

THE MEAN PAIN INTENSITY DIFFERENCE OF TRAMADOL ANALGESICS WITH MEFENAMIC ACID ON THE VAS VALUE IN POST-CESAREAN SECTION PATIENTS

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Background

The rate of delivery by cesarean method is increasing worldwide and exceeds the recommended range limit of the *World Health Organization* (WHO) by 10-15%. Based on the Basic Health Research (Riskesdas 2018), the prevalence of cesarean delivery was 17.6%, where the highest was found in the Special Capital Region of Jakarta (31.3%) and the lowest was in Papua (6.7%).¹ Caesarean section is a method of delivery by removing the fetus through an incision in the abdominal wall and uterine wall.^{2,3} The indications for cesarean section are categorized into absolute and relative indications. Broadly speaking, the indications are narrow pelvic section and mechanical dystocia, previous surgery on the uterus, bleeding caused by placenta previa or placental abruption, toxemia gravidarum, and fetal indications.⁴

Pain is defined as unpleasant sensory and emotional experiences associated with actual or potential tissue damage.^{5,6} Pain is subjective and varies in each woman who underwent CS. There are several factors that influence post-SC pain in the form of *Body Mass Index* (BMI)⁷, marital status⁷, blood type⁸, duration of surgery⁷, types of sedation⁹, anticipated pain¹⁰, and consumption of anticipated pain plus pain medication that has been anticipated¹¹. Postoperative pain causes patient discomfort, decreased levels of satisfaction, prolonged recovery, and health care costs are higher.¹² In particular, in any post-cesarean section patient, poor pain control can interfere with ambulation, breastfeeding, and early maternal bonding with the infant. Adequate postoperative analgesia accelerates ambulation, reduces maternal morbidity, improves *outcome* patient, and facilitates care of the newborn.¹³ In addition, inadequate pain management can lead to chronic post-cesarean pain for months.¹⁴

There is currently no gold standard for the management of cesarean section pain.¹⁵ Non-pharmacological and pharmacological therapy are important components of postoperative pain management.¹⁵ Many options are available for the treatment of postoperative pain, including systemic analgesics (ie, opioids and nonopioids) and regional (ie, neuraxial and peripheral) analgesic techniques.¹⁶ Administration of *non-steroidal anti-inflammatory drugs* (NSAIDs) and oral acetaminophen is recommended within 2-3 days after cesarean section.¹⁴ Administration of NSAIDs in the form of mefenamic acid is the most commonly given.¹⁷ Opioids may be given if the pain is moderate to severe.

Tramadol is a synthetic codeine analogue which is a weak μ receptor agonist.¹⁸ Tramadol can be given by mouth, intravenous injection, IM injection and intravenous infusion. The dose of tramadol is 0.5-1 mg / kg. The maximum dose of tramadol per day is 400 mg. Tramadol is metabolized in the liver by cytochrome isoenzymes P-450 2D6, P450 2B6, and P450 3A4.¹⁸ 60% of tramadol will be excreted in urine and the rest will be excreted in feces. The elimination half-life is 6 hours for tramadol and 7.5 hours for its active metabolites. Analgesic effect occurs after 1 hour of oral use and peaks within 2 hours. The long duration of the analgesic effect is up to 6 hours.¹⁸ Generally, the side effects of giving tramadol are nausea, vomiting, dizziness, dry mouth, headache, and sedation.¹⁸

Mefenamic acid is used as an analgesic and anti-inflammatory. Mefenamic acid is a derivative of anthranilic acid. binds to the prostaglandin synthetase receptors COX-1 and COX-2 thus inhibiting prostaglandin synthetase.¹⁹⁻²¹ The half-life is 4 hours. The peak time is at 2 hours post administration. Dosage forms are in the form of tablets, capsules, and suspensions. Due to its short half-life, its consumption is given several times a day. The dosage for using mefenamic acid is 2-3 x 250-500mg daily.¹⁹⁻²¹ The side effects of mefenamic acid use are dyspepsia, diarrhea to bloody diarrhea and symptoms of gastric mucosal irritation.^{19,20}

In Indonesia, there is no study on the effectiveness of using oral opioids such as oral tramadol in the management of post-cesarean pain yet. Therefore, this study was conducted to compare the mean pain intensity of oral single agent tramadol with oral mefenamic acid single agent within 12 hours after Caesarean section.

Methods

This research is a randomized controlled clinical trial (*randomized clinical trial*) with a *one group posttest design*. The sampling location was in Sundari Medan Hospital. The study sample was all pregnant women who gave birth in the operating room and met the research criteria. The sample was divided into 2 groups, namely the group given a single dose of opioid oral analgesic agent (tramadol) 50 mg and the group that was given a single dose of oral analgesic agent NSAID (mefenamic acid)) 500 mg at 12 hours post cesarean section selected randomly then assessed pain intensity as assessed by *Visual Analog Scale*. Samples were obtained by *consecutive sampling*.²² The minimum sample in each group is 25 subjects.

The inclusion criteria in this study were pregnant women who underwent cesarean section surgery without complications, live births, received spinal anesthesia at the time of surgery, and were willing to participate in the study and signed a consent form. The exclusion criteria were experiencing pain in other parts of the body, decreased consciousness, cesarean section operation time of more than 60 minutes, smoking, nervous system disorders, psychosocial disorders, and drinking alcohol, a history of pre-existing opioid dependence, and drug allergies.

The classification of pain intensity used based on the VAS score is as follows:

- a. No pain: VAS score 0
- b. Mild pain: VAS score 1-3
- c. Moderate pain: VAS score 4-6
- d. Severe pain: VAS score 7-9
- e. Very severe pain: score 10

Results

The number of samples was 50 people in which 25 subjects were divided into group A (given a single dose of oral analgesic agent NSAID / mefenamic acid) and 25 subjects in group B (given a single dose of oral analgesic agent opioid / tramadol) at 12 hours post cesarean section. The following are the characteristics of the age and parity of the study sample.

Table 1. Distribution of research sample characteristics in groups A & B

Characteristics of	Group A (Mefenamic Acid)	Group B (Tramadol)	P value
Age (years)	28.64 ± 6.23	30.72 ± 4.13	
Parity			
Nullipara	28%	28%	
Primipara	36%	32%	
Multipara	36%	40%	
Education			0.190*
SD	4%	4%	
SMP	4%	12%	
SMA	80%	52%	
D3 / S1	12%	32%	

Work			1,000*
Not working	76%	76%	
Working	24%	24%	
Previous SC			0.777*
No	48%	44%	
Yes	52%	56%	

* test *Chi square*

By testing Shappiro Wilk, it was found that the data were normally distributed ($p < 0.05$) so that the data were presented in mean \pm standard deviation. Based on **Table 1**, it appears that the mean age for group A is 28.64 ± 6.23 and for group B is 30.72 ± 4.13 . For the number of parity, it appears that the two groups were balanced with group A, 28% nulliparous, 36% primiparous, and 36% multiparous, while in group B, 28% were nulliparous, 32% primiparous, and 40% multiparous. In both groups, most of them have high school education where group A 80% and group B 52%; do not work where each group is 76%, and more have a history of SC where group A 48% and group B 56%. In the analysis test, it was *Chi-square* found that there were no significant differences in terms of education, occupation and history of SC between group A and group B ($p > 0.005$).

Results of *Visual Analog Scale* after 1 hour and 2 hours after intervention

Table 2 below shows that 80% of the *Visual Analog Scale* (VAS) in group A was moderate intensity, while the most in group B was mild intensity (64%). In the test, it was *chi square* found that the value of $p = 0.001$ ($p < 0.05$), which indicates that there was a significant difference in VAS values between groups A and B at 1 hour post intervention.

Table 2. *Visual Analog Scale* after 1 hour and 2 hours post intervention in Group A & B

VAS	Group A (Mefenamic Acid)	Group B (Tramadol)	P value*

Post 1 hour

None	0%	8%	0.001*
Mild	20%	64%	
Moderate	80%	28%	

Post 2 hours

None	12%	48%	0.002*
Mild	24%	40%	
Moderate	60%	12%	
Severe	4%	0%	

*test *chi square*

After 2 hours of administration, the Visual Analog Scale (VAS) in group A was 60% moderate intensity and 4% heavy intensity while in group B, 48% felt no pain and 40% had light intensity. After getting analyzed by *chi square* test found that the value of $p = 0.002$ ($p < 0.05$), which indicates that there was a significant difference in VAS values between groups A and B at 2 hours post intervention.

Side effects experience after 1 hour and 2 hours post intervention**Table 3. Side effects experience after 1 hour and 2 hours after the intervention in Group A & B**

Side effects	Group A (mefenamic acid)	Group B (Tramadol)	p value *
Post 1 hour			
No	92%	96%	0.6
Dyspepsia	4%	4%	
Headache	4%	0%	
Post 2 hours			
No	100%	100%	. ^a

* *chi square* test

Based on **Table 3** below shows that 92% and 96% of the samples in groups A and B, respectively, did not experience any side effects. Whereas only a small proportion experienced side effects of treatment, namely dyspepsia as much as 4% for each group and headache as much as 4% only experienced in group A. Based on analysis with *chi square* test, found that the value of $p = 0.6 (> 0.05)$ which indicates that there is no significant difference in side effects between the two groups. After 2 hours of administration, neither group A nor group B experienced any symptoms of side effects.

Discussion

Postoperative analgesia comparable to opioids has been demonstrated with non-steroidal anti-inflammatory drugs (NSAIDs). The μ -opioidergic and monoaminergic pathways (5-hydroxytryptamine and noradrenaline) and individual prostaglandin-dependent mechanisms are important in pain modulation. By inhibiting the cyclooxygenase enzyme and preventing central and peripheral synthesis of prostaglandins, NSAIDs reduce the inflammatory component of pain formation and also effectively relieve pain of uterine contractions in the postpartum period and after cesarean delivery.²³

Tramadol is a centrally acting analgesic and is structurally related to codeine and morphine, consisting of two enantiomers, both of which contribute to their analgesic activity via different mechanisms. Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID). It's most commonly used to treat dysmenorrhea pain in the short term (seven days or less), as well as mild to moderate pain including headaches, toothaches, postoperative and postpartum pain.²⁴ In general, paracetamol and ordinary NSAIDs in short-term use are safe and levels in milk are low. Ibuprofen (600-800 mg orally every 8 hours) has the best documented safety, followed by mefenamic acid (most commonly prescribed in our environment) and ketorolac. The use of specific COX2 inhibitors such as celecoxib and parecoxib also showed no signs of harm. The use of naproxen and indomethacin, however, is less recommended.²⁵

Characteristics of Research Samples

In this study the mean age for group A was $28.64 + 6.23$ and for group B was $30.72 + 4.13$. For the number of parity, it appears that the two groups were balanced with group A, 28% nulliparous, 36% primiparous, and 36% multiparous, while in group B, 28% were nulliparous, 32% primiparous, and 40% multiparous. In both groups, most of them have high school education where group A 80% and group B 52%; do not work where each group is 76%, and more have a history of SC where group A 48% and group B 56%. In the analysis test, it was Chi-square found that there were no significant differences in terms of education, occupation and history of SC between group A and group B ($p > 0.005$).

The study by Kintu showed that most of the post-caesarean patients who took analgesics were between the ages of 21-30 years (61%) with a total parity of 39% multiparity (>3) and 63% had no history of CS.51 Research by Adeniji showed that the mean age of the samples using tramadol as an anti-pain after cesarean section was 30.12 ± 3.43 years with a total parity of 1.76 ± 0.98 .52 Whereas in the study, the average age of tramadol users was 25.41 ± 3.94 .60 Research by Chi et al showed that the mean age of patients using tramadol after cesarean section was 30.12 ± 4.82 years.61 Likewise, the study by Borges showed 78.1% of patients aged between 20-35 years, 64.4% had a history of ≥ 11 years of education, and 54.6% were employed.62 This shows a picture that is not much different from the characteristics of the respondents in this study.

VAS values at 1 hour and 2 hours after intervention

In this study the Visual Analog Scale (VAS) in group A was 20% including light intensity and 80% moderate intensity. Then VAS in group B, 8% felt no pain, 64% moderate intensity and 28% heavy intensity. After analysis with *chi square* test found that the value of $p = 0.001$ ($p < 0.05$), which indicates that there is a significant difference in VAS values between groups A and B at 1 hour after the intervention. Meanwhile, the Visual Analog Scale (VAS) in group A was 12% painless, 24% light intensity, 60% moderate intensity, and 4% heavy intensity. Then VAS in group B, 48% felt no pain, 40% moderate intensity and 12% heavy intensity. After analysis with *chi square* test found that the value of $p = 0.002$ ($p < 0.05$), which indicates that there was a significant difference in VAS values between groups A and B at 2 hours post intervention.

A study by Moll et al showed that the proportion of decreased pain intensity in up to 50% after 6 hours of intervention with mefenamic acid 500 mg was 48% with a *need to treat rate* of 4.0 (2.7–7.1).²⁴ The study by Borges showed a 92.7% incidence of postoperative pain (95% CI: 90.9 - 94.2). The main pain intensity referred to at the worst time (“strongest” pain) was 6.6 (sd = 2.2) and “weakest” pain 3.3 (sd = 2.0), triggered by movement. Only 22.5% mentioned mild pain or no pain.¹⁰ Research by Adeniji showed the mean VAS value of tramadol users after cesarean section was 5.86 ± 0.67 which was of moderate intensity.²⁷ A study by Hasa showed that the VAS in tramadol users in post-hysteroscopy patients was 0.6 ± 0.95 after 30 minutes of tramadol use.³¹ In the study by Ambika, it showed a VAS value of around 4.87 ± 0.67 in patients using Tramadol with a significant change from 2 hours post use to 12 hours post use, from 7.65 ± 0.48 to 2.9 ± 0.7 with a p value < 0.001 which indicates a significant difference. .²⁸ Tramadol may be better if given 4-6 hours after surgery.²⁴ In the United States, where mefenamic acid is licensed only for the treatment of moderate pain in adults, it is recommended that it is not given for longer than seven days. Mefenamic acid is widely available in several European countries, as well as Australia, New Zealand, Hong Kong, India, Malaysia, Thailand, Singapore, Brazil, Chile, USA, and Canada. The usual oral dose is up to 500 mg three times a day.²⁴

Side effects at 1 hour and 2 hours after intervention

In this study, 92% and 96% of the samples in groups A and B, respectively, did not experience symptoms of side effects. Meanwhile, only a small proportion experienced side effects of treatment, namely dyspepsia as much as 4% for each group and headache as much as 4% only experienced in group A. Meanwhile, in the evaluation 2 hours after the intervention, none experienced side effects. In contrast to the research by Ambika, it was found that quite a number of patients experienced side effects with various symptoms, namely 13.33% tending to be drowsy, 3.33% experiencing nausea, abdominal pain, coughing sequentially and 76.6% experiencing no symptoms.²⁸ A study by Chi et al showed 17.8% of patients experienced side effects of nausea after taking tramadol.²⁹ Likewise studies showed few and comparable side effects, except for nausea (significantly more in the tramadol group than in the acetaminophen group, 15% vs 2%, $P = 0.001$).³²

Conclusion

In this study, it was found that there was a significant difference in pain intensity after 1 hour ($p = 0.002$) and 2 hours ($p = 0.002$) of drug administration between the groups given tramadol compared to the mefenamic acid group. The intensity of pain and side effects of tramadol are less severe than mefenamic acid. Therefore, administration of oral tramadol in pain management 12 hours after cesarean section is recommended. However, it is necessary to explore the optimal dose and duration so that pain management in post-cesarean delivery mothers is better and can avoid serious side effects such as opioid abuse.

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