

**ORIGINAL ARTICLE**

**Comparison of the Incidence of Nausea and Vomiting in the Administration of Tramadol 100 mg Suppositories with Intravenous Post-Spinal Anesthesia for Lower Extremity Surgery**

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**Abstract** : Postoperative nausea vomiting (PONV) after intravenous administration of tramadol has a high incidence rate, so it needs alternative drug administration to overcome this problem. This study aims to compare the incidence of postoperative nausea and vomiting in the intravenous administration of tramadol suppositories. A double-blind analytical experimental study, involving 36 subjects divided into tramadol suppositories and intravenous tramadol post-extremity surgery with spinal anesthesia at Haji Adam Malik Hospital and Network Hospital in 2013. The incidence of PONV in tramadol suppository subjects was much lower than in intravenous tramadol subjects.

**Keywords:** tramadol, suppository, PONV

**INTRODUCTION**

One of the complications that often occur within 24 hours postoperatively is nausea and vomiting, known as postoperative nausea vomiting (PONV) with an incidence of up to 30% to 40%. PONV occurs due to the administration of pain relievers that act on the central nervous system to manage postoperative pain.<sup>1</sup> One of the most commonly used pain relievers is Tramadol, an opiate analgesic that inhibits serotonin (5HT3) reuptake in the central nervous system. Tramadol has the undesirable effect of stimulating the vomiting center by the chemoreceptor trigger zone (CTZ) in the brain due to the large amount of serotonin that fails to dissolve.<sup>2</sup>

Various attempts to minimize the side effects of Tramadol administration have been carried out through variations in drug administration and by a combination of non-opiate analgesics and the administration of adjuvant drugs.<sup>2</sup>

K Liukkonen et al. Reported a 16% incidence of nausea and vomiting with Tramadol administration in 75 subjects out of 156 populations in the postoperative arthroscopy study.<sup>3</sup> Lee et al. Compared the incidence of vomiting on intravenous administration of tramadol in combination with oral paracetamol with ketorolac in combination with oral paracetamol in trauma-induced muscle pain, in which the incidence of nausea and vomiting was higher in the group receiving Tramadol.<sup>4</sup>

Zamiri et al. Compared ibuprofen, celecoxib, and oral tramadol after Graham tooth extraction and found a 58% incidence of nausea and vomiting in the Tramadol group.<sup>5</sup> This study aims to compare the incidence of nausea and vomiting after administration of tramadol 100 mg suppository intravenously in lower limb surgery patients who received spinal anesthesia.

## METHODS

This study was a double-blind randomized experimental study, involving 36 research subjects at the H. Adam Malik General Hospital Medan and the Network Hospital in June - October 2013 who underwent lower limb surgery with spinal anesthesia using Bupivacaine 0.5% hyperbaric 20 mg. . The research subjects were divided into 2 groups, 18 subjects each, group A received 100 mg tramadol suppository and intravenous placebo and group B received 100 mg intravenous tramadol and placebo suppository. Subjects were evaluated for 24 hours postoperatively, starting from 1,6,12 and 24 hours, recorded the incidence of nausea and vomiting, and conducted hypothesis testing between the two treatment groups with paired T test.<sup>6</sup>

## RESULTS

### 4.1 Types of surgery

**Table 1. Distribution of surgical procedures types**

Types of surgical procedures	Groups		Total
	A	B	
Debridement	1 (5,6%)	(0 %)	1 (2,8%)
Excision	2 (11,1%)	(0 %)	2 (5,5%)
Abscess incision	(0%)	1 (5,6%)	1 (2,8%)
Incisional biopsy	(0%)	1 (5,6%)	1 (2,8%)
OREF femur	1 (5,6%)	(0%)	1 (2,8%)
OREF tibia	2 (11,1%)	2 (11,1%)	4 (11,1%)
ORIF	1 (5,6%)	(0%)	1 (2,8%)
ORIF Ankle	(0%)	1 (5,6%)	1 (2,8%)
ORIF Femur	2 (11,1%)	5 (27,8%)	7 (19,4%)
ORIF tibia	1 (5,6%)	1 (5,6%)	2 (5,5%)
Release+skeletal traction	3 (16,7%)	1 (5,6%)	4 (11,1%)
Removal Implant	4 (22,2%)	2 (11,1%)	6 (16,7%)
Skeletal traction	1 (5,6%)	1 (5,6%)	2 (5,5%)
STSG	(0%)	3 (16,7%)	3 (8,3%)
Total	18 (100%)	18 (100%)	36 (100%)

Nausea at the first hour in group A was 5.6% and group B was 66.7% with a value of  $p = 0.000$  meaning that there was a significant difference. Nausea at the 6th hour in group A was 16.7% and in group, B was 5.6% with a  $p$ -value = 0.289 meaning there was no significant difference.

**Table 2. Distribution of Nausea**

Duration	Groups				P
	A		B		
	Positive	Negative	Positive	Negative	
1 <sup>st</sup> hour	1 (5,6%)	17 (94,4%)	12 (66,7%)	6 (33,3%)	0,000
6 <sup>th</sup> hours	3 (16,7%)	15 (83,3%)	1 (5,6%)	17 (94,4%)	0,289
12 <sup>th</sup> hours	2 (11,1%)	16 (88,9%)	8 (44,4%)	10 (55,6%)	0,026
24 <sup>th</sup> hours	1 (5,6%)	17 (94,4%)	2 (11,1%)	16 (88,9%)	0,546
Total	7		23		

Table 3 Distribution of Vomiting

Duration	Group				P
	A		B		
	positive	Negative	Positive	Negative	
1 <sup>st</sup> hour	(0%)	18 (100%)	3 (16,7%)	15 (83,3%)	0,070
6 <sup>th</sup> hours	2 (11,1%)	16 (88,9%)	1 (5,6%)	17 (94,4%)	0,546
12 <sup>th</sup> hours	1 (5,6%)	17 (94,4%)	6 (33,3%)	12 (66,7%)	0,035
24 <sup>th</sup> hours	(0%)	18 (100%)	(0%)	18 (100%)	
Total	3		10		

Nausea on the 12th hour in group A was 11.1% and in group B was 44.4% with a p-value = 0.026, meaning that there was a significant difference. Nausea at 24 hours in group A was 5.6% and in the group, B was 11.1% with a p-value = 0.546 meaning there was no significant difference.

Vomiting at the first hour in group A was 0% and in the group, B was 16.7% with a p-value = 0.070 meaning there was no significant difference. Vomiting at the 6th hour in group A was 11.1% and in the group B was 5.6% with a value of p = 0.546 meaning there was no significant difference. Vomiting at 12 hours in group A was 5.6% and in group B was 33.3% with a value of p = 0.035, meaning that there was a significant difference.

## DISCUSSION

From the results of the study, it is very clear that the incidence of PONV is lower in the group that received Tramadol suppositories, this is strongly suspected because the difference in the rate of drug absorption by suppositories to achieve systemic blood circulation is much slower than intravenous administration, this is because the rectum is the final part of the system. The intestinal has a much lower absorption function compared to the small intestine, besides that

drug administration through the intestinal tract also undergoes the first-pass metabolism in the liver which results in much less bioavailability of the drug in the circulation when compared to intravenous administration. The low bioavailability of drugs results in a low amount of free drugs in the blood circulation, which in turn results in much less drug concentration on the surface of the receptors so that the possibility to bind to analog receptors in other tissues is much less so than the drug administration effect is also much smaller than that by giving intravenously.<sup>2</sup>

One of the mechanisms for vomiting is due to stimulation at the Chemoreceptor Trigger Zone (CTZ) in posttrauma which stimulates the vomiting center in the medulla. Chemoreceptors that can be found on CTZ are 5-HT<sub>3</sub>, dopamine type 2 (D<sub>2</sub>), opioids, and neurokinin-1 (NK-1). Tramadol is a  $\mu$ -opioid receptor-selective agonist and inhibits serotonin (5-HT) reuptake. Whereas (-) - tramadol mainly inhibits noradrenaline (NA) reuptake, stimulates  $\alpha$ <sub>2</sub>-adrenergic receptors but has little affinity for  $\mu$ -opioid receptors.<sup>7,8</sup> Based on this theory, if we relate it to the drug administration mechanism given, it is clear that the

administration of tramadol suppositories will prolong absorption and increase drug degradation compared to intravenous administration of tramadol, this will also lead to less drug bioavailability in blood plasma. and the time to reach peak drug levels is much longer on suppositories, what then happens is that the 5HT3 reuptake inhibition is also less and slower so that the stimulation of 5HT3 chemoreceptors in CTZ is also much less.<sup>9</sup>

Linz in 1998 conducted a crossover study of 10 subjects who were given a single dose of 100 mg of tramadol HCL and 100 mg in 2 mL of injection solution where previously a washout procedure was carried out for 1 week to get the result that the maximum serum level in suppository administration was achieved within 2 -6 hours post-administration, with a bioavailability ratio of 2933 +/- 304 h.ng/ml (suppositories) and 3775 +/- 446 h.ng/ml (iv).

From the results of the study, it can be seen that the lower bioavailability in intravenous administration causes the drug concentration at the receptor surface to be less than intravenous so that the possibility of stimulation of the vomiting center by CTZ as a result of high circulating serotonin concentrations is lower on suppository administration.<sup>10</sup>

In addition, to differences in the bioavailability of tramadol in plasma, suppositories can also reduce the irritation of the gastrointestinal surface by the acidic tramadol, this can prevent the stimulation of

the vagus nerve which is also involved in the occurrence of nausea and vomiting.<sup>11,12,13</sup>

Differences in the pharmacokinetics of giving tramadol suppositories have also been investigated by Zwaveling J et al in 2004, in this study it appears that the administration of rectal tramadol suppositories is well absorbed and shows a relatively low absorption and clearance process when compared to oral or intravenous administration.<sup>14</sup>

## CONCLUSION

Administration of Tramadol suppositories causes less nausea and vomiting than intravenous tramadol.

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