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Intravenous Granisetron Combined with Dexamethasone in Cesarean Section Patients Undergoing Spinal Anesthesia

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Abstract

BACKGROUND: Regional anesthesia, including spinal anesthesia, is the technique-of-choice over general anesthesia for cesarean section (C-section). Nausea, vomiting, and shivering are common after spinal anesthesia. Granisetron and dexamethasone are used as a premedication to prevent these reactions.

AIM: This study determined the effect of different doses of granisetron combined with dexamethasone for the prevention of nausea, vomiting, and shivering.

PATIENTS AND METHODS: This double-blind randomized clinical trial included patients undergoing C-section under spinal anesthesia at several hospitals in Makassar, Indonesia. Forty-five cases were divided into three equal-sized groups: G5, administered intravenous (IV) granisetron at 5 mcg/kg body weight (BW); G10, administered IV granisetron at 10 mcg/kgBW; and G25, administered IV granisetron at 25 mcg/kgBW. All patients also received IV dexamethasone at 0.1 mg/kgBW.

RESULTS: In the G10 group, three cases experienced mild nausea, while, in the G5 and G25 groups, there were no incidences of nausea; this was a statistically significant difference ($p = 0.043$). Vomiting was not reported in any group. The G25 group had the lowest number of patients experiencing shivering (one case with a score of 3), but there were no significant differences in shivering incidence between groups ($p = 0.164$).

CONCLUSION: Granisetron is effective in reducing nausea and shivering at certain dosage.

Introduction

Cesarean section (C-section) surgery is often performed in obstetrics [1], [2]. Due to certain risks, such as maternal morbidity and mortality, greater hemodynamic fluctuations during induction, and the need for additional analgesia during recovery, regional anesthesia is often chosen over general anesthesia [3], [4].

Nausea, vomiting, and shivering can occur after spinal anesthesia and are stressful for patients, potentially hindering surgical procedures. Nausea and vomiting incidence during surgery in non-obstetrics cases can reach 42%, and up to 80% in obstetrics cases, while post-neuraxial anesthesia shivering incidence can reach 55% during surgery. Spinal anesthesia can also decrease the core body temperature more rapidly (within 30 min) than epidural anesthesia [5], [6].

The mechanism of action (MOA) of 5-hydroxytryptamine type 3 (5-HT3) antagonist antiemetic drugs involves binding with the serotonin receptor in the chemoreceptor trigger zone (CTZ) and vagal afferent of the gastrointestinal tract. However, the MOA of dexamethasone in preventing nausea and vomiting is still not clearly defined. It is thought that dexamethasone, a prostaglandin antagonist, releases endorphins and decreases tryptophan, which play some roles in antiemetic effect. Dexamethasone could reduce nausea and vomiting incidence post-surgery and has several advantages such as low cost, lack of a sedative effect, and long duration of action [7], [8].

According to Kushwaha *et al*., prophylactic antiemetic therapy comprising the 5-HT3 antagonist granisetron at a dose of 40 mcg/kg body weight (BW) combined with 8 mg dexamethasone was superior to granisetron alone in middle ear surgery [9]. In addition, Dehghani *et al*. reported that granisetron at a dose of 40 mcg/kgBW significantly reduced the prevalence and severity of post-anesthetic shivering, and Manunggal *et al*. found that administering 1 mg intravenous (IV)

granisetron before spinal anesthesia in C-section patients reduced the post-anesthetic shivering incidence compared to placebo [10], [11].

Based on these results, the present study investigated the effect of different doses of granisetron combined with dexamethasone for the prevention of nausea, vomiting, and shivering incidence in C-section patients undergoing spinal anesthesia.

Material and Methods

Study design

This double-blind randomized clinical trial was performed at Siti Khadijah 1 Muhammadiyah Mother and Child Hospital, Makassar, Indonesia, and several networking teaching hospitals from December 2020 to April 2021.

Before the study commenced, we received clearance from the Ethical Commission for Biomedical Study in Humans of the Faculty of Medicine, Hasanuddin University (no 822/UN4.6.4.5.31/PP36/2020). All patients who met the inclusion criteria were given a verbal explanation of the study and signed an informed consent form to agree to participate voluntarily in this study.

Study population and sample selection

The study population comprised patients who underwent a C-section procedure after a minimum of 6 h of fasting. Participants were selected by consecutive sampling from among all those patients who met the inclusion criteria and gave their consent to participate.

The inclusion criteria were as follows:

a. Age: 19–40 years
b. BW: 50–70 kg
c. Body height (BH): 150–170 cm
d. Body mass index (BMI): 18.5–29.9 kg/m^2
e. American Society of Anesthesiologists (ASA) Physical Status (PS) classification II
f. Fasting for at least 6 hours
g. Approval from the patient's primary treating physician

The exclusion criteria were as follows:

a. Refusal of spinal anesthesia or a regional anesthesia contraindication including a lack of patient satisfaction
b. History of hypertension
c. Heart and cardiovascular disease
d. History of dyspepsia
e. History of diabetes mellitus (DM)
f. Temporary fever (>37.8°C)
g. History of long-term steroid use
h. History of allergy to the study materials.

Study procedure

The participants were divided into three groups: group G5, the members of which received IV granisetron (Emegran®, KalbeMed, Indonesia) premedication at a dose of 5 mcg/kgBW; group G10, the members of which received IV granisetron premedication at a dose of 10 mcg/kgBW; and group G25, the members of which received IV granisetron premedication at a dose of 25 mcg/kgBW. The members of all groups also received IV dexamethasone premedication at a dose of 0.1 mg/kgBW.

Before spinal anesthesia, colloid-fluid loading with 500 ml hydroxyethyl starch (HES) 6% was administered. Spinal anesthesia was performed at the L3–L4 intervertebral space in the left lateral decubitus (LLD) position with a 25-G spinal needle (Spinocan®, BBraun, Indonesia). The patients were given a local anesthetic injection of 8 mg (1.6 ml) of 0.5% hyperbaric bupivacaine (Regivell®, Novell, Indonesia) with 25 mcg (0.5 ml) of fentanyl (Etanyl®, Kimia Farma, Indonesia) as an adjuvant. After sensory block was achieved, the patient was placed in a supine position. The level of the autonomic block was checked with the cold test, sensory block was checked with the pin prick test, and motor block was assessed with the Bromage score [12]. Surgery was initiated if the sensory block was at the level of the sixth thoracic vertebrae. The Bromage scale target for motor block was 3/3.

Nausea, vomiting, and shivering incidences were recorded after the drug was injected into the subarachnoid space for up to 60 min. Nausea incidence was defined as the frequency of wanting to vomit expressed by the patient during surgery and was assessed by the scoring system used for nausea incidence and a special assessment for nausea and vomiting incidence in pregnant women. Vomiting incidence was defined as the frequency, in which gastric contents were passed from the patient's mouth during surgery and was assessed by the Common Terminology Criteria for Adverse Events. Shivering incidence was defined as a feeling of coldness expressed by the patient during surgery and was scored by a five-point Wrench score.

The scoring for nausea, vomiting, and shivering was as follows:

1. Nausea score
   0 = none
   1 = mild nausea that improves during rest
   2 = moderate nausea that sometimes persists during rest
   3 = severe nausea that does not improve during rest
2. Vomiting score
   0 = no vomiting
   1 = 1–2 episodes/24 h.
   2 = 3–5 episodes/24 h.
   3 = ≥6 episodes/24 h/hospital admission indication

4 = life threatening
5 = fatal

3. Shivering score
0 = no shivering
1 = peripheral vasoconstriction without visible muscle activity
2 = visible muscle activity limited to one muscle group
3 = visible muscle activity in more than one muscle group
4 = highly visible muscle activity involving the whole body.

Data analysis

The obtained data were analyzed and the results presented descriptively, in tables or in graphs, as means, standard deviations (SDs), frequencies, and percentages using SPSS 25 for Windows (IBM Corp. Armonk, NY). The data collected consisted of the mean and frequency for age, weight, height, BMI, nausea, vomiting, and shivering incidence in each group. The Shapiro–Wilk test for normality of data was applied.

Numerical variables were presented as the mean ± standard deviation (SD), while categorical variables were presented as the median±minimum–maximum. To determine the differences between the two treatment groups for numerical data, the independent sample t-test was used if the data were normally distributed. However, if the data were not normally distributed, the Mann–Whitney U test was used. To determine the differences between variables with categorical data, the Chi-square test was used if there were no expected counts <5; otherwise, the Fisher-exact test was applied. The one-way analysis of variance (ANOVA) test was used to determine the differences between treatment groups with normally distributed data, and the Kruskal–Wallis test was used for data that were not normally distributed or homogeneous.

Results

A total of 45 patients met the inclusion criteria and were willing to participate in the study. They were divided into three groups (G5, G10, and G25) with 15 patients in each.

Table 1 outlines the patient characteristics. Age, body weight, height, and BMI variables were tested by one-way ANOVA, while surgery duration, operating room temperature, and ASA PS variables were analyzed by the Kruskal–Wallis test. The statistical analysis showed no significant differences among the three groups. They could therefore be considered homogeneous.

Table 1: Patient characteristics

Patient characteristics	Mean ± SD			p
	G5 (n = 15)	G10 (n = 15)	G25 (n = 15)	
Age (years)	31.33 ± 5.341	31.93 ± 7.896	31.87 ± 6.221	0.963[a]
BW (kg)	62.53 ± 9.334	63.80 ± 6.416	65.67 ± 7.442	0.549[a]
BH (cm)	153.27 ± 5.216	154.93 ± 5.775	155.60 ± 6.243	0.526[a]
BMI (kg/m^2)	26.36 ± 2.881	26.59 ± 2.121	27.40 ± 1.747	0.43[a]
Surgery duration (min)	71.00 ± 15.260	63.67 ± 8.338	67.73 ± 10.653	0.764[b]
Operating room temperature (°C)	23.107 ± 0.464	23.507 ± 0.626	23.247 ± 0.647	0.138[b]
ASA PS	2.00 ± 0.000	2.00 ± 0.000	2.00 ± 0.000	1.000[b]

Data are presented as mean ± SD and analyzed by [a]One-way ANOVA test; [b]Kruskal–Wallis test. ANOVA: Analysis of variance, SD: Standard deviation, BW: Body weight, BH: Body height, ASA PS: American Society of Anesthesiologists Physical Status.

Table 2 outlines the nausea, vomiting, and shivering incidences and scores. In the G10 group, 12 patients did not experience nausea (score 0) and three experienced mild nausea (score 1). In the G5 and G25 groups, there were no incidences of nausea (score 0). When comparison tests were carried out between pairs of groups, there were significant differences between G5 and G10, G5 and G25, and G10 and G25. A comparison test among all three groups showed a significant difference (p = 0.043).

Table 2: Nausea, vomiting, and shivering incidences and scores

Incidence	Grade	G5 (n = 15)	G10 (n = 15)	G25 (n = 15)	p			
					G5–G10	G5–G25	G10–G25	G5-G10–G25
Nausea	0	15	12	15	0.073[a]	1.000[a]	0.073[a]	0.043*
	1	0	3	0				
	2	0	0	0				
	3	0	0	0				
Vomiting	0	15	15	15	1.000[a]	1.000[a]	1.000[a]	1.000[b]
	1	0	0	0				
	2	0	0	0				
	3	0	0	0				
	4	0	0	0				
	5	0	0	0				
Shivering	0	11	10	14	0.738[a]	0.125[a]	0.057[a]	0.164[b]
	1	1	1	1				
	2	0	1	0				
	3	3	3	0				
	4	0	0	0				

Data are presented as n and analyzed by [a]Mann–Whitney U-test, [b]Kruskal–Wallis test, *Statistically significant at p < 0.05.

There was no incidence of vomiting in any group. In the G5 group, 11 patients experienced no shivering (score 0), one patient experienced peripheral vasoconstriction without visible muscle activity (score 1), and three patients showed activity in more than one muscle group (score 3). In the G10 group, 10 patients did not experience shivering (score 0), one patient experienced peripheral vasoconstriction without visible muscle activity (score 1), one sample showed activity limited to one muscle group (score 2), and three patients showed activity in more than one muscle group (score 3). In the G25 group, 14 patients did not experience shivering (score 0) and one patient showed activity in more than one muscle group (score 3). However, none of the three groups showed highly visible muscle activity involving the whole body (score 4). Statistical tests in the second and third groups showed statistically insignificant results.

Table 3 outlines the nausea incidence based on categorical data. Nausea was experienced by three patients (6.67%) in the G10 group, but no patients in the G5 or G25 groups. There was a statistically significant difference in nausea incidence among the three groups (p = 0.040).

Table 3: Incidence of nausea, vomiting, and shivering

Incidence	Group (n)			p
	G5 (15), n (%)	G10 (15), n (%)	G25 (15), n (%)	
Nausea	15 (33.3)	12 (26.67)	15 (33.3)	0.040*
No nausea	0	3 (6.67)	0	
Vomiting	15 (33.3)	15 (33.3)	15 (33.3)	[a]
No vomiting	0	0	0	
Shivering	11 (24.44)	10 (22.22)	14 (31.11)	0.188 (NS)
No shivering	4 (8.88)	5 (11.11)	1 (2.22)	

Data are presented as n and analyzed with the Chi-square test. [a]No difference, *Significant difference at $p < 0.05$. NS: Non-significant difference.

There was no significant difference among the three groups in terms of vomiting incidence. The highest shivering incidence was found in the G10 group (11.11%); however, there were no statistically significant differences among the three groups in terms of shivering incidence ($p > 0.05$).

Table 4 shows a comparison of patients experiencing nausea, vomiting, and shivering at specific time points. In the G5 and G25 groups, none of the patients experienced nausea between the start and 60 min. However, one patient in the G10 experienced nausea at 10 min, two patients experienced nausea at 20 min, and one patient still experienced nausea at 30 min. Statistical analysis showed a significant difference among the three groups in terms of nausea incidence at specific time points ($p = 0.034$).

Table 4: Comparison of patients who experienced nausea, vomiting, and shivering at specific time points

Incidence	Group (n)	Time point						p
		10 min	20 min	30 min	40 min	50 min	60 min	
Nausea	G5 (15)	0	0	0	0	0	0	0.034*
	G10 (15)	1	2	1	0	0	0	
	G25 (15)	0	0	0	0	0	0	
Vomiting	G5 (15)	0	0	0	0	0	0	1.000
	G10 (15)	0	0	0	0	0	0	(NS)
	G25 (15)	0	0	0	0	0	0	
Shivering	G5 (15)	0	2	3	1	1	1	0.074
	G10 (15)	2	1	2	2	0	1	(NS)
	G25 (15)	0	0	1	1	0	0	

Data are presented as n and analyzed with the Kruskal–ruskalalyzed *Significant difference at $p < 0.05$. NS: Non-significant difference.

There were no incidences of vomiting, so there was no statistically significant difference in its prevalence between the three groups ($p > 0.05$). The greatest incidence of shivering was found in the G10 group (11.11%); however, there were no statistically significant differences in shivering incidence at specific time points ($p > 0.05$).

Table 5 shows the pethidine administration to patients experiencing shivering in each group. Pethidine was given to one patient in the G5 group, two patients in the G10 group, and none of the patients in the G25 group. Statistical analysis revealed no significant difference among the three groups ($p > 0.05$).

Table 6 shows the effect of confounding factors on nausea, vomiting, and shivering incidence. Mean arterial pressure (MAP), pulse, body temperature, and granisetron at 5 mcg/kgBW or 10 mcg/kgBW did not have statistically significant effects on nausea incidence. Vomiting was not analyzed, because there were no incidences in any group. Granisetron at 10 mcg/kgBW caused more shivering than granisetron at 25 mcg/kgBW ($p = 0.044$).

Discussion

Nausea and vomiting during regional anesthesia in C-section are caused by many factors. Patient-related factors include age, smoking habits, history of motion sickness, and the physiology of pregnancy itself. Surgical stimulation factors include uterine expulsion, peritoneal exploration and traction, and intra-abdominal manipulation. Anesthetic factors include technique and use of drugs. Nausea and vomiting incidences during regional anesthesia for C-section are relatively high without prophylactic antiemetics. The etiology of vomiting in these cases is complex. Maternal hypotension after spinal anesthesia could trigger nausea and vomiting center due to hypoxia [11], [13], [14].

Granisetron is a selective 5-HT3 receptor antagonist and an effective antiemetic during and after regional anesthesia for C-section. The combination of granisetron and dexamethasone has been reported to be more potent than granisetron alone. The use of granisetron was introduced in 1991 and has no drawbacks compared to traditional antiemetics, does not affect vital signs, and has no interaction with concomitant anesthetics [15], [16], [17].

Dexamethasone is known to have multiple effects on the central nervous system affecting neurotransmitter concentration, receptor density, signal transduction, and neuron configuration. Many glucocorticoid receptors are found in the solitary tract nucleus, raphe nucleus, and area postrema. These nuclei are reported to have important roles in the regulation of vomiting symptoms [16], [18].

Megahed *et al*. found that prophylactic administration of 1 mg granisetron 5 min before spinal anesthesia significantly reduced the nausea incidence [13], [14]. Zhu *et al*. concluded that the combination of granisetron and dexamethasone was more effective than granisetron alone in laparoscopic surgery [19]. The current results concurred with these studies. It should be noted that the nausea incidence in

Table 5: Pethidine administration in patients experiencing shivering

IV pethidine at dosages of 25–30 mg	Dose			p			
	G5 (n = 15), n (%)	G10 (n = 15), n (%)	G25 (n = 15), n (%)	G5–G10	G5–G25	G10–G25	G5–G10–G25
Present	14 (31.1)	13 (28.9)	15 (33.3)	0.550[a]	0.317[a]	0.150[a]	0.351[b]
Absent	1 (2.2)	2 (4.4)	0				
Total IV pethidine dosage (mg)	25	50	0				

Data are presented as n and percentage and analyzed with [a]Mann–Whitney U-test, [b]Kruskal–Wallis test. IV: Intravenous.

Table 6: Confounding factors of nausea, vomiting, and shivering incidence

Variable	Factor	p	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Nausea	MAP	0.998	0.038	0.000	
	HR	0.996	0.126	0.000	
	Temperature	0.995	2.834E+30	0.000	
	5 mcg/kgBW	1.000	8.269E+16	8.269E+16	8.269E+16
	10 mcg/kgBW	0.996	2.459E-27	0.000	
Shivering	MAP	0.431	0.915	0.734	1.141
	HR	0.200	1.080	0.960	1.215
	Temperature	0.058	0.037	0.001	1.117
	5 mcg/kgBW	0.103	0.097	0.006	1.610
	10 mcg/kgBW	0.044*	0.045	0.002	0.923

*Data are presented as p values. *Statistically significant difference at $p < 0.05$. MAP: Mean arterial pressure, HR: Heart rate, BW: Body weight, CI: Confidence interval.

this study might have been caused by surgical stimulation factors; however, exploring this consideration is not within the scope of the current report.

Granisetron is used primarily for post-operative nausea and vomiting prophylaxis or treatment, and many previously published studies support our results in this aspect. Nanjundaswamy *et al*. concluded that both granisetron and ondansetron combined with dexamethasone were effective in reducing nausea and vomiting incidences in laparoscopic cholecystectomy surgery patients [20]. Daria and Kumar reported that for patients undergoing gynecologic laparoscopic surgery under general anesthesia, granisetron alone had a lower success rate in the prevention of post-surgery nausea and vomiting compared to a combination of granisetron and dexamethasone [21].

The current result concerning shivering was in accordance with a study by Manunggal *et al*. who compared the effects of 1 mg granisetron with placebo in preventing shivering incidence after spinal anesthesia in C-section. They reported that in the granisetron group, 15.78% of patients experienced grade 2 shivering, 5.26% of patients experienced grade 3, and no patients experienced grade 4. In the placebo group, grade 2 shivering was experienced by 26.31% of patients, 21.05% of patients experienced grade 3 shivering, and 5.26% of patients experienced grade 4 shivering [11].

In the present study, the granisetron 10 mcg/kgBW group showed more shivering than the granisetron 25 mcg/kgBW group. Different results were found in a study by Dehghani *et al*. that compared the effects of granisetron at 10 mcg/kgBW with granisetron at 40 mcg/kgBW, granisetron at 10 mcg/kgBW with placebo, and granisetron at 40 mcg/kgBW with placebo, to prevent shivering after spinal anesthesia during lower abdominal surgery. There were no differences between the treatment groups [10]. This discrepancy suggests that IV dexamethasone exerts better effects when combined with larger doses of granisetron.

Gholami *et al*. compared the effects of IV dexamethasone at 0.6 mg/kgBW with IV pethidine at 0.5 mg/kgBW, IV dexamethasone at 0.6 mg/kgBW with placebo, and IV pethidine at 0.5 mg/kgBW with placebo to prevent shivering after spinal anesthesia in C-section. No difference was found among the three groups; however, the authors still recommended dexamethasone as a post-anesthesia shivering treatment, because other drug interactions with pethidine could cause respiratory depression [22].

The present study had several limitations. First, the effect of surgical stimulation factors on nausea and vomiting were not investigated. Second, there was a relatively small sample size. Third, although granisetron appeared to be effective in reducing nausea, vomiting, and shivering incidence, this has not been verified. Further reviews with larger sample sizes are needed to study the extent of surgical factors in affecting nausea and vomiting, as well as comparing granisetron in combination with other antiemetics to prove its effectiveness.

Conclusion

The combination of higher dose granisetron and dexamethasone was superior in treating nausea, vomiting, and shivering. A lower dose of IV granisetron was as effective as the higher dose granisetron when combined with IV dexamethasone in reducing nausea incidence when used as a premedication in C-section. Higher dose of granisetron combined with IV dexamethasone was more effective than just low-dose granisetron in reducing shivering incidence. All doses of granisetron were equally effective in preventing vomiting and no adverse event was found.

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