

The Antinociceptive Effects of Pregabalin on Post-Operative Hysterectomy Patient

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Abstract

Postoperative pain experienced by patients who completed surgery should receive serious attention, because of effective postoperative pain management will reduce morbidity and mortality, accelerate the mobilization and reducing hospitalization time of patients. These studies aim to determine the effect of pregabalin on antinociception and substan-glutamate levels in the blood of patients with postoperative P hysterectomy. This research is an experimental study, namely the Controlled Trial Randomized clinical trials in which patients were randomly divided into two groups by the number of patients who be included 52 people (aged 20-50 years) who underwent hysterectomy surgery. They were divided into group I (n=26) orally administered pregabalin 3 mg/kg body weight and group II (n=26) placebo given orally, 1 hour before surgery. All patients are given general anesthesia that premedication with atropine sulfate and fentanyl injection, induction with propofol and atracurium injection, intubation and breath control, and maintenance of anesthesia with N₂O:O₂ and isoflurane. The total of postoperative use of morphine injection is assessed until 24 hours postoperative. Examination of the levels of glutamate and substan-P performed preoperative blood before administration and 1 hour postoperative pregabalin. The results showed a marked increase in the level of pain (VAS), blood pressure, heart rate and the amount of postoperative morphine consumption in patients who were given the placebo group, compared with patients given pregabalin group. It was concluded that preoperative pregabalin administration can suppress the increase in glutamate production and can reduce postoperative production of substan-P, and the subsequent decline in glutamate levels in the blood substan-P will provide antinociception effect is a decrease in the level of postoperative pain experienced by patients.

Keywords: Glutamate; Substan-P; Postoperative pain

Introduction

Postoperative pain is a problem for patients who undergo surgery. This should be given due attention with good postoperative pain management will reduce morbidity and mortality, accelerate the mobilization and reduce hospitalization time of patients. Postoperative pain is acute pain that occurs due to tissue damage and because there is no inflammatory reaction [1]. Pregabalin and Gabapentin was originally a class of drugs known to have anticonvulsant effects and is used as an anti-epileptic drugs [2], but later it was discovered that this drug is also effective for neuropathic pain such as postherpetic neuralgia and diabetic neuropathy. Lately, pregabalin and gabapentin reported its use to help cope with nociceptive pain and inflammation in patients with postoperative pain. Fassoulaki in his research found that gabapentin may reduce consumption of analgesics after surgery mastectomy [3]. Dirks get the same result, namely a reduction in postoperative morphine analgesic consumption after mastectomy oral gabapentin 1 hour preoperative [4]. Similarly Turan found that gabapentin may reduce the use of other postoperative analgesic [5]. Dahl reported on the role of gabapentin and pregabalin for postoperative pain management, but is encouraged to do further research on this subject [6]. Seib get the ideal take gabapentin used to treat chronic neuropathic pain, but not ideal for acute postoperative pain management [2]. Bartholdy not get a significant difference in postoperative morphine consumption and pain scale in patients given and not given gabapentin [7] Drugs were introduced for preemptive analgesia that is pregabalin, pregabalin in this case is preferred because of the better effects of gabapentin. They get the results that the use of pregabalin can reduce postoperative morphine analgesic consumption and thus also reduce the side effects caused by drugs postoperative analgesia [8]. This study aimed to find out about the effects of preemptive pregabalin antinociception against glutamate levels and substan-P in the blood and the degree of postoperative pain.

Location and Design

The study was conducted in patients undergoing hysterectomy surgery with the aid of anesthesia, at the Central Surgical Room at Professor Kandou Hospital Manado from January to May 2012 This research is experimental (interventional), with clinical trials Randomized Controlled trial (=RCT). This study is an approved clinical trial. Patients who meet the criteria as many as 52 people were divided into 2 groups randomly each-each of 26 people, which were given pregabalin treatment group and the control group were given a placebo. Administration of pregabalin is to examine how the effect of preemptive pregabalin on glutamate levels and substan-P in the blood, postoperative pain, and the number of postoperative analgesic consumption [9].

Data Collection

All patients were examined taken based on the order entry implementation surgery, and patients were divided into two groups randomly put random way with tables of random numbers. Intervention is done by double blind (double mask). The second group consisted of patients with treatment group and control group. Before treatment all patients' blood samples were taken for examination of

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neurotransmitter levels, and the levels chosen here is an examination of the levels of glutamate and substan-P.

Group I (treatment group)

1 hour before surgery pregabalin given 3 mg/kg orally, then half an hour before surgery given premedication with atropine sulfate injection of 0.01 mg/kg and fentanyl injection of 0.1 µg/kg intramuscularly.

Group II (control group)

1 hour before surgery was given a placebo in the form of starch glucose (in the same form with the pregabalin capsules) orally, then half an hour before surgery given premedication with atropine sulfate injection of 0.01 mg/kg and fentanyl injection of 0.1 µg/kg intramuscularly.

Pregabalin is a drug that is used here under the trade name Lyrica (Pfizer), in the form of 150 mg capsules, while placebo capsules containing flour supplied glucose. Both groups postoperative analgesic morphine given iv injection in Patient Controlled Analgesia (PCA) with the help of PCA infuser. The level of pain experienced by patients was monitored for 24 hours after completion of surgery, the assessment of Visual Analogue Scale (VAS). Monitor conducted on the effects on the cardiovascular pain, morphine consumption by PCA injection unused, Morphine side effects (nausea, vomiting) and drug side effects pregabalin (feelings of dizziness, drowsiness) [10].

In each treatment group and the control group, made the following assessment:

1) Systolic and diastolic blood pressure, and heart rate were assessed at preoperative, early postoperative and 1 hour, 8 hours, and 24 hours postoperative.

2) The level of perceived pain was assessed by VAS (Visual Analogue Scale) on early postoperative, 1 hour, 8 hours, and 24 hours postoperative.

3) The number of unused drugs morphine injection in 24 hours, with the PCA.

4) The level of glutamate and substan-P levels in the blood, at the time of preoperative administration of pregabalin or placebo before and 1 hour after completion of surgery. Measurement of levels of glutamate and substan-P in the blood is done by using Elisa kit (USCN, Wuhan Science Co.Ltd EIAab Cat No.E0393h).

5) Do also assessment whether there are any side effects of the drug pregabalin and morphine, such as dizziness, drowsiness, nausea, vomiting, in the early postoperative, 1 hour, 8 hours, and 24 hours postoperative.

Operational Definitions

Assessment of pain level by VAS

- Not pain: (Figures<30 mm)
- Pain: (Figures 30-60 mm)
- Severe pain: (Numbers>60 mm)

Systolic blood pressure, diastolic and heart rate

- Decreases: When systolic blood pressure, diastolic and heart rate decreased postoperative>10% compared with preoperative.
- Stable: When the systolic blood pressure, diastolic and

postoperative heart rate equal or increased/decreased but not>10% compared with preoperative.

- Increases: When the systolic blood pressure, diastolic and postoperative heart rate increased>10% compared with preoperative.

levels of glutamate and substan-P

- Declined: If levels of glutamate and substan-P postoperative smaller than the preoperative levels.

- Fixed: When the levels of glutamate and substan-P postoperative together with preoperative levels.

- Increases: If levels of glutamate and substan-P postoperative larger than preoperative levels.

The number of postoperative morphine consumption

- Little: When the number of morphine injections were unused to 7.5 mg.

- Quite: If the number of unused morphine injection>7.5 mg to 15 mg.

- Many: When the amount of used morphine injection>15 mg.

Data Analysis

Processing and data analysis here uses several statistical tests, such as the Independent t-test, Mann-Whitney U test, Chi square test and Spearman correlation test. To test the homogeneity between the two groups based on the characteristics of age, body weight, height, duration of surgery, consumption of fentanyl, and isoflurane consumption analysis conducted by the Independent t-test. As for seeing the dynamics of pain level, systolic blood pressure, diastolic blood pressure, heart rate, levels of glutamate, substan-P levels, and the amount of morphine consumption in both groups during the observation time analyzed with the Mann-Whitney U Test. Changes in systolic blood pressure, diastolic blood pressure, heart rate, levels of glutamate, and substan-P levels in both groups during the observation time analyzed by Chi square test. To see the relationship change in pain levels with systolic blood pressure, diastolic blood pressure, heart rate, levels of glutamate, substan-P levels, and the amount of morphine consumption analyzed by Spearman correlation test.

Results

This study was conducted on 52 patients sampled randomly divided into treatment group and control group consisted of 26 patients per group, with individual variations evenly distributed in both groups. Results of homogeneity test between the two groups based on the characteristics of age, body weight, height, duration of surgery, fentanyl consumption, and age variables obtained isoflurane consumption well on pregabalin group and the control group at between 36-48 years, with a mean age in the pregabalin group 41.7 years and 40.7 years in the control group, as well as the results of independent t-test analysis showed $p=0.240$ ($p>0.05$). The mean weight of 54.6 kg in the pregabalin group whereas in the control group 54.9 kg and $p=0.861$ ($p>0.05$). The mean height 158.8 cm in the pregabalin group whereas in the control group 157.9 cm and $p=0.390$ ($p>0.05$). The mean duration of surgery in the pregabalin group 114.6 minutes, while the control group of 109 minutes and a value of $p=0.118$ ($p>0.05$). The mean amount of fentanyl consumption at 86.5 mg pregabalin group whereas in the control group and 82.7 mg p -value= 0.557 ($p>0.05$). The mean number of isoflurane consumption at 1.04 Vol% pregabalin group whereas in the control

group 1.08 Vol% and $p=0.657$ ($p>0.05$). Thus variations in age, weight, height, duration of surgery, fentanyl consumption, and consumption of isoflurane between the pregabalin group and the control group there was no significant difference, and can be judged homogeneous [11-14].

Level of pain (vas)

To observe the level of pain experienced by patients was assessed with the Visual Analogue Scale (VAS) for both groups during the preoperative, early postoperative, postoperative 1 hour, 8 hours postop, and 24 postoperative hours (Table 1). From this table it was found that at the time of preoperative there is no difference of VAS in both groups. When the early postoperative pregabalin group median VAS 50 mm while the control group of 60 mm and $p=0.000$ ($p<0.05$). When 1 hour postoperative pregabalin group median VAS 40 mm while the control group of 55 mm and $p=0.000$ ($p<0.05$). When the 8-hour postoperative pregabalin group median VAS 40 mm while the control group of 50 mm and $p=0.000$ ($p<0.05$). When the 24-hour postoperative pregabalin group median VAS 20 mm and 30 mm in the control group and $p=0.003$ ($p<0.05$). Postoperative VAS in both groups tended to increase, but the increase in the control group was higher than in the pregabalin group. The difference in VAS in both groups at each time were analyzed with the Mann-Whitney U test and showed significant differences in improvement ($p<0.05$) between the control group with both pregabalin groups in early postoperative, postoperative 1 hour, 8 hours postoperative, or at 24 hours postoperative.

Blood pressure

Analysis of the dynamics of systolic blood pressure for both groups performed during the preoperative, early postoperative, postoperative 1 hour, 8 hours postsurgery, and 24 hours postoperative. It was found that when preoperative pregabalin group median systolic blood pressure 120 mm Hg, while in the control group and 130 mmHg $p=0.001$ ($p<0.05$). When the early postoperative pregabalin group median systolic blood pressure of 127.5 mm Hg, while in the control group and 130 mmHg $p=0.891$ ($p>0.05$). When 1 hour postoperative pregabalin group median systolic blood pressure 130 mm Hg, while in the control group and 140 mmHg $p=0.000$ ($p<0.05$). When the 8-hour postoperative pregabalin group median systolic blood pressure 120 mm Hg while 137.5 mmHg in the control group and $p=0.000$ ($p<0.05$). When the 24-hour postoperative pregabalin group median systolic blood pressure 115 mm Hg, while in the control group and 120 mmHg $p=0.000$ ($p<0.05$). Since the observation of preoperative to 24 postoperative hours, the median systolic blood pressure tended to be higher in the control group compared with the pregabalin group. The results of the analysis Mann-Whitney U Test showed that systolic blood pressure difference was significant ($p<0.05$) between the control group with pregabalin group during the observation time

of preoperative, postoperative 1 hour, 8 hours perioperative and postoperative 24 hours. The results of the analysis of changes in systolic blood pressure in both groups found that while the control group of early postoperative systolic blood pressure stabilized at 12 of the 26 people (46.15%) and systolic blood pressure were elevated in 14 of 26 (53.84%), while in the pregabalin group stable systolic blood pressure 18 of 26 people (69.23%) and systolic blood pressure increased by 8 of 26 people (30.76%). When the first postoperative hour in the control group systolic blood pressure stabilized at 6 of 26 people (23.07%) and systolic blood pressure increased in 20 of the 26 people (76.92%), whereas in the pregabalin group systolic blood pressure stabilized at 17 of 26 people (65.38%) and systolic blood pressure increased in 9 of 26 people (34.61%). When 8 hours postsurgery in the control group systolic blood pressure stabilized at 8 of the number of people (30.76%) and systolic blood pressure increased in 18 of the 26 people (69.23%), whereas in the pregabalin group systolic blood pressure stabilized at 24 of 26 people (92.30%) and systolic blood pressure increased in 2 of 26 people (7.69%). When the 24-hour postoperative in the control group contained a stable systolic blood pressure at 24 of the 26 people (92.30%), and systolic blood pressure increased in 2 of 26 people (7.69%), whereas in the pregabalin group systolic blood pressure are stable on 26 of the 26 people (100%), and no increase in systolic blood pressure (0%). The results observed in the two groups are generally the same postoperative systolic blood pressure increased even grouped controls on early postoperative there is also a systolic blood pressure remained stable. But the number increased systolic blood pressure tended to be higher in the control group than in the pregabalin group. Chi Square Test results showed an increase in systolic blood pressure differences were significant ($p<0.05$) at 1 hour and 8-hour postoperative in the control group than in the pregabalin group. The results of the analysis of the dynamics of diastolic blood pressure for both groups performed during the preoperative, early postoperative, postoperative 1 hour, 8 hours postsurgery, and 24 hours postoperative. It was found that when preoperative pregabalin group median diastolic blood pressure 80 mm Hg, while in the control group was also 80 mm Hg and a value of $p=0.500$ ($p>0.05$). When the early postoperative pregabalin group median diastolic blood pressure 80 mm Hg, while in the control group and 90 mmHg $p=0.001$ ($p<0.05$). When 1 hour postoperative pregabalin group median diastolic blood pressure 80 mm Hg, while in the control group and 90 mmHg $p=0.000$ ($p<0.05$). When the 8-hour postoperative pregabalin group median diastolic blood pressure 80 mm Hg, while 90 mm Hg in the control group and $p=0.000$ ($p<0.05$). When the 24-hour postoperative pregabalin group median diastolic blood pressure 80 mm Hg, while in the control group to 80 mmHg and the value of $p=0.137$ ($p>0.05$). Since the early postoperative observation up to 8 hours postop, median diastolic blood pressure tended to be higher in the control group compared with the pregabalin group. The results of the analysis Mann-Whitney U test showed a significant difference ($p<0.05$) between the control group with pregabalin group during the early postoperative observation time, 1 hour postoperative, and 8 hours postoperative.

From the data it was found that while the control group of early postoperative diastolic blood pressure stabilized at 10 of the 26 people (38.46%) and diastolic blood pressure increased in 16 of the 26 people (61.53%), whereas in the pregabalin group diastolic blood pressure stable 11 of 26 people (42.30%) and diastolic blood pressure increased 11 of 26 people (42.30%), and diastolic blood pressure decreased 4 of 26 people (15.38%). When the first postoperative hour in the control group diastolic blood pressure was stable at 2 of 26 people (7.69%) and diastolic blood pressure increased in 24 of the 26 people (92.30%),

Duration of Observation	V AS (mm)				P value
	Pregabalin Group (n=26)		Control Group (n=26)		
	Min-Max	Median	Min-Max	Median	
Before surgery	0-20	0	0-20	0	$P>0.05$
Early after surgery	30-60	50	50-75	60	$p=0.000^*$
1 hr after surgery	30-50	40	40-75	55	$p=0.000^*$
8 hr after surgery	30-50	40	40-60	50	$p=0.000^*$
24 hr after surgery	20-40	20	20-40	30	$p=0.003^*$

Data are shown in minimal, maximal and mean value, deviation standard and probability were tested with Mann Whitney-U test, $p<0.05$ is significant. *P value<0.05.

Table 1: VAS variation on both groups during observation.

whereas in the pregabalin group diastolic blood pressure stabilized at 15 of 26 people (57.69%) and diastolic blood pressure increased in 11 out of 26 people (42.30%). When 8 hours postsurgery in the control group diastolic blood pressure stabilized at 8 of 26 people (30.76%) and diastolic blood pressure increased in 18 of the 26 people (69.23%), whereas in the pregabalin group diastolic blood pressure stabilized at 20 of 26 people (76.92%) and diastolic blood pressure increased in 6 of 26 people (23.07%). When the 24-hour postoperative control group diastolic blood pressure are stable in 18 of the 26 people (69.23%), and diastolic blood pressure increased in 6 of 26 people (23.07%), and diastolic blood pressure decreased in 2 of 26 people (7.69%), whereas in the pregabalin group diastolic blood pressure are stable in 21 of 26 (80.76%), and diastolic blood pressure increased in 3 of the 26 people (11.53%), and diastolic blood pressure decreased in 2 of 26 people (7.69%). In the postoperative observation in both groups generally experience an increase in diastolic blood pressure, but the increase in the control group is higher than in the pregabalin group. Chi Square Test results showed a significant difference ($p < 0.05$) only at precisely 1 hour and 8 hours postoperative.

Heart rate

The results of dynamics analysis of heart rate for both groups performed during the preoperative, early postoperative, postoperative 1 hour, 8 hours postsurgery, and 24 hours postoperative. From this it was found that when preoperative pregabalin group median heart rate of 80 x/m, while the control group was also 80 x/m and a value of $p=0.959$ ($p > 0.05$). When the early postoperative pregabalin group median heart rate of 88 x/m, while in the control group 93 x/m and $p=0.001$ ($p < 0.05$). When 1 hour postoperative pregabalin group median heart rate of 88 x/m, while in the control group 96 x/m and the value of $p=0.000$ ($p < 0.05$). When the 8-hour postoperative pregabalin group median heart rate of 84 x/m, while in the control group 94 x/m and the value of $p=0.000$ ($p < 0.05$). When the 24-hour postoperative pregabalin group median heart rate of 81 x/m, while in the control group to 80 x/m and a value of $p=0.740$ ($p > 0.05$). Since the early postoperative observation up to 8 hours postop, the median heart rate tended to be higher in the control group compared with the group pregabalin. Hasil analysis Mann-Whitney U test showed a significant difference ($p < 0.05$) between the control group with pregabalin group over time early postoperative observation, 1 hour postoperative, and 8 hours postoperative. From the available data it was found that while the control group of early postoperative heart rate stabilized at 8 of 26 people (30.76%) and heart rate increased in 18 of the 26 people (69.23%), whereas in the pregabalin group heart rate stable 16 of 26 people (61.53%) and increased heart rate 10 of 26 people (38.46%). When 1 hour postoperative heart rate in the control group was stable at 3 of 26 people (11.53%) and heart rate increased in 23 of the 26 people (88.46%), whereas in the pregabalin group heart rate stabilized at 15 of the 26 people (57.69%) and heart rate increased in 11 out of 26 people (42.30%). When the 8-hour postoperative heart rate in the control group was stable at 9 of 26 people (34.61%) and heart rate increased in 17 of the 26 people (65.38%), whereas in the pregabalin group heart rate stabilized at 23 of the 26 people (88.46%) and heart rate increased in 3 of the 26 people (11.53%). When the 24-hour postoperative heart rate in the control group are stable in 24 of 26 (92.30%), and heart rate increased in 2 of 26 people (7.69%), whereas in the pregabalin group also contained a stable heart rate at 24 of 26 people (92.30%), and heart rate increased in 2 of 26 people (7.69%). In the postoperative observation in both groups are generally in the control group increased more than the heart rate pregabalin group. Results of Chi Square Test showed a significant difference in the increase in heart rate ($p < 0.05$) in the early

postoperative, postoperative 1 hour and 8 hours postoperative.

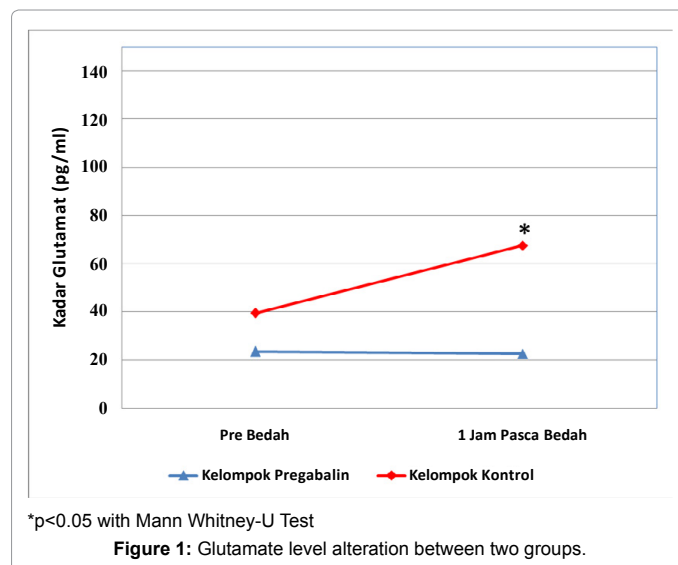
Neurotransmitter levels

To observe the dynamic response of the neurotransmitter, glutamate levels measured and substan-P blood preoperative and 1 hour after surgery. The results of the analysis of the dynamics of blood glutamate levels in the two groups can be seen in Table 2 and Figure 1. From this table it was found that when the preoperative levels of glutamate in the pregabalin group varies between 2-114 pg/ml with a median of 23.5 pg/ml while the control group between 8-95 pg/ml with a median of 39.5 pg/ml and the value of $p=0.093$ ($p > 0.05$). When 1 hour postoperative levels of glutamate in the pregabalin group varies between 1 to 92.8 pg/ml with a median of 22.6 pg/ml, while in the control group between 10.8 to 118.9 pg/ml with a median of 67.6 pg/ml and the value of $p=0.000$ ($p < 0.05$). In observation of preoperative and postoperative 1 hour, the median levels of glutamate were higher in the control group compared with the pregabalin group. The results of the analysis Mann-Whitney U test showed a significant difference in glutamate levels ($p < 0.05$) at 1 hour postoperative observation time between the control group and the pregabalin group. The results of the analysis of changes in glutamate levels in the two groups showed that the current 1-hour postoperative in the control group increased glutamate levels found in 25 of the 26 people (96.15%) and decreased levels of glutamate are present in 1 out of 26 people (3.84%), while in the pregabalin group increased glutamate levels found in 4 of 26 people (15.38%) and glutamate levels were decreased/ remained present in 22 of the 26 people (84.61%). Results of X^2 test observation time test showed no difference increased production of glutamate levels were significantly ($p < 0.05$) 1 h postsurgery in the control group compared with the pregabalin group. So pregabalin suppress the increased production

Duration of Observation	Glutamate Level (pg/ml)				P value
	Pregabalin Group (n=26)		Control Group (n=26)		
	Min-Max	Median	Min-Max	Median	
Before Surgery	2-114	23,5	8-95	39,5	$p=0.093$
1 hr After Surgery	1-92.8	22.6	10.8-118.9	67.6	$p=0.000^*$

Data are shown in minimal, maximal and mean value, deviation standard and probability were tested with Mann Whitney-U test, $p < 0.05$ is significant. *P value < 0.05 .

Table 2: Glutamate level alteration between two groups.



Duration of Observation	Substance-P Level (pg/ml)				P value
	Pregabalin Group (n=26)		Control Group (n=26)		
	Min-Max	Median	Min-Max	Median	
Before Surgery	11-185	48.5	6-154	60.5	p=0.510
1 hr After Surgery	2.3-173.5	19.3	23.6-205.6	59.6	p=0.000*

Data are shown in minimal, maximal and mean value, deviation standard and probability were tested with Mann-Whitney-U test, p<0.05 is significant. *P value<0.05.

Table 3: Substance-P level alteration between two groups.

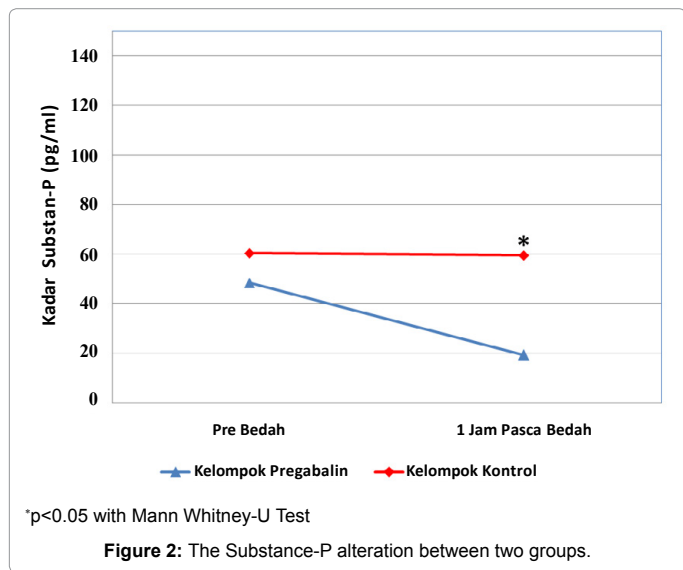


Figure 2: The Substance-P alteration between two groups.

of glutamate 1 hour postoperative. The results of the analysis of the dynamics of substan-P serum levels in both groups can be seen in Table 3 and Figure 2. From this table it was found that when preoperative pregabalin group substan-P levels varied between 11-185 pg/ml with a median of 48.5 pg/ml whereas in the control group between 6-154 pg/ml with a median of 60.5 pg/ml and the value of p=0.510 (p>0.05). When 1 hour postoperative pregabalin group substan-P levels varied between 2.3 to 173.5 pg/ml with a median of 19.3 pg/ml, while in the control group between 23.6 to 205.6 pg/ml with a median of 59.6 pg/ml and the value of p=0.000 (p<0.05). In observation of preoperative and postoperative median 1 hour substan-P levels were higher in the control group compared with the pregabalin group. The results of the analysis Mann-Whitney U Test showed differences substan-P levels were significantly (p<0.05) between the control group and the pregabalin group for 1 hour postoperative observation time. The results of the analysis of changes in levels of Substan-P in both groups showed that the current 1-hour postoperative levels of the control group increased substan-P were present in 20 of the 26 people (76.92%) and substan-P levels are decreased in 6 of 26 people (23.07%), whereas in the pregabalin group substan-P levels are increased in 5 of the 26 people (19.23%) and substan-P levels are decreased/remained present in 21 of the 26 people (80.76%). Test results at the time of observation X² test showed differences substan-P levels were significantly (p<0.05) 1 h postsurgery in the control group compared with the pregabalin group. So pregabalin reduce the production of substan-P 1 hour postoperative.

Total consumption of morphine

To observe the level of pain experienced by patients was assessed amount of used injection of morphine consumption by PCA in 24

hours. The results of the analysis of the dynamics of the unused amount of morphine injection in both groups showed that the amount of morphine consumption in the 24 hours postoperative pregabalin group between 5-10 mg with a median of 7 mg whereas in the control group between 6-15 mg to 10 mg and the median value of p=0.000 (p<0.05). The results of the analysis Mann-Whitney U Test showed different numbers of injections of morphine consumption were significantly (p<0.05) at 24 hours postoperative observation time between the control group and the pregabalin group.

VAS relationship with and vital sign

The relationship level of pain (VAS) with blood pressure, heart rate, levels of glutamate, substan-P levels, and the amount of morphine consumption is done by correlation test and found that changes in postoperative pain scores (VAS) were significantly associated (p<0.05) with changes in systolic blood pressure, diastolic blood pressure changes, changes in heart rate, changes in glutamate levels, changes in levels of substan-P, and the amount of use of morphine in the 24 hours postoperative.

Comparison of levels and content substan-p and glutamate

Comparison of the levels of glutamate and substan-P levels in the blood 1 hour postop in the control group and the pregabalin group, can be seen in Tables 2 and 3 and it can be concluded that both the production of glutamate and production of substan-P significantly different in the pregabalin group compared with the control group. In addition, a graph of Figures 1 and 2, it can be seen that the administration of preemptive pregabalin led to postoperative levels of glutamate remained but substan-P levels decreased. It can be concluded that the administration of preemptive pregabalin can suppress the increase in glutamate production and can reduce the production of substan-P, in the first 1 hour postoperative neurons (Figures 1 and 2).

Discussion

In this study, pain scores were lower in patients given pre-emptive pregabalin compared with patients who were not given. The results of the VAS assessment of pain levels in both groups at postoperative patients has increased, but the increase in VAS was higher in the control group than in the group given preemptive pregabalin. Also the results of the analysis with the Mann-Whitney U test showed a significant difference (p<0.05) in both groups, either at the time of early postoperative, or in 1 hour, 8 hours, and 24 hours postoperative. These results indicate that administration of preemptive pregabalin is effective for reducing postoperative pain. Tissue damage due to surgery and peripheral sensitization with several chemical mediators produced, will trigger a neuroendocrine response simpato-adrenal activation with consequent including blood pressure and heart rate increases. In this study it was found that systolic and diastolic blood pressure increased postoperative higher in the control group compared with the group given preemptive pregabalin. Increased heart rate also was higher in the control group compared with the group given preemptive pregabalin. In statistical tests are significant differences between the two groups in the early postoperative, 1 hour and 8-hour postoperative postop. Tissue damage and inflammatory reaction due to surgery will cause peripheral sensitization. Furthermore, through the process of transmission, noksius impulses from peripheral nociceptors are forwarded up to the first order neuron (the presynaptic neuron). This impulse in the presynaptic neuron will result in Ca²⁺ will enter the cell through Ca²⁺ channels. Ca²⁺ influx into these cells causes of the end of the presynaptic neurons release several neurotransmitters

such as glutamate and substance P which will go to the second order neuron (postsynaptic), subsequently resulting in feelings of pain. Therefore, postoperative pain has close association with elevated levels of glutamate and substance P in the blood. In this study, the levels of glutamate and substance P postoperative rise much higher than the preoperative levels in the control group compared with the group given preemptive pregabalin. The results of statistical tests also found differences in changes in the levels of glutamate and substance P were significantly ($p < 0.05$) in both groups. From the results of statistical tests with Spearman correlation test, a significant association ($p < 0.005$) between the change in the level of pain (VAS) with changes in systolic blood pressure, change in systolic blood pressure, changes in heart rate, changes in glutamate levels, changes in levels of substance P, and changes in the amount of consumption of morphine injection. There are significant differences in the levels of glutamate and substance P in the blood in patients with postoperative control group compared with the group given preemptive pregabalin. In addition, a graph of Figures 1 and 2, it can be seen that the administration of preemptive pregabalin led to postoperative levels of glutamate remained but substance P levels decreased. In other words preemptive pregabalin administration can suppress the increase in glutamate production and can reduce the production of substance P postoperative, and thus lower levels of postoperative pain experienced by patients.

Conclusions and Recommendations

Administration of pregabalin preemptive antinociception effect in patients with postoperative thus decreasing postoperative pain perception, visible from curbing the increase in postoperative VAS values, systolic blood pressure, diastolic blood pressure, as well as postoperative heart rate, and reduced the use of morphine in the 24 hours postoperative. Administration of preemptive pregabalin suppress glutamate increased production and lower production of substance P on the first neurons of the spinal cord dorsal horn 1 hour postoperative. Thus the transmission of pain to the second dorsal horn neurons of the spinal cord and decreased postoperative pain perception also decreased. Substance P is more responsive to the effects of glutamate than pregabalin. In a subsequent study, the examination should be performed and the levels of glutamate levels substance P also at 8 hours and 24 hours postoperative postop. In future studies should also be examined levels of COX-2 in the blood to determine

the relationship of the levels of glutamate and substance P. May consider granting preemptive preoperative pregabalin to patients before surgery, to reduce postoperative analgesic requirements.

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