h after surgery. There were no significant differences in sedation scores between the P0 and P75 groups.

Table 3: Comparison of sedation scores in each group

Sedation score	Post-operative measurement time	Group	Mean ± SD	p
RSS	2 h	P0	2.00 ± 0.00	0.146^{ns}
		P75	2.20 ± 0.42	
		P0	2.00 ± 0.00	**0.000***
		P150	3.80 ± 0.42	
		P75	2.20 ± 0.42	**0.000***
		P150	3.80 ± 0.42	
	6 h	P0	2.00 ± 0.00	0.317^{ns}
		P75	2.10 ± 0.31	
		P0	2.00 ± 0.00	**0.000***
		P150	3.60 ± 0.51	
		P75	2.10 ± 0.31	**0.000***
		P150	3.60 ± 0.51	
	12 h	P0	2.00 ± 0.00	1.000^{ns}
		P75	2.00 ± 0.00	
		P0	2.00 ± 0.00	1.000^{ns}
		P150	2.00 ± 0.00	
		P75	2.00 ± 0.00	1.000^{ns}
		P150	2.00 ± 0.00	
	24 h	P0	2.00 ± 0.00	1.000^{ns}
		P75	2.00 ± 0.00	
		P0	2.00 ± 0.00	1.000^{ns}
		P150	2.00 ± 0.00	
		P75	2.00 ± 0.00	1.000^{ns}
		P150	2.00 ± 0.00	

Data were analyzed with Mann–Whitney test. *: Significant, ^{ns}Not significant.

Table 4: Comparison of cortisol level in each group

Cortisol level	Measurement time	P0 group (n: 10)	P75 group (n: 10)	P150 group (n: 10)	p
		Mean ± SD	Mean ± SD	Mean ± SD	
Cortisol	K0	57.84 ± 20.32	45.08 ± 16.45	48.07 ± 15.98	0.259^{ns}
	K1	49.90 ± 27.49	42.68 ± 26.71	47.99 ± 8.34	0.764^{ns}
	K2	22.93 ± 16.50	20.52 ± 23.19	16.74 ± 10.43	0.730^{ns}

Data were analyzed with one-way ANOVA test. ^{ns}Not significant.

Cortisol level

Table 4 outlines the comparison of cortisol levels in each group. There were no significant differences in cortisol levels between any groups. Table 5 outlines the changes in cortisol levels in each group. In all groups, there was a significant decrease in cortisol levels from K0 to K2 and K1 to K2. However, there was no significant decrease in cortisol level from K0 to K1 in any groups.

Table 5: The comparison of cortisol changes on each group

Cortisol level	Group	Measurement time	Mean ± SD	p
Cortisol	P0	K0	57.84 ± 20.32	0.190^{ns}
		K1	49.90 ± 27.49	
		K0	57.84 ± 20.32	0.001*
		K2	22.93 ± 16.50	
		K1	49.90 ± 27.49	0.025*
		K2	22.93 ± 16.50	
	P75	K0	45.08 ± 16.45	0.729^{ns}
		K1	42.68 ± 26.71	
		K0	45.08 ± 16.45	0.014*
		K2	20.52 ± 23.19	
		K1	42.68 ± 26.71	0.001*
		K2	20.52 ± 23.19	
	P150	K0	48.07 ± 15.98	0.982^{ns}
		K1	47.99 ± 8.34	
		K0	48.07 ± 15.98	0.000*
		K2	16.74 ± 10.43	
		K1	47.99 ± 8.34	0.000*
		K2	16.74 ± 10.43	

Data were analyzed with Repeated ANOVA test. *: Significant, ^{ns}Not significant.

Discussion

There was a significant difference in pain scores between the placebo group and both the pregabalin 75 and 150 mg groups, but there was no significant difference in the pain score between the pregabalin 75 and 150 mg group in this study. These support the conclusion that pregabalin can reduce pain scores at either dose, a finding supported by a study conducted by Agarwal *et al*., in 2008, which found that pre-operative administration of pregabalin 150 mg 1 h before surgery reduced visual analog score (VAS) and opioid consumption after laparoscopic cholecystectomy surgery under general anesthesia [17]. A study from Eskandar and Ebeid in 2013 found that preemptive administration of pregabalin 300 mg at 12 h and again

at 1 h before surgery reduced VAS after shoulder arthroscopic surgery under general anesthesia [18]. These studies used 150 and 300 mg doses, whereas our study used 75 and 150 mg doses, both of which decreased NRS. We showed that a small dose of pregabalin (75 mg) did not differ significantly from 150 mg for reduced NRS. Pregabalin's mechanism of action is to suppress the release of excitatory neurotransmitters, which prevent neuronal excitability and central sensitization [19]. This proves that pregabalin has an opioid sparring effect, and administering a larger dose of pregabalin can increase its efficacy, but the side effects that arise from using a larger dose also increase. The mechanism of action of pregabalin is to suppress the release of excitatory neurotransmitters and prevent central sensitization.

There was a significant difference in sedation scores between the pregabalin 150 mg group and the 75 mg and placebo groups at 2 and 6 h after C-section surgery, indicating that pregabalin 150 mg has higher sedation efficacy up to 6 h after C-section surgery. This aligns with the study by Bala *et al*. in 2019, where they found that a group given preemptive pregabalin 150 mg 90 min before surgery had a higher sedative effect at 1 h after thoracolumbar spine surgery under general anesthesia when compared with a placebo group. However, at 2 h and thereafter, all patients had the same sedation score [20].

The sedative effect arises from pregabalin's mechanism of action, which potently binds the group α2-δ subunit of calcium channel and modulates calcium influx at nerve endings, thereby reducing the release of excitatory neurotransmitters (glutamate). It is similar to the mechanism of action of various intravenous and inhaled anesthetic agents [21]. Administration of pregabalin 75 mg in our study did not differ significantly from placebo, which indicates that a small dose of pregabalin could reduce the incidence of sedation side effects.

There was no significant difference in cortisol level amongst placebo, pregabalin 75 mg and 150 mg groups in this study, and it could be concluded that pregabalin did not significantly affect cortisol levels in patients who undergoing C-section surgery regardless of dose. Similar findings were also reported by Naby *et al*. in 2021, where they found that preemptive administration of pregabalin 150 mg at 1 h before surgery did not affect mean pulse rate, blood pressure, and glucose and cortisol levels during the intubation process in patients who underwent C-section surgery under general anesthesia [22]. Pregabalin attenuates the stress response in a dose-dependent manner. According to a 2016 study by Meena *et al*., it was found that preemptive administration of pregabalin 300 mg 1 h before surgery was associated with a significant decrease in pulse rate and mean arterial pressure after airway instrumentation in patients with controlled hypertension when compared to administration of pregabalin 150 mg or placebo [23]. Similar findings were also reported by Rastogi *et al*. in 2012 [24]. Cortisol level might be decreased with the use of a large pregabalin dose, but its side effects will also increase.

Pregabalin's mechanism of action does not directly suppress cortisol secretion, but instead binds the 2-δ subunit of the calcium channel and further modulates calcium entry into nerve terminals, decreasing the release of several excitatory neurotransmitters such as glutamate and substance P. Decreased glutamate release causes inactivation of NMDA receptors, which inhibits neuronal excitability and decreases central sensitization. This inhibitory process occurs especially in areas of the central nervous system that are dense with synapses, such as the neocortex, amygdala, and hippocampus [19], [25], [26], [27].

The suppressive effect of cortisol in all treatment groups in our study could be due to the use of spinal anesthesia, as spinal anesthesia might reduce the stress response to surgery. Spinal anesthesia blocks somatic and autonomic (sympathetic) afferent pathways caused by surgical incisions, therefore reducing the stress response. Spinal anesthesia with a local anesthetic agent has only a temporary effect in reducing the stress response. It has been known for many years that opioids suppress hypothalamic and pituitary hormone secretions. The combination of local anesthetic and intrathecal opioids in spinal anesthesia will suppress endocrine and metabolic responses, which will inhibit hypothalamic-pituitary and sympathoadrenal axis activation. These events prevent the increase of cortisol level after surgery [28], [29], [30] which in this study could be seen from the decrease of cortisol levels during surgery in all groups.

The limitation of this study is that elective C-section surgeries were performed in the morning (08:00–12:00 AM), so there were variations in the time of surgery that can affect the results of the examination because there are diurnal variations in cortisol levels, where cortisol levels decrease gradually from morning to night. This can cause bias in the results of the examination of cortisol levels in this study.

Conclusions

Pregabalin can reduce NRS at rest and movement. In addition, pregabalin 150 mg has a higher sedation score up to 6 h after C-section surgery. Spinal anesthesia can reduce cortisol levels. Preemptive administration of pregabalin 75 mg is recommended for C-section surgery because it might reduce NRS with minimal side effects, and further study is needed to determine the effect of preemptive pregabalin for other types of surgery.

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