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ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Comparative effect of preoperative oral pregabalin 50 mg vs. 75 mg on nerve growth factor (NGF) levels in parturients undergoing cesarean section

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ABSTRACT

Background & objectives: Postoperative pain after cesarean section (CS) is a crucial problem faced by the parturients. Pregabalin is a choice of preventive analgesia to reduce neuropathic pain, inflammation, tissue irritation, and post-cesarean section pain. The purpose of this study was to compare the effect of giving pregabalin 50 mg or 75 mg in combination with paracetamol 1 g on nerve growth factor (NGF) levels after cesarean section.

Methodology: A prospective, comparative model was used in this study. The study took place at Mother and Children Hospital of Sitti Khadijah I, Makassar, Indonesia. A total of 30 patients who underwent CS were randomly divided into two groups; group P1 who received pregabalin 50 mg orally and 1 g paracetamol intravenously, 1 h before surgery (n = 15), and group P2 who received pregabalin 75 mg orally and 1 g paracetamol intravenously, 1 h before surgery (n = 15). Nerve Growth Factor (NGF) levels were measured 2 h before surgery, and at 4 and 6 h post-surgery. Data were analyzed by the Mann-Whitney test using SPSS 26.0.

Results: There was a decrease in NGF levels in the pregabalin 75 mg group at 6 h post-surgery, while in the pregabalin 50 mg group it tended to increase at 4 and 6 h post-surgery. In the pregabalin 50 mg group, there was a significant increase in NGF levels from measurements of NGF1 to NGF2 and NGF0 to NGF2 ($P < 0.05$), whereas, in the pregabalin 75 mg group, there was a significant decrease in NGF levels from measurements of NGF1 to NGF2 and NGF0 to NGF2 ($P < 0.05$).

Conclusion: The combination of pregabalin 75 mg orally with paracetamol 1 g intravenously is effective as perioperative multimodal analgesia by reducing nerve growth factor levels after cesarean section surgery.

Abbreviations: BDNF- brain-derived neurotrophic factor; CS- Cesarean section; GABA- Gamma Amino Butyric Acid; NGF- Nerve Growth Factor

Keywords: Cesarean section; Nerve Growth Factor (NGF); Postoperative; Pregabalin

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1. INTRODUCTION

Postoperative pain is the acute pain caused by surgical trauma, inflammatory reactions, and irritation of afferent nerves, and it usually ends with wound healing. Pain is also influenced by the patient's cultural, social, and psychological factors. Moreover, in patients receiving long-term opioid therapy, a tolerance to the

narcotics may have developed. Therefore, individual-based pain assessment and the selection of appropriate analgesic therapy are essential. Postoperative pain is a crucial problem faced by postoperative patients.[1] Postoperative pain will affect the cardiovascular, respiratory, and endocrine systems associated with postoperative complications. Even though our knowledge about the mechanisms of postoperative pain has made significant progress, the management of postoperative pain is not always optimal and is still often neglected. Postoperative pain control is associated with lower rates of morbidity and mortality, as well as shorter hospital stays, and reduced treatment costs.[2]

Preemptive analgesia refers to actions regarding pain prevention, sensory afferents, and CNS sensitization before nociceptive stimulation, and to reduce the effects of pain.[2] In cesarean section (CS) surgery. Pain due to incision and uterine contractions affects the recovery of the mother after childbirth.[3]

Pregabalin is an analogue of gamma amino butyric acid (GABA) with anticonvulsant and anxiolytic properties. A large number of clinical trials demonstrated that pregabalin is effective in early postoperative pain. Currently, pregabalin is very commonly used in reducing neuropathic pain, inflammation, tissue irritation, fibromyalgia neuralgia, and postoperative pain.[4]

Nerve Growth Factor (NGF) is a protein, and belongs to the family of neurotrophin proteins, consisting of brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4-5). In humans, NGF levels are elevated in acute and chronic pain conditions. The relationship between increased NGF levels and pain has been established in various studies in animals and humans. [5,6] Pregabalin plays a role in preventing nociceptive pain and acute inflammation, so we assessed the effect of preventive analgesia with two different doses of pregabalin and paracetamol on NGF levels after CS surgery.

2. METHODOLOGY

This prospective study was conducted at the Mother and Child Hospital of Sitti Khadijah I, Makassar, Indonesia. The research method was approved by the Health Research Ethics Committee of the Hasanudin University Hospital. All subjects provided written informed consent to participate in this study. We enrolled 30 patients who underwent elective CS under spinal anesthesia (SA), ASA II, age 20-40 y, Body Mass Index (BMI) 18.5-29.9 kg/m^2. Exclusion criteria included contraindications to SA, history of asthma, hypertension, cardiovascular disease, epilepsy or currently taking antiepileptic drugs, history of chronic pain, psychiatric disorders, diabetes mellitus, impaired kidney or liver function, alcohol use, previously received opioid therapy, neuropathic analgesic drugs, and anti-inflammatory drugs, receiving chemotherapy, and history of allergy to research materials. Patients receiving other anesthetic techniques, experiencing complications during surgery, and having incomplete medical records were excluded from the study.

The patients were divided into two groups; group P1, who received pregabalin 50 mg orally and paracetamol 1 g intravenously, one hour before surgery. Group P2 received pregabalin 75 mg orally and paracetamol 1 g intravenously, 1 hour before cesarean section under SA. Pregabalin was continued 12 h after initial administration.

Patients underwent the elective preparation procedure. NGF levels (NGF0) were measured 2 h before the cesarean section. The drugs included in the study were administered one hour before the expected time of the surgical incision. Before SA, 250 ml of colloid HES 6% was administered. Spinal anesthesia was performed in the left lateral decubitus position in the L3-L4 interspace. Both groups underwent SA with a Spinocane® 25G spinal needle, bupivacaine hyperbaric 0.5% 10 mg with adjuvant fentanyl 25 mg was injected. The patient was positioned supine. The height of the autonomic block was examined by the cold test, the sensory block by the pinprick test, and the motor block by Bromage score. Surgery was started if the sensory block was at the level of the dermatome of the T6 vertebral level. Oxygen 2-4 L/min was given. If the MAP fell below 25% of the basal value, ephedrine 5-10 mg/iv was administered.

Postoperative pain management was administered by oral pregabalin 50 mg and 75 mg for each group 12 h after the initial dose, ketorolac 30 mg every 8 h IV, and paracetamol 1 g every 6 h IV. After surgery, the patient was transferred to the PACU. Examination of NGF levels was carried out at the 4th hour (NGF1) and the 6th hour post-surgery (NGF2).

Statistical analysis

The sample size was calculated based on the minimum number of participants with the proportion using a 95% confidence interval (CI). Based on the calculations, the minimum number of patients in each group was 15 people. The data were analyzed using the Mann Whitney test using SPSS 26.0 software (IBM Corp, Chicago, IL, USA).

3. RESULTS

The results of the analysis in Table 1 show no significant differences in demographic data of the patients including age, weight, height, BMI, and

Table 1: Demographic characteristics

Variable	Pregabalin 50 mg	Pregabalin 75 mg	p
Age (y)	31.20 ± 6.51	29.73 ± 5.39	0.507
weight (kg)	63.60 ± 7.68	63.67 ± 6.70	0.980
Height (cm)	159.07 ± 7.17	158.73 ± 6.15	0.967
BMI (kg/m2)	25.05 ± 1.58	25.22 ± 1.66	0.776
Surgery Time (minutes)	61.13 ± 20.63	59.00 ± 12.13	0.838

Data displayed as mean ± standard deviation. Data were analyzed by unpaired t test. P < 0.05 considered as significant

Table 2: Comparison of NGF levels between the two groups.

Measurement Time	NGF Levels (Mean ± SD)		p
	Pregabalin 50 mg	Pregabalin 75 mg	
NGF0	251.50 ± 229.35	276.70 ± 136.71	0.081
NGF1	251.50 ± 229.35	278.44 ± 168.10	0.202
NGF2	266.65 ± 211.37	222.37 ± 107.74	0.285

Data displayed as mean ± standard deviation. Data were analyzed by Mann Whitney test. P < 0.05 was significant

duration of surgery (P > 0.05) between the two groups, so the data can be stated homogeneous.

Level of NGF

The summary of the analysis results in Table 2 show no significant difference in the levels of NGF between the pregabalin 50 mg and 75 mg groups (P > 0.05). However, NGF levels in the pregabalin 75 mg group at 6 h post-surgery was decreased, while in the pregabalin 50 mg group, it tended to increase at 6 h post-surgery.

Table 3 shows a comparison of the changes in NGF levels. There were significant differences in the measurements of NGF0 to NGF2 and NGF1 to NGF2 between the pregabalin 50 mg and 75 mg groups (P < 0.05). NGF levels in the pregabalin 50 mg group increased at 4 and 6 h post-surgery, while the pregabalin 75 mg group tended to decrease at 6 h post-surgery.

Based on table 4, the results in the pregabalin 50 mg group showed a significant increase in NGF levels from NGF1 to NGF2 and NGF0 to NGF2 measurements (P < 0.05), while in the pregabalin 75 mg group, there was a significant decrease in NGF levels measured from NGF1 to NGF2 and NGF0 to NGF2 (P < 0.05).

4. DISCUSSION

In humans, NGF levels are elevated in acute and chronic pain conditions, such as in rheumatoid arthritis and spondyloarthritis, neurogenic overactive bladder and interstitial cystitis, cancer-induced pain, endometriosis and in patients with degenerative intervertebral disc disease. The relationship between increased NGF levels and pain has been demonstrated in various animal and human studies by modulating NGF levels and observing their effect on pain levels. In humans, IM injection of NGF in a randomized double-blind trial increased pressure pain sensitivity in injected muscles compared to the controls, and the effect was resistant to local anesthetics. NGF also induces post-injection localized mechanical and thermal non-inflammatory hypersensitivity in human skin. Similar observations on injection of NGF into the masseter muscle induce hyperalgesia and mechanical allodynia that lasts for seven days.[5,6]

There is a lot of evidence showing that NGF mediates and potentiates pain which is used as a mechanistic-based biomarker, and the development of NGF antagonists as potential analgesics and anti-hyperalgesic. One of the NGF antagonists used is an anti-NGF antibody, which will block signals from NGF in the process of pain.[7]

Table 3: Comparative changes in NGF levels based on time of measurement

Measurement Time	Group	Δ NGF Levels (Mean ± SD)	NGF Levels Velocity (%)	p
NGF0- NGF1	Pregabalin 50 mg	↑ 4.66 ± 54.03	↑ 3.52 %	0.653
	Pregabalin 75 mg	↑ 1.74 ± 46.55	↑ 1.19 %	
NGF1- NGF2	Pregabalin 50 mg	↑ 10.48 ± 54.95	↑ 18.02 %	0.001*
	Pregabalin 75 mg	↓ 56.07 ± 147.40	↓ 13.24 %	
NGF0- NGF2	Pregabalin 50 mg	↑ 15.15 ± 42.36	↑ 21.58 %	0.000*
	Pregabalin 75 mg	↓ 54.33 ± 112.98	↓ 16.22 %	

*Data displayed as mean ± standard deviation. Data analyzed by Mann Whitney test. * P < 0.05: significantly different*

Table 4. Comparison of NGF levels in each group.

Group	Measurement Time	NGF Levels (ng/ml)	p
Pregabalin 50 mg	NGF0	251.50 ± 229.35	0.955
	NGF1	256.16 ± 228.84	
	NGF1	256.16 ± 228.84	0.041*
	NGF2	266.65 ± 211.37	
	NGF0	251.50 ± 229.35	0.173*
	NGF2	266.65 ± 211.37	
Pregabalin 75 mg	NGF0	276.70 ± 136.71	0.776
	NGF1	278.44 ± 168.10	
	NGF1	278.44 ± 168.10	0.047*
	NGF2	222.37 ± 107.74	
	NGF0	276.70 ± 136.71	0.008*
	NGF2	222.37 ± 107.74	

*Data displayed as mean ± standard deviation. Data analyzed by Wilcoxon test. *: P < 0.05 significant*

NGF plays a role in modulating nociception through its releasing effect of inflammatory mediators, the activity of nociceptive receptors/ion channels, and the expression of nociceptive genes.[8]

In this study, there was a decrease in NGF levels in the 75 mg pregabalin group at 6 h post-surgery, while in the pregabalin 50 mg group, it tended to increase at 4 h and 6 h post-surgery. In the pregabalin 50 mg group, there was a significant increase in NGF levels from measurements of NGF1 to NGF2 and NGF0 to NGF2 ($P < 0.05$), whereas, in the pregabalin 75 mg group, there was a significant decrease in NGF levels from measurements of NGF1 to NGF2 and NGF0 to NGF2 ($P < 0.05$).

Changes in NGF levels are delayed more than other mediators.[9] This is in line with the increase in NGF levels in acute and chronic pain conditions. The association between increased NGF levels and pain has been demonstrated in various human studies by modulating NGF levels and observing their effect on pain levels.[5,6]

Research conducted by Carvalho regarding mediators and cytokines during cesarean section surgery using TAP block with an analgesic effect of 12 to 48 h is not followed by a delayed increase in NGF levels.[9]

A study by Kivitz, et al. showed a relationship between NGF levels and perceived pain intensity. The use of Tanezumab, as an anti-NGF therapy in patients with back pain, shows a significant reduction in pain intensity compared to placebo or naproxen.[10] Research conducted by Lane et al. stated that giving anti-NGF therapy correlated with a decrease in VAS values in patients with osteoarthritis.[11]

The increase in pro-inflammatory cytokines is closely related to pain as part of the neuroinflammatory response and can be inhibited by pregabalin. Neuropathic and inflammatory pain have different etiologies but have similar underlying mechanisms. Gabapentin can reduce inflammatory mediators and suppress dorsal horn activity. In animal models of inflammatory pain, gabapentin is effective as an antinociceptive. In this study, there was a decrease in the postoperative NRS score, which correlated with the NGF levels in the blood. It proves that gabapentin not only acts at the transmission, modulation, and perception levels of pain pathways, but also at the transduction level in the inflammatory mechanism. These findings make gabapentin a viable option for multimodal analgesia as acute or neuropathic pain therapy.[12]

These findings can be evidence that NGF has a role in pain modulation, thereby confirming its function as a biomarker of pain which in the future can make our assessment of pain more objective. It proves that gabapentin works at the level of transduction in pain pathways, and at this level, NGF acts as an inflammatory mediator.[8] NGF can also induce or promote a program of gene expression related to axonal growth. It may have consequences for nociceptive processing. This anatomical growth is very apparent in several clinical states. One is in osteoarthritis, in which healthy cartilage is usually aneural. However, in diseased tissue, sensory and sympathetic nerve fibers are often found, and NGF-induced growth is the most parsimonious explanation (because NGF levels are increased in these states). [13]

This finding is consistent with a study conducted by Lowe et al. in 1997, who found that NGF levels increased in pain and inflammation. Aloe et al. in 1992, found that reduced levels of NGF correlated with reduced pain during therapy with NGF antibodies. The two findings above show a close relationship between NGF levels in the blood and pain levels.[7] NGF supply from the innervation field influences the neuronal plasticity that allows the adult nervous system to modify its structure and functions in response to stimuli. [14,15]

NGF has a role in mediating and potentiating pain. In this case, NGF functions as a mechanistic-based biomarker. The development of antagonists from NGF as new analgesics and anti-hyperalgesic have the

potential to prove the role of NGF in modulating pain, either directly by lowering the threshold for action potentials of nociceptive neurons or indirectly by influencing the actions from cells that are inflamed and act as inflammatory mediators that will induce the release of pain mediators such as histamine, bradykinin, ATP, serotonin, protons, prostaglandins and NGF itself from mast cells, which activate receptors and ion channels in peripheral nociceptor terminals, which results in neural depolarization and sensitization thus forming a positive-feedback loop which further sensitizes nociceptive neurons.[7]

5. CONCLUSION

The combination of pregabalin 75 mg orally with paracetamol 1 g intravenously, administered one hour before surgery is effective as perioperative multimodal analgesia by reducing Nerve Growth Factor levels after cesarean section surgery.

6. Data availability

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

7. Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

8. Conflict of interest

No potential conflict of interest relevant to this article was reported.

9. Authors' contribution

MRA: Concept, conduction of the study work and manuscript editing

MWH, NSWS: Conduction of the study work and manuscript editing

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