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The Effect of Pregabalin Levels on Pain and Substance P Level Post-Cesarean Section

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Abstract

BACKGROUND: Post-operative pain is a very important problem faced by post-operative patients. Antihyperalgesia is caused by the inhibition of the neurotransmitter glutamate and substance P (SP) by pregabalin. This study aimed to compare the effect of preventive administration of 50 mg oral pregabalin and 1 g paracetamol with 75 mg oral pregabalin and 1 g intravenous paracetamol on Numeric Rating Scale (NRS) scores and SP levels after cesarean section with spinal anesthesia.

AIM: The objective of the study was to compare the effect of preventive administration of 50 mg oral pregabalin and 1 g paracetamol with 75 mg oral pregabalin and 1 g intravenous paracetamol on NRS scores and SP levels after cesarean section with spinal anesthesia.

METHODS: This study used a double-blind randomized trial design. Samples were selected randomly and consecutively from the entire population that met the inclusion criteria. There were a total of 30 samples. SP levels were measured 2 h before cesarean section. The study drug was administered by mouth with a sip of water 1 h before the expected time of the surgical incision. SP levels were checked at the 4th h (SP 1) and 6th h (SP 2) postoperatively. The assessment of the degree of pain using the NRS was carried out at 2 h, 4 h, 6 h, 12 h, and 24 h postoperatively. This study used the Mann–Whitney U-test to compare both the levels of SP and NRS between the two groups.

RESULTS: The results of this study showed that there was a significant difference in the NRS scores between the 50 mg and 75 mg pregabalin groups ($p < 0.05$). In the 75 mg pregabalin group, the NRS scores were lower than in the 50 mg pregabalin group in patients undergoing CS surgery under spinal anesthesia. There was a significant difference in SP levels between the 50 mg and 75 mg pregabalin groups ($p < 0.05$). SP levels in the 50 mg pregabalin group increased at 4 h and 6 h postoperatively, while in the 75 mg pregabalin group, it tended to decrease at 4 h and 6 h postoperatively.

CONCLUSION: The quiescent and mobile NRS scores in the 75 mg pregabalin group were lower than the 50 mg pregabalin group with a combination of 1 g intravenous paracetamol after SC surgery. SP levels in the 75 mg pregabalin group decreased compared to the 50 mg pregabalin group with a 1 g intravenous paracetamol combination which experienced an increase after CS surgery. Pregabalin 75 mg is recommended for preventive use in CS surgery.

Introduction

Post-operative pain is a very important problem faced by post-operative patients. Although our knowledge of the mechanisms of post-operative pain has advanced a lot, the management of post-operative pain is not optimal and is often neglected [1], [2], [3].

Post-operative pain is characterized by peripheral and central sensitization of the nervous system. Once there is sensitization of the nervous system, a weak stimulus that would normally not cause pain will feel painful, but a strong stimulus that is sufficient to cause intense pain. Post-operative sensitization will cause suffering for the patient; therefore, post-operative pain management should be aimed at preventing and minimizing the occurrence of the sensitization process [4].

Clinical data show that post-operative wound repair is closely related to various cytokines and inflammatory mediators by releasing large numbers of lysosomes and toxic microorganisms, resulting in local tissue damage. However, statistical reports show that substance P (SP) plays a key role in tissue damage. When trauma occurs, primary sensory nerve terminals are disrupted, and C and Aδ fibers release the pain information neurotransmitter SP. This neuropeptide has long been associated with pain processing because it is located in primary afferents, is small in diameter, and is released after tissue damage. Large amounts of SP in the spinal cord affect nociceptive transmission. At the same time, the nociceptors around the wound are activated and then release SP. Meanwhile, more nociceptors are activated, which form a vicious circle and affect postpartum wound healing. It has also been

reported that SP can also increase arachidonic acid metabolism [2], [5].

Pregabalin is a gamma aminobutyric acid (GABA) analog with anticonvulsant and anxiolytic properties. Pregabalin has a structure similar to GABA but acts through presynaptic Ca^{2+} channels, blocking Ca^{2+} from entering the cell. This condition will suppress the production of glutamate, and SP from the presynaptic will reduce sensitization and hyperalgesia. Antihyperalgesia in this case is caused by the inhibition of the neurotransmitters glutamate and SP by pregabalin. Hyperalgesia is also found in neuropathic and post-operative pain. Therefore, it is expected that the use of pregabalin can reduce hyperalgesia in post-operative care because it is antinociceptive and reduces the perception of post-operative pain [3].

In recent years, many studies have been conducted regarding the perioperative treatment of pregabalin. In a study conducted by Elvidiansyah et al. in 2014, it was stated that pregabalin 300 mg was better than pregabalin 150 mg in reducing Numeric Rating Scale (NRS) values after abdominal hysterectomy surgery but giving pregabalin 300 mg was not better than pregabalin 150 mg in reducing postoperative analgetic needs in abdominal hysterectomy [4]. Research conducted by Cho *et al*. in 2019 stated that pregabalin treatment of 150 mg 1 h before surgery and 12 h after the initial dose could reduce the NRS of passive knee flexion at 24 h and 36 h after anterior cruciate ligament reconstruction surgery [6]. Research conducted by Mishriky *et al*. in 2015 showed that perioperative treatment of pregabalin was associated with a significant reduction in opioid consumption and a decrease in post-operative NRS values [7]. The dose of pregabalin based on body weight is 3 mg/kg with a dose range of 50–300 mg [3]. Therefore, a study was conducted using the lowest doses of 50 and 75 mg.

Paracetamol is a non-opioid and non-salicylic analgesic that has been used for more than 40 years to treat mild-to-moderate pain. Paracetamol works by increasing the pain threshold by inhibiting N-methyl-D-aspartate (NMDA) or called SP and central prostaglandin E. Paracetamol has analgesic and antipyretic effects without anti-inflammatory effects which are safe to use, have minimal side effects, and are well tolerated. Paracetamol also has an opioid-sparing effect when used together with low-dose opioids, so it provides good analgesia by minimizing opioid side effects such as respiratory depression, bradycardia, and hypoxia [8], [9].

This study aimed to compare the effect of preventive administration of 50 mg oral pregabalin and 1 g paracetamol with 75 mg oral pregabalin and 1 g intravenous paracetamol on NRS scores and SP levels after cesarean section with spinal anesthesia.

Methods

This study used a double-blind randomized trial design. The population included in this study were patients who were about to undergo an elective cesarean section in the central operating room of RSIA Sitti Khadijah I, Makassar. Samples were selected randomly and consecutively from all populations that met the inclusion and exclusion criteria and agreed to participate in this study. Hence, the sample size in this study was 15 patients in each group. Therefore, the total sample was 30 samples. The drug used in this spinal anesthesia process, apart from pregabalin and paracetamol, is hyperbaric bupivacaine 0.5% (Regivell) of 10 mg with adjuvant fentanyl of 25 μg.

Based on the type and form of the data obtained, the appropriate statistical test method was determined. The normality test of the data using Shapiro–Wilk with a significance value of $p > 0.05$ indicates that the data are normally distributed. If a normal distribution is obtained ($p > 0.05$), then the repeated ANOVA test is used. Meanwhile, if an abnormal distribution was obtained ($p = 0.05$), the Friedman test was used to compare the levels of SP before and after the treatment of pregabalin and paracetamol in each group. Statistical tests were continued to examine the SP levels differences between the two groups. If the data are normally distributed ($p > 0.05$), then the general linear model hypothesis test is used, and if the distribution is not normal ($p < 0.05$), then the Mann–Whitney U-test is used to compare the levels of SP between the two groups. The Mann–Whitney U-test was also used to compare the NRS between the two groups.

Inclusion criteria in this study were as follows: Age 20–40 years, weight 50–70 kg, height 150–170 cm, BMI: 18.5–29.9 kg/m^2, ASA PS II, and cesarean section with the elective procedure. ASA PS is an assessment of the patient's physical status to assess the risk of anesthesia and surgery based on the American Society of Anesthesia Physical Status criteria. ASA PS II: Patients with mild systemic disorders or mild disease with no substantive functional impairment.

Exclusion criteria in this study were contraindications to subarachnoid block, patients with a history of asthma, patients with a history of hypertension, heart and cardiovascular disease, patients with a history of epilepsy or currently using antiepileptic drugs, patients with a history of chronic pain, patients with psychiatric disorders, patients with a history of DM, patients with impaired kidney or liver function, and patients with alcohol users.

Group P1 was the treatment group that received pregabalin of 50 mg/oral and 1 g intravenous paracetamol 1 h preoperatively. Group P2 is the treatment group that received pregabalin of 75 mg/oral

and 1 g intravenous paracetamol 1 h preoperatively. The level of SP (SP 0) was measured 2 h before the cesarean section. The study drug was administered by mouth with a sip of water 1 h before the expected time of the surgical incision. Both groups underwent spinal anesthesia with Spinocan®, 25G, hyperbaric bupivacaine 0.5% (Regivell) 10 mg with adjuvant fentanyl 25 μg with an injection speed of 3 s/cc. Then, the level of SP was checked at the 4th h (SP 1) and 6th h (SP 2) postoperatively. The assessment of the degree of pain using the NRS was carried out at 2 h, 4 h, 6 h, 12 h, and 24 h after surgery.

The blind process was carried out by asking pharmacists to put pregabalin with each dose into capsules without being known by researchers, doctors, and patients. After sampling, the contents of the capsules were then asked by the pharmacist.

Results

Univariate test

Table 1 shows that there is no significant difference in age, weight, height, BMI, and duration of surgery ($p > 0.05$) between the 50 and 75 mg pregabalin groups undergoing CS surgery, so the data can be said to be homogeneous.

Table 1: Sample characteristics

Characteristics	50 mg pregabalin	75 mg pregabalin	p
	Mean ± SD	Mean ± SD	
Age (years)	31.20 ± 6.51	29.73 ± 5.39	0.507^{ns}
Weight (kg)	63.60 ± 7.68	63.67 ± 6.70	0.980^{ns}
Height (cm)	159.07 ± 7.17	158.73 ± 6.15	0.967^{ns}
BMI (kg/m^2)	25.05 ± 1.58	25.22 ± 1.66	0.776^{ns}
Surgery time (minutes)	61.13 ± 20.63	59.00 ± 12.13	0.838^{ns}

Data ditampilkan dengan mean ± standard deviation. Data dianalisa dengan uji T tidak berpasangan. ns: Not significant different.

Normality test

Table 3 shows that the sample data is not normally distributed because it has a $p < 0.05$. Therefore, the Mann-Whitney test was used to compare the levels of SP between the two groups. Similarly, to compare the NRS between the two groups, the Mann-Whitney test was used.

Pain score (NRS)

Table 4 shows that there were significant differences between quiescent NRS and mobile NRS between the 50 mg pregabalin group and 75 mg pregabalin ($p < 0.05$) at 2, 4, 6, and 12 h after CS surgery. However, at 24 h, there was no significant difference between the two groups.

Table 2: Descriptive

Substance P Level	Group	Statistic	SE
P_Rate_preop	Control		
	Mean	382.14353	76.670476
	95% confidence interval for mean		
	Lower bound	217.70172	
	Upper bound	546.58535	
	5% trimmed mean	339.24798	
	Median	266.51400	
	Variance	88175.428	
	SD	296.943476	
	Minimum	188.207	
	Maximum	1348.200	
	Range	1159.993	
	Interquartile range	210.543	
	Skewness	2.795	0.580
	Kurtosis	8.675	1.121
	Intervention		
	Mean	368.59440	50.768415
	95% confidence interval for mean		
	Lower bound	259.70698	
	Upper bound	477.48182	
	5% trimmed mean	358.89678	
	Median	310.01700	
	Variance	38661.479	
	SD	196.625226	
	Minimum	70.303	
	Maximum	841.443	
	Range	771.140	
	Interquartile range	116.333	
	Skewness	1.355	0.580
	Kurtosis	1.800	1.121
P_Rate_4hour_postop	Control		
	Mean	397.72660	55.830923
	95% confidence interval for mean		
	Lower bound	277.98118	
	Upper bound	517.47202	
	5% trimmed mean	371.28517	
	Median	338.11100	
	Variance	46756.379	
	SD	216.232234	
	Minimum	215.134	
	Maximum	1056.265	
	Range	841.131	
	Interquartile range	217.233	
	Skewness	2.294	0.580
	Kurtosis	6.054	1.121
	Intervention		
	Mean	350.98853	53.288442
	95% confidence interval for mean		
	Lower bound	236.69619	
	Upper bound	465.28087	
	5% trimmed mean	336.13926	
	Median	298.92200	
	Variance	42594.870	
	SD	206.385247	
	Minimum	32.365	
	Maximum	936.899	
	Range	904.534	
	Interquartile range	129.690	
	Skewness	1.730	0.580
	Kurtosis	4.365	1.121
P_Rate_6h_postop	Control		
	Mean	468.31680	74.207871
	95% confidence interval for mean		
	Lower bound	309.15675	
	Upper bound	627.47685	
	5% trimmed mean	426.17972	
	Median	364.90800	
	Variance	82602.121	
	SD	287.405847	
	Minimum	289.398	
	Maximum	1405.703	
	Range	1116.305	
	Interquartile range	105.284	
	Skewness	2.855	0.580
	Kurtosis	8.811	1.121
	Intervention		
	Mean	306.20727	39.212974
	95% confidence interval for mean		
	Lower bound	222.10380	
	Upper bound	390.31073	
	5% trimmed mean	305.03441	
	Median	300.42200	
	Variance	23064.860	
	SD	151.871197	
	Minimum	11.866	
	Maximum	621.660	
	Range	609.794	
	Interquartile range	78.343	
	Skewness	−0.041	0.580
	Kurtosis	1.275	1.121

(*Contd...*)

Table 2: (*Continued*)

Substance P Level	Group	Statistic	SE
diff_preand4hpostop	Control		
	Mean	−15.58307	27.129279
	95% confidence interval for mean		
	Lower bound	−73.76958	
	Upper bound	42.60345	
	5% trimmed mean	−25.45596	
	Median	−42.51800	
	Variance	11039.967	
	SD	105.071246	
	Minimum	−145.389	
	Maximum	291.935	
	Range	437.324	
	Interquartile range	100.688	
	Skewness	2.012	0.580
	Kurtosis	4.910	1.121
	Intervention		
	Mean	17.60587	12.977646
	95% confidence interval for mean		
	Lower bound	−10.22842	
	Upper bound	45.44015	
	5% trimmed mean	19.11613	
	Median	26.20400	
	Variance	2526.289	
	SD	50.262207	
	Minimum	−95.456	
	Maximum	103.483	
	Range	198.939	
	Interquartile range	64.471	
	Skewness	−0.630	0.580
	Kurtosis	0.829	1.121
diff_4hoursand6hours	Control		
	Mean	−70.59020	27.340271
	95% confidence interval for mean		
	Lower bound	−129.22925	
	Upper bound	−11.95115	
	5% trimmed mean	−63.31606	
	Median	−53.62700	
	Variance	11212.356	
	SD	105.888415	
	Minimum	−349.438	
	Maximum	77.323	
	Range	426.761	
	Interquartile range	127.973	
	Skewness	−1.134	0.580
	Kurtosis	2.433	1.121
	Intervention		
	Mean	44.78127	45.525903
	95% confidence interval for mean		
	Lower bound	−52.86208	
	Upper bound	142.42462	
	5% trimmed mean	18.53113	
	Median	2.47300	
	Variance	31089.117	
	SD	176.321063	
	Minimum	−85.586	
	Maximum	647.651	
	Range	733.237	
	Interquartile range	55.148	
	Skewness	3.251	0.580
	Kurtosis	11.338	1.121
diff_pre_6hours	Control		
	Mean	−86.17327	14.214002
	95% confidence interval for mean		
	Lower bound	−116.65927	
	Upper bound	−55.68727	
	5% trimmed mean	−88.31580	
	Median	−91.36100	
	Variance	3030.568	
	SD	55.050591	
	Minimum	−168.586	
	Maximum	34.805	
	Range	203.391	
	Interquartile range	87.202	
	Skewness	0.522	0.580
	Kurtosis	0.054	1.121
	Intervention		
	Mean	62.38713	39.101275
	95% confidence interval for mean		
	Lower bound	−21.47676	
	Upper bound	146.25103	
	5% trimmed mean	41.94054	
	Median	31.04600	
	Variance	22933.645	
	SD	151.438585	
	Minimum	−59.382	
	Maximum	552.195	
	Range	611.577	
	Interquartile range	89.973	
	Skewness	2.706	0.580
	Kurtosis	8.460	1.121
delta_percent_pre_4 h	Control		

(*Contd...*)

Table 2: (*Continued*)

Substance P Level	Group	Statistic	SE
	Mean	−13.99307	6.460991
	95% confidence interval for mean		
	Lower bound	−27.85052	
	Upper bound	−0.13563	
	5% trimmed mean	−12.55975	
	Median	−13.21601	
	Variance	626.166	
	SD	25.023309	
	Minimum	−75.440	
	Maximum	21.654	
	Range	97.093	
	Interquartile range	39.700	
	Skewness	−0.745	0.580
	Kurtosis	1.398	1.121
	Intervention		
	Mean	7.57952	4.371775
	95% confidence interval for mean		
	Lower bound	−1.79700	
	Upper bound	16.95605	
	5% trimmed mean	6.55215	
	Median	9.72528	
	Variance	286.686	
	SD	16.931811	
	Minimum	−20.312	
	Maximum	53.964	
	Range	74.275	
	Interquartile range	21.230	
	Skewness	1.126	0.580
	Kurtosis	3.545	1.121
delta_percent_4 h_6 h	Control		
	Mean	−19.40311	6.562652
	95% confidence interval for mean		
	Lower bound	−33.47860	
	Upper bound	−5.32762	
	5% trimmed mean	−18.43191	
	Median	−12.39974	
	Variance	646.026	
	SD	25.417043	
	Minimum	−72.427	
	Maximum	16.139	
	Range	88.567	
	Interquartile range	35.777	
	Skewness	−0.376	0.580
	Kurtosis	−0.250	1.121
	Intervention		
	Mean	10.34092	8.662431
	95% confidence interval for mean		
	Lower bound	−8.23814	
	Upper bound	28.91999	
	5% trimmed mean	8.97875	
	Median	0.76586	
	Variance	1125.566	
	SD	33.549449	
	Minimum	−35.186	
	Maximum	80.387	
	Range	115.573	
	Interquartile range	21.062	
	Skewness	1.198	0.580
	Kurtosis	0.515	1.121
delta_percent_pre_6h	Control		
	Mean	−32.86784	6.964815
	95% confidence interval for mean		
	Lower bound	−47.80589	
	Upper bound	−17.92980	
	5% trimmed mean	−32.46133	
	Median	−30.02917	
	Variance	727.630	
	SD	26.974613	
	Minimum	−81.025	
	Maximum	7.972	
	Range	88.998	
	Interquartile range	50.238	
	Skewness	−0.461	0.580
	Kurtosis	−0.757	1.121
	Intervention		
	Mean	16.01665	8.860310
	95% confidence interval for mean		
	Lower bound	−2.98682	
	Upper bound	35.02013	
	5% trimmed mean	14.40280	
	Median	8.76944	
	Variance	1177.576	
	SD	34.315835	
	Minimum	−22.039	
	Maximum	83.122	
	Range	105.161	
	Interquartile range	28.294	
	Skewness	1.156	0.580
	Kurtosis	0.247	1.121
NRS_2h_ quiescent	Control		

(*Contd...*)

Table 2: (*Continued*)

Substance P Level	Group	Statistic	SE
	Mean	2.1333	0.09085
	95% confidence interval for mean		
	Lower bound	1.9385	
	Upper bound	2.3282	
	5% trimmed mean	2.0926	
	Median	2.0000	
	Variance	0.124	
	SD	0.35187	
	Minimum	2.00	
	Maximum	3.00	
	Range	1.00	
	Interquartile range	0.00	
	Skewness	2.405	0.580
	Kurtosis	4.349	1.121
	Intervention		
	Mean	1.6000	0.13093
	95% confidence interval for mean		
	Lower bound	1.3192	
	Upper bound	1.8808	
	5% trimmed mean	1.6111	
	Median	2.0000	
	Variance	0.257	
	SD	0.50709	
	Minimum	1.00	
	Maximum	2.00	
	Range	1.00	
	Interquartile range	1.00	
	Skewness	−0.455	0.580
	Kurtosis	−2.094	1.121
NRS_4h_ quiescent	Control		
	Mean	3.2667	0.24817
	95% confidence interval for mean		
	Lower bound	2.7344	
	Upper bound	3.7989	
	5% trimmed mean	3.2963	
	Median	4.0000	
	Variance	0.924	
	SD	0.96115	
	Minimum	2.00	
	Maximum	4.00	
	Range	2.00	
	Interquartile range	2.00	
	Skewness	−0.616	0.580
	Kurtosis	−1.776	1.121
	Intervention		
	Mean	1.4667	0.21529
	95% confidence interval for mean		
	Lower bound	1.0049	
	Upper bound	1.9284	
	5% trimmed mean	1.4074	
	Median	1.0000	
	Variance	0.695	
	SD	0.83381	
	Minimum	1.00	
	Maximum	3.00	
	Range	2.00	
	Interquartile range	1.00	
	Skewness	1.400	0.580
	Kurtosis	0.138	1.121
NRS_6h_ quiescent	Control		
	Mean	2.4667	0.16523
	95% confidence interval for mean		
	Lower bound	2.1123	
	Upper bound	2.8211	
	5% trimmed mean	2.4074	
	Median	2.0000	
	Variance	0.410	
	SD	0.63994	
	Minimum	2.00	
	Maximum	4.00	
	Range	2.00	
	Interquartile range	1.00	
	Skewness	1.085	0.580
	Kurtosis	0.398	1.121
	Intervention		
	Mean	1.4000	0.19024
	95% confidence interval for mean		
	Lower bound	0.9920	
	Upper bound	1.8080	
	5% trimmed mean	1.3333	
	Median	1.0000	
	Variance	0.543	
	SD	0.73679	
	Minimum	1.00	
	Maximum	3.00	
	Range	2.00	
	Interquartile range	1.00	
	Skewness	1.632	0.580
	Kurtosis	1.320	1.121
NRS_12h_ quiescent	Control		

(*Contd...*)

Table 2: (*Continued*)

Substance P Level	Group	Statistic	SE
	Mean	1.5333	0.13333
	95% confidence interval for mean		
	Lower bound	1.2474	
	Upper bound	1.8193	
	5% trimmed mean	1.5370	
	Median	2.0000	
	Variance	0.267	
	SD	0.51640	
	Minimum	1.00	
	Maximum	2.00	
	Range	1.00	
	Interquartile range	1.00	
	Skewness	−0.149	0.580
	Kurtosis	−2.308	1.121
	Intervention		
	Mean	0.3333	0.18687
	95% confidence interval for mean		
	Lower bound	−0.0675	
	Upper bound	0.7341	
	5% trimmed mean	0.2593	
	Median	0.0000	
	Variance	0.524	
	SD	0.72375	
	Minimum	0.00	
	Maximum	2.00	
	Range	2.00	
	Interquartile range	0.00	
	Skewness	1.981	0.580
	Kurtosis	2.550	1.121
NRS_24h_ quiescent	Control		
	Mean	0.4000	0.13093
	95% confidence interval for mean		
	Lower bound	0.1192	
	Upper bound	0.6808	
	5% trimmed mean	0.3889	
	Median	0.0000	
	Variance	0.257	
	SD	0.50709	
	Minimum	0.00	
	Maximum	1.00	
	Range	1.00	
	Interquartile range	1.00	
	Skewness	0.455	0.580
	Kurtosis	−2.094	1.121
	Intervention		
	Mean	0.2000	0.10690
	95% confidence interval for mean		
	Lower bound	−0.0293	
	Upper bound	0.4293	
	5% trimmed mean	0.1667	
	Median	0.0000	
	Variance	0.171	
	SD	0.41404	
	Minimum	0.00	
	Maximum	1.00	
	Range	1.00	
	Interquartile range	0.00	
	Skewness	1.672	0.580
	Kurtosis	0.897	1.121
NRS_2h_ mobile	Control		
	Mean	2.8667	0.09085
	95% confidence interval for mean		
	Lower bound	2.6718	
	Upper bound	3.0615	
	5% trimmed mean	2.9074	
	Median	3.0000	
	Variance	0.124	
	SD	0.35187	
	Minimum	2.00	
	Maximum	3.00	
	Range	1.00	
	Interquartile range	0.00	
	Skewness	−2.405	0.580
	Kurtosis	4.349	1.121
	Intervention		
	Mean	2.3333	0.12599
	95% confidence interval for mean		
	Lower bound	2.0631	
	Upper bound	2.6036	
	5% trimmed mean	2.3148	
	Median	2.0000	
	Variance	0.238	
	SD	0.48795	
	Minimum	2.00	
	Maximum	3.00	
	Range	1.00	
	Interquartile range	1.00	
	Skewness	0.788	0.580
	Kurtosis	−1.615	1.121
NRS_4h_ mobile	Control		

(*Contd...*)

Table 2: (*Continued*)

Substance P Level	Group	Statistic	SE
	Mean	4.4667	0.29059
	95% confidence interval for mean		
	Lower bound	3.8434	
	Upper bound	5.0899	
	5% trimmed mean	4.4630	
	Median	5.0000	
	Variance	1.267	
	SD	1.12546	
	Minimum	3.00	
	Maximum	6.00	
	Range	3.00	
	Interquartile range	2.00	
	Skewness	−0.425	0.580
	Kurtosis	−1.383	1.121
	Intervention		
	Mean	2.4000	0.19024
	95% confidence interval for mean		
	Lower bound	1.9920	
	Upper bound	2.8080	
	5% trimmed mean	2.3333	
	Median	2.0000	
	Variance	0.543	
	SD	0.73679	
	Minimum	2.00	
	Maximum	4.00	
	Range	2.00	
	Interquartile range	1.00	
	Skewness	1.632	0.580
	Kurtosis	1.320	1.121
NRS_6h_ mobile	Control		
	Mean	3.4667	0.21529
	95% confidence interval for mean		
	Lower bound	3.0049	
	Upper bound	3.9284	
	5% trimmed mean	3.4630	
	Median	3.0000	
	Variance	0.695	
	SD	0.83381	
	Minimum	2.00	
	Maximum	5.00	
	Range	3.00	
	Interquartile range	1.00	
	Skewness	0.547	0.580
	Kurtosis	−0.044	1.121
	Intervention		
	Mean	2.2000	0.10690
	95% confidence interval for mean		
	Lower bound	1.9707	
	Upper bound	2.4293	
	5% trimmed mean	2.1667	
	Median	2.0000	
	Variance	0.171	
	SD	0.41404	
	Minimum	2.00	
	Maximum	3.00	
	Range	1.00	
	Interquartile range	0.00	
	Skewness	1.672	0.580
	Kurtosis	0.897	1.121
NRS_12h_ mobile	Control		
	Mean	2.2000	0.14475
	95% confidence interval for mean		
	Lower bound	1.8895	
	Upper bound	2.5105	
	5% trimmed mean	2.2222	
	Median	2.0000	
	Variance	0.314	
	SD	0.56061	
	Minimum	1.00	
	Maximum	3.00	
	Range	2.00	
	Interquartile range	1.00	
	Skewness	0.112	0.580
	Kurtosis	0.378	1.121
	Intervention		
	Mean	1.1333	0.09085
	95% confidence interval for mean		
	Lower bound	0.9385	
	Upper bound	1.3282	
	5% trimmed mean	1.0926	
	Median	1.0000	
	Variance	0.124	
	SD	0.35187	
	Minimum	1.00	
	Maximum	2.00	
	Range	1.00	
	Interquartile range	0.00	
	Skewness	2.405	0.580
	Kurtosis	4.349	1.121
NRS_24h_ mobile	Control		
	Mean	1.3333	0.12599
	95% confidence interval for mean		
	Lower bound	1.0631	
	Upper bound	1.6036	
	5% trimmed mean	1.3148	
	Median	1.0000	
	Variance	0.238	
	SD	0.48795	
	Minimum	1.00	
	Maximum	2.00	
	Range	1.00	
	Interquartile range	1.00	
	Skewness	0.788	0.580
	Kurtosis	−1.615	1.121
	Intervention		
	Mean	1.0667	0.06667
	95% confidence interval for mean		
	Lower bound	0.9237	
	Upper bound	1.2097	
	5% trimmed mean	1.0185	
	Median	1.0000	
	Variance	0.067	
	SD	0.25820	
	Minimum	1.00	
	Maximum	2.00	
	Range	1.00	
	Interquartile range	0.00	
	Skewness	3.873	0.580
	Kurtosis	15.000	1.121

SD: Standard deviation.

Level of SP

From the results of the analysis in Table 4 and Table 5, it was found that there was a significant difference in SP levels between the 50 mg and 75 mg pregabalin groups ($p < 0.05$). SP levels in the 50 mg pregabalin group increased at 4 h and 6 h postoperatively, while in the 75 mg pregabalin group, it tended to decrease at 4 h and 6 h postoperatively.

Based on Table 6, the results showed that in the 50 mg pregabalin group, there was a significant increase in SP levels from measurements P1 to P2 and P1 to P2 ($p < 0.05$), while in the 75 mg pregabalin group, there was a decrease in SP levels but not significant ($p < 0.05$) from measurements P0–P1, P1–P2, and P0–P2.

Discussion

Post-operative pain management aims to produce optimal analgesia and inhibit the stress response due to surgery. Transduction process used NSAIDs, the transmission process used local anesthesia, and the modulation process used opioids and gabapentinoids. With this multimodal approach, the dose of each drug is lower, with a more optimal analgesia effect [10]. Pregabalin (3-isobutyl gamma) is a new synthetic molecule that is an analog of GABA, which is an inhibitor of neurotransmitters, such as gabapentin, which can act as an inhibitor of neuronal hyperexcitability. Pregabalin acts by modulating calcium channel activity. Although its structure is closely related to GABA, pregabalin does not act directly on GABA

Table 3: Normality test

Substance P Level	Kolmogorov-Smirnov[a]			Shapiro–Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
P_Rate_preop						
Control	0.297	15	0.001	0.633	15	0.000
Intervention	0.283	15	0.002	0.821	15	0.007
P_Rate _4 h_postop						
Control	0.251	15	0.012	0.745	15	0.001
Intervention	0.287	15	0.002	0.810	15	0.005
P_Rate_6 h_postop						
Control	0.346	15	0.000	0.594	15	0.000
Intervention	0.229	15	0.033	0.904	15	0.109
diff_pre and 4 h postop						
Control	0.237	15	0.023	0.789	15	0.003
Intervention	0.219	15	0.050	0.952	15	0.556
diff_4 h and 6h						
Control	0.130	15	0.200*	0.923	15	0.212
Intervention	0.385	15	0.000	0.552	15	0.000
diff_pre_6 h						
Control	0.106	15	0.200*	0.972	15	0.888
Intervention	0.282	15	0.002	0.686	15	0.000
delta_percent_pre_4 h						
Control	0.138	15	0.200*	0.937	15	0.343
Intervention	0.222	15	0.045	0.872	15	0.036
delta_percent_4 h_6 h						
Control	0.142	15	0.200*	0.958	15	0.663
Intervention	0.273	15	0.004	0.825	15	0.008
delta_percent_pre_6 h						
Control	0.189	15	0.156	0.939	15	0.374
Intervention	0.240	15	0.020	0.838	15	0.012
NRS_2 h_ quiescent						
Control	0.514	15	0.000	0.413	15	0.000
Intervention	0.385	15	0.000	0.630	15	0.000
NRS_4 h_ quiescent						
Control	0.377	15	0.000	0.661	15	0.000
Intervention	0.445	15	0.000	0.581	15	0.000
NRS_6 h_ quiescent						
Control	0.367	15	0.000	0.713	15	0.000
Intervention	0.440	15	0.000	0.596	15	0.000
NRS_12 h_ quiescent						
Control	0.350	15	0.000	0.643	15	0.000
Intervention	0.477	15	0.000	0.514	15	0.000
NRS_24 h_ quiescent						
Control	0.385	15	0.000	0.630	15	0.000
Intervention	0.485	15	0.000	0.499	15	0.000
NRS_2 h_ mobile						
Control	0.514	15	0.000	0.413	15	0.000
Intervention	0.419	15	0.000	0.603	15	0.000
NRS_4 h_ mobile						
Control	0.349	15	0.000	0.765	15	0.001
Intervention	0.440	15	0.000	0.596	15	0.000
NRS_6 h_ mobile						
Control	0.312	15	0.000	0.845	15	0.015
Intervention	0.485	15	0.000	0.499	15	0.000
NRS_12 h_ mobile						
Control	0.373	15	0.000	0.734	15	0.001
Intervention	0.514	15	0.000	0.413	15	0.000
NRS_24 h_ mobile						
Control	0.419	15	0.000	0.603	15	0.000
Intervention	0.535	15	0.000	0.284	15	0.000

*This is a lower bound of the true significance. [a]Lilliefors significance correction.

receptors, rather by modifying synaptic or non-synaptic GABA release [11], [12].

Table 4: Comparison of NRS between groups of 50 and 75 mg pregabalin

NRS	Measurement Time	Group	Mean ± SD	p
Quiescent	2 h	50 mg pregabalin	2.13 ± 0.35	0.023*
		75 mg pregabalin	1.60 ± 0.51	
	4 h	50 mg pregabalin	3.27 ± 0.96	0.000*
		75 mg pregabalin	1.47 ± 0.83	
	6 h	50 mg pregabalin	2.47 ± 0.64	0.000*
		75 mg pregabalin	1.40 ± 0.74	
	12 h	50 mg pregabalin	1.53 ± 0.52	0.000*
		75 mg pregabalin	0.33 ± 0.72	
	24 h	50 mg pregabalin	0.40 ± 0.51	0.367[ns]
		75 mg pregabalin	0.20 ± 0.41	
Mobile	2 h	50 mg pregabalin	2.87 ± 0.35	0.011*
		75 mg pregabalin	2.33 ± 0.49	
	4 h	50 mg pregabalin	4.47 ± 1.13	0.000*
		75 mg pregabalin	2.40 ± 0.74	
	6 h	50 mg pregabalin	3.47 ± 0.83	0.000*
		75 mg pregabalin	2.20 ± 0.41	
	12 h	50 mg pregabalin	2.20 ± 0.56	0.000*
		75 mg pregabalin	1.33 ± 0.35	
	24 h	50 mg pregabalin	1.33 ± 0.49	0.217[ns]
		75 mg pregabalin	1.07 ± 0.26	

Data are displayed with mean ± standard deviation. Data were analyzed by *Mann–Whitney U-test*.
*: p < 0.05, significantly different; ns: Not significantly different.

Table 5: Comparison of substance *P* levels between the two groups

Measurement time	Group	Substance P levels (Mean ± SD)	p
P0	50 mg pregabalin	382.14 ± 296.94	0.300[ns]
	75 mg pregabalin	368.59 ± 196.63	
P1	50 mg pregabalin	397.73 ± 216.23	0.384[ns]
	75 mg pregabalin	350.99 ± 206.39	
P2	50 mg pregabalin	469.32 ± 287.41	0.010*
	75 mg pregabalin	306.21 ± 151.87	

Data are displayed with mean ± standard deviation. Data were analyzed by *Mann–Whitney U-test*. *: p < 0.05, significantly different; ns: Not significantly different.

Pregabalin has exerted an anti-nociceptive effect on nociceptive responses in neuropathic or inflammatory conditions by modulating the SP-mediated neurokinin-1 (NK1/SP receptor) response. Studies evaluating the effects of pregabalin have shown that pregabalin can suppress the production of IL-6 which has been induced by substances P and IL-8. Pregabalin also inhibits SP-induced phosphorylation of p38 *mitogen-activated protein kinase* (MAPK) and nuclear factor (NF)-κB [13].

Table 6: Comparison of changes in P substance levels based on time of measurement between the two groups

Measurement time	Group	Δ Substance P levels (Mean ± SD)	Substance P levels velocity (%)	p
P0–P1	50 mg pregabalin	↑ 15.58 ± 105.07	↑ 13.99	0.021*
	75 mg pregabalin	↓ 17.06 ± 50.26	↓ 7.58	
P1–P2	50 mg pregabalin	↑ 70.59 ± 105.88	↑ 19.40	0.019*
	75 mg pregabalin	↓ 44.78 ± 176.32	↓ 10.34	
P0–P2	50 mg pregabalin	↑ 86.17 ± 55.05	↑ 32.87	0.000*
	75 mg pregabalin	↓ 62.39 ± 151.49	↓ 16.02	

Data are displayed with mean ± standard deviation. Data were analyzed by *Mann–Whitney U-test*.
*: p < 0.05, significantly different.

Pregabalin given orally is absorbed more rapidly, with maximum plasma concentrations achieved within 1–2 h. Most studies of pre-operative gabapentinoids have administered preoperative doses between 1 and 2 h before surgery. It has been reported that the time to peak plasma levels after oral administration of pregabalin is approximately 1 h. However, it has also been reported that the time to peak cerebrospinal fluid levels may be longer. Among patients undergoing knee replacement surgery, peak cerebrospinal fluid levels of pregabalin occurred at a median time of 8 h after administration [14]. In a study of patients undergoing dental surgery, the onset of pregabalin analgesia was achieved within 24 min of administration. Pregabalin is excreted through the kidneys, with an elimination half-life of about 4.6–6.8 h. Stability is achieved within 24–48 h after the start of repeated dosing [15].

SP is an 11-amino acid long neuropeptide produced by both neuronal and non-neuronal cells,

Table 7: Comparison of substance P levels in each group

Group	Measurement time	Substance P levels (ng/ml)	p
50 mg pregabalin	P0	382.14 ± 296.94	0.125[ns]
	P1	397.73 ± 216.23	
	P1	397.73 ± 216.23	0.027*
	P2	469.32 ± 287.41	
	P0	382.14 ± 296.94	0.001*
	P2	469.32 ± 287.41	
75 mg pregabalin	P0	368.59 ± 196.63	0.112[ns]
	P1	350.99 ± 206.39	
	P1	350.99 ± 206.39	0.955[ns]
	P2	306.21 ± 151.87	
	P0	368.59 ± 196.63	0.125[ns]
	P2	306.21 ± 151.87	

Data are displayed with mean ± standard deviation. Data were analyzed by *Mann–Whitney U-test*.
*: p < 0.05, significantly different; ns: Not significantly different.

including immune cells. SP with its biological activity, through neurokinin receptors, coupled with G proteins (NKRs) named neurokinin-1 receptors (NK-1R), NK-2R, and NK-3R. Among the three, NK1R has the highest affinity for SP. SP-NK1R interactions are widely reported to regulate immune cell function and immunity against microbial infections [16], [17].

SP is secreted by nerves and inflammatory cells such as macrophages, eosinophils, lymphocytes, and dendritic cells that act by increasing the receptor neurokinin-1 (NK-1R). SP has a pro-inflammatory effect on immune cells and epithelial cells that play a role in inflammatory diseases of the respiratory, gastrointestinal, and musculoskeletal systems. Many substances induce the release of neuropeptides from sensory nerves in the lungs, including allergens, histamine, prostaglandins, and leukotrienes [18].

SP is a derivative of the tachykinin compound which is then characterized as a neurotransmitter. Elevated serum or plasma SP and/or its receptor (NK-1R) can be observed in a variety of disorders, including inflammatory bowel disease, sickle cell crisis, depression and anxiety, rheumatic diseases, infectious diseases such as AIDS, and syncytial virus infections, as well as cancer. Recently, the role of SP as a neurotransmitter has been expanded as it is known to play a role in the regulation of immune responses. Even today, SP whose receptor is NK-1R, and several NK-1R antagonists have received considerable attention as potential therapeutic agents for depression, pain, and emesis [19].

The pain signaling pathway involving the SP is a pathway that facilitates nociceptive sensitization in various inflammatory pains where SP signaling is thought to contribute to the development of post-operative hyperalgesia. SP is a neuromodulator with a well-described role in pain signaling and has the unique feature of being released only in nociception by intense stimulation. For example, spinal cord internalization of the NK-1 receptor, an index of SP release, occurs only to a small extent in lamina I neurons during normal threshold-level heat stimulation of animals. However, the same degree of heat stimulation led to a greater percentage of NK-1 internalization in lamina I neurons and receptor internalization in deeper spinal cord laminae after inflammation. Interestingly, SP does not appear to be required for coding the normal heat intensity or peak firing of these neurons across a wide range of temperatures but rather likely prolongs the response to heat stimulation [20].

The results of this study showed a significant difference in the NRS scores between the 50 mg pregabalin and 75 mg pregabalin groups ($p < 0.05$). In the 75 mg pregabalin group, the NRS scores were noticeably lower than that of 50 mg pregabalin in patients undergoing CS surgery under spinal anesthesia. This is to the research of Hassab *et al*. in 2020, where pre-operative administration of 300 mg of pregabalin continued for 12 h and then the combination of 1 g intravenous paracetamol as multimodal analgesia was better than paracetamol alone by lowering VAS scores and post-hip opioid consumption with spinal anesthesia [8]. Other studies by Lalenoh *et al*. in 2014 showed that giving 150 mg pregabalin orally 1 h preoperatively compared to placebo in hysterectomy surgery under general anesthesia resulted in a decrease in post-operative pain scores and a decrease in the need for post-operative opioids [3].

The previous studies used doses of 150 and 300 mg, while this study used doses of 50 and 75 mg, which obtained lower NRS scores and rescue analgesia at a dose of 75 mg. This proves that pregabalin has an opioid sparring effect and the administration of a larger dose of pregabalin can increase its efficacy without side effects arising from the use of a larger dose, namely, at a dose of 75 mg. The mechanism of action of pregabalin is to suppress the release of excitatory neurotransmitters and prevent central sensitization [11].

The results of this study also showed a significant difference in SP levels between the 50 mg and 75 mg pregabalin groups ($p < 0.05$). SP levels in the 50 mg pregabalin group increased at 4 h and 6 h postoperatively, while in the 75 mg pregabalin group, it tended to decrease at 4 h and 6 h postoperatively. These results are consistent with a study conducted by Lalenoh *et al*. in 2012, where pregabalin 150 mg oral administration 1 h preoperatively showed a decrease in postoperative SP levels compared to placebo in hysterectomy surgery under general anesthesia.[3] Another study by Yu *et al*. in 2017 showed that administration of parecoxib 30 min before induction with a lower increase in SP levels at 30 min, 4 h, and 8 h postoperatively and a higher decrease in SP at 12 h postoperatively compared to placebo at cesarean section surgery [2].

Tissue injury and inflammatory reactions resulting from surgical procedures will cause peripheral sensitization. The next stage, through the transmission of noxious impulses from peripheral nociceptors, will be forwarded to the first-level neurons (presynaptic neurons). In this presynaptic neuron, the impulse will induce Ca^{2+} into the cell through Ca^{2+} channels. This condition will cause the release of several neurotransmitters (glutamate and SP) from the end of the presynaptic neuron to the second-order neuron (postsynaptic) which will cause the sensation of pain. Therefore, post-operative pain is closely related to increased levels of glutamate and SP in the blood [3]. The mechanism of the action of pregabalin binds to the $\alpha 2$-δ subunit calcium channel, thereby modulating the entry of calcium into nerve terminals and decreasing the release of several excitatory neurotransmitters such as glutamate, noradrenaline, serotonin, dopamine, and SP. Decreased glutamate release causes NMDA receptors to be inactivated. This will inhibit neuronal excitability and decrease central sensitization. This inhibitory

process occurs, especially in areas of the central nervous system that is dense with synapses, such as the neocortex, amygdala, and hippocampus [9]. IL-6 and IL-8 are released during trauma causing inflammation and pain. Pregabalin, given preoperatively, can increase the analgesic effect and decrease the release of IL-6 and IL-8 (inflammation). Several authors have shown that the use of pregabalin causes a decrease in inflammatory cytokines before a pain stimulus is administered [21].

Acetaminophen selectively inhibits neural tissue cyclooxygenase *in vitro*. Apart from the central inhibition of prostaglandin generation, other possible mechanisms have been proposed. Hunskaar *et al*. reported that acetaminophen inhibits spinal SP-mediated hyperalgesia, suggesting that acetaminophen-induced analgesia may be associated with the modulation of nociceptive transmission in spinal and supraspinal pathways. This observation is particularly interesting in light of recent evidence showing that postsynaptic structures in the CNS generate nitric oxide (NO) from L-arginine through an enzymatic process in response to SP activation as well as excitation of amino acid receptors [22].

Conclusion

The scores on the quiescent NRS and mobile NRS in the 75 mg pregabalin group were lower than in the 50 mg pregabalin group with 1 g intravenous paracetamol combination after CS surgery. SP levels in the 75 mg pregabalin group decreased compared to the 50 mg pregabalin group with a 1 g intravenous paracetamol combination which experienced an increase after CS surgery. It is advisable to use preventive pregabalin 75 mg in CS surgery because it can reduce NRS scores and rescue fentanyl without side effects. The clinical impact of this study is to reduce post-operative pain in cesarean surgery patients and become one of the options for pre-emptive analgesia. Further research is needed to determine the effect of pregabalin preventive administration on other types of surgery.

Limitation and suggestion

The obstacle faced in this study was that some patients were hesitant to take the drug, but the researcher gave informed consent so that the patient understood well about the procedure and the safety of the action taken. Pregabalin administration in this study was limited to cesarean section surgery with spinal anesthesia. Suggestions for further researchers, this method should be investigated in other anesthetic methods and other types of surgery as well.

Ethical Clearance

Yes, from Hasanuddin University.

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