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Research Article

Efficacy of Granisetron in the Treatment of Nausea and Vomiting Post-Cesarean Section (A Single Centre Retrospective Cohort Study)

Nanako Jonai[1], Tadahiro Shoji[2*], Tomonobu Kanasugi[1], Yuki Yodogawa[1], Ryosuke Takeshita[1], Rikako Ito[1], Marina Abe[1]

[1]Department of Obstetrics and Gynecology, Iwate Prefectural Ofunato Hospital, Ofunato city, Iwate, 022-0002, Japan

[2]Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Yahaba town, Iwate, 028-3695, Japan

***Corresponding author**: Tadahiro Shoji, Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Yahaba town, Iwate, 028-3695, Japan

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Abstract

Background: The prevention of postoperative nausea and vomiting (PONV) post-cesarean section improves clinical outcomes. We introduced granisetron (GS) administration for PONV prevention post-cesarean section soon after its approval by Japanese insurance. In this study, we retrospectively evaluate the efficacy and safety of GS.

Materials and Methods: Eighty patients who underwent cesarean section between November 2021 and September 2022 were included in the study. GS was administered intravenously post-cesarean section delivery of fetus. The presence of nausea and vomiting, and the number of antiemetic medications administered within 24 h post spinal anesthesia were evaluated from medical records. Complete response (CR) and complete control (CC) rates were calculated and compared between the 0-6 and 6-24 h periods post spinal anesthesia. Treatment-related adverse events (AEs) were evaluated as per the Common Terminology Criteria for CTCAE v5.0-JCOG.

Results: CR and CC rates were 96.2% and 93.8% at 0-6 h and 100% and 97.5% at 6-24 h post spinal anesthesia, respectively. No grade 3 or higher AEs were associated with GS administration.

Conclusions: GS administration for prevention of PONV in cesarean section resulted in high CR and CC rates, as well as manageable AEs. GS administration thus demonstrates a high potential for complete prevention of PONV.

Keywords: Granisetron; PONV; Cesarean Section

Introduction

Postoperative nausea and vomiting (PONV) cause significant distress and pain that lead to a delay in recovery [1]. PONV is frequently observed after cesarean sections, with an over 50% rate of occurrence that is determined by a variety of factors [2]. PONV increases the burden on patients and medical staff apart from adversely affecting newborns [3]. The Society for Obstetric Anesthesia and Perinatology (SOAP) statement issued by the American Society of Obstetric Anesthesiologists recommends the use of at least two of three distinct categories of antiemetic agents, including 5-hydroxytryptamine 3 (5-HT3) receptor antagonists, steroids, and D2 receptor antagonists to prevent PONV in cesarean sections [4]. Our institution, routinely administered 10 mg metoclopramide, a D2 receptor antagonist, prior to admission to the operating room, and an additional 10 mg postoperatively on the appearance of symptoms. The 5-HT3 receptor antagonist's ondansetron (OND) and granisetron (GS) were sanctioned to be

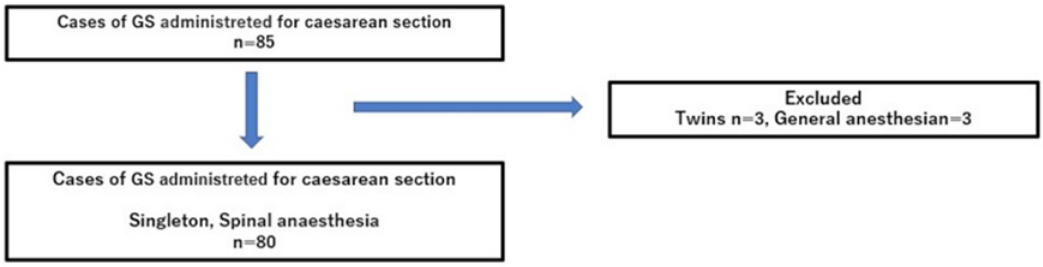
covered by insurance for the prevention and treatment of PONV on August 30, 2021 in Japan. Subsequently, our institution adopted a policy of administering 1 mg GS in September 2021, and specifically for the prevention of PONV in November 2021. This retrospective cohort study was conducted as a pilot for future prospective studies in order to evaluate the usefulness of GS administration to prevent and treat PONV in cesarean sections.

Patients and Methods

This study was approved by the Ethics Committee of Iwate Prefectural Ofunato Hospital (Approval number: R4-18). The need for informed consent was waived on account of the nature of the study.

Patients

Of the 85 cesarean sections performed at our institution from November 2021 to September 2022, 80 patients who were administered 1 mg GS intravenously post-delivery via cesarean section were included. The five excluded cases comprised three cases that were converted to general anesthesia, and two cases of twin pregnancies (Figure 1). Clinical characteristics, including age, height, weight, BMI, number of previous cesarean sections, gestational age at which cesarean section was performed, duration of operation, volume of blood loss, complaints of nausea and vomiting at 0-6 h and 6-24 h post spinal anesthesia, and details of antiemetic's administered were retrieved from medical records.



Abbreviations: GS, Granisetron

Figure 1: Patient disposition.

Spinal Anesthesia and Cesarean Section

Patients were allowed to eat until the evening before the day of scheduled surgery and drink water up to 2 h prior to entering the operating room. Immediately after entering the operating room, 10 mg metoclopramide was administered intravenously. This was followed by single-shot spinal anesthesia via rapid administration of a colloidal solution containing 10-12 mg high-density bupivacaine, 10 μg fentanyl, and 0.1 mg morphine. Post initiation of anesthesia, patients were managed with phenylephrine and ephedrine to maintain a systolic blood pressure above 100 mmHg. Oxytocin, a uterine constricting agent was injected intravenously at a dose of 2.5 units post fetus delivery, while an additional 5 units were infused with 100 ml of saline simultaneously. In the case with poor uterine contraction after 2 min, an additional bolus of 2.5 units was injected intravenously, with provisions in our standard operating protocol to employ a second-line if contractions remained poor thereafter. Postoperative pain was managed with 1000 mg acetaminophen every 6 h, and 60 mg loxoprofen as per requirement after patients started receiving water. Additionally, 10 mg metoclopramide was administered within 24 h of spinal anesthesia to counter PONV.

Evaluation

The following definitions were employed to assess response to GS: i) complete response (CR) i.e., complete arrest/prevention of vomiting with no vomiting-related events and no requirement for antiemetic treatment or rescue therapy; and ii) complete control (CC) i.e., complete control of vomiting-related episodes characterized by mild nausea with no requirement for antiemetic treatment or rescue therapy. CR and CC rates were calculated 0-6 h and 6-24 h post spinal anesthesia and compared. Treatment-related adverse events (AEs) were evaluated as per the Common Toxicity Criteria for Adverse Events v5.0 JCOG Japanese version (CTCAE v5.0-JCOG) [5]. The severity of nausea and vomiting were classified as follows: Nausea Grade 1: Loss of appetite without alteration in eating habits, Grade2: Oral intake decreased without significant weight loss, dehydration or malnutrition, Grade3: Inadequate oral caloric or fluid intake; tube feeding, TPN (Total Parenteral Nutrition), or hospitalization indicated. Vomiting Grade1: Intervention not indicated, Grade2: Outpatient IV hydration; medical intervention indicated, Grade3: Tube feeding, TPN, or hospitalization indicated, Grade4: Life-threatening consequences, Grade5: Death.

Statistical analysis

The Student's t-test was used for continuous variables, and the chi-squared test was used to compare statistical differences between the two groups. Statistical significance was set at P <0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) which is a modified version of R commander designed to add statistical functions frequently used in biostatistics [6].

Results

The clinical characteristics of the 80 patients are presented in Table 1. Of these, 41 patients underwent a cesarean section for the first time and 39 patients underwent repeat cesarean sections. The patients had a median age of 31 (range 19-42) years, and the median height, weight, and BMI were 157 (range 148-172) cm, 65 (range 44.8-93.7) kg, and 26.2 (range 19.6-37.6) respectively. The median gestational age at the time of cesarean section was 38 (range 34-41) weeks. Additionally, the median duration of operation and blood loss were 49 (range 29-81) min and 620 (range190-2230) g, respectively.

	Median	Range
Age (years)	31	19-43
Height (cm)	157	148-172
Weight (kg)	65	44.8-93.7
BMI	26.2	19.6-37.6
Week of cesarean section performed (weeks)	38	32-41
Operating time (minutes)	49	29-81
Blood loss (g)	620	190-2230

Table 1: Patients characteristics.

Grade1 nausea that did not affect oral intake was reported by 5 and 2 patients in the 0-6 and 6-24 h periods post spinal anesthesia, respectively. A total of 3 patients complained of grade2 vomiting that led to the administration of a single dose of metoclopramide in the 0–6 h period post spinal anesthesia and none complained of the same in the ensuing 6-24 h period. Notably, none of the patients suffered severe nausea that precluded oral intake. The CR and CC rates were 96.2% and 93.8% at 0–6 h, and 100% and 97.5% at 6-24 h after spinal anesthesia, respectively. No statistically significant differences were evident between the CR and CC rates calculated for the 0-6 and 6-24 h periods post-cesarean section (CR: P=0.443, CC: P=0.245) (Table2).

	0-6h after spinal anesthesia (%)	6-24h after spinal anesthesia (%)	P value
Complete response rate	96.2	100	0.443
Complete control rate	93.8	97.5	0.245
Grade1 nausea	5 (7.5)	2 (2.5)	NA
Grade2 vomiting	3 (3.7)	0 (0)	NA
Administrated of metoclopramide	3 (3.7)	0 (0)	NA

Abbreviations: h, hours; NA, not available

Table 2: Results.

Two patients were found to develop grade 1 AST and ALT elevation within 24 h of spinal anesthesia and no other grade 3 or higher AEs due to GS administration were observed.

Discussion

While PONV is not a life-threatening complication, nausea- and vomiting-related AEs accounted for approximately 30% of postoperative AEs that patients want to avoid, as per a survey [7]. The well-established Apfel score for PONV risk assessment awards one point for each of the following: female, non-smoker, history of PONV or motion sickness, and postoperative opioid use [7,8] (Table3).

Preoperative factor
- female
- History of PONV or motion sickness
- Non-smoking
- Younger age
Intraoperative factor
- General anesthesia
- Used of volatile anesthetics and nitrous oxide
- Duration of anesthesia
- Type of surgery (cholecystectomy, laparoscopic, gynecological)
Postoperative factor
- Postoperative opioids

Abbreviations: PONV, Postoperative nausea and vomiting

Table 3: Risk factors for PONV.

Apart from the Apfel score, age, duration of anesthesia, surgical technique, and use of general or inhalation anesthesia have been cited as risk factors for PONV. The implementation of 3-4 countermeasures, including GS and OND is recommended in high-risk PONV cases [1]. All patients who underwent cesarean section were unambiguously female, with several being non-smokers. Further, on account of the postoperative usage of opioids at our institution, most patients were categorized as high risk for PONV with an Apfel score of 3 or more. The SOAP statement recommends the following: (1) Thorough management of blood pressure using crystalloid fluid load in combination with vasopressors; (2) not removing the uterus from the abdominal cavity during uterine suturing and not performing routine intraperitoneal lavage; and (3) using at least two of the three distinct categories of antiemetic agents, including 5-HT3 receptor antagonists, steroids, and D2 receptor antagonists [4] (Table4).

- Limit fasting interval
(Solids up to 8 h, Clear fluids up to 2 h before cesarean delivery)
- Preoperative and intraoperative fluid management and use of vasopressor
- Avoiding uterine exteriorization
- Avoidance of intraabdominal saline irrigation
- Used prophylactic antiemetic's with different mechanisms of action
(5-HT3 antagonist, Glucocorticoid, D2 receptors antagonist)

Abbreviations: h, hours; 5HT3, 5-hydroxytryptamine 3; D, dopamine; SOAP, Society for Obstetric Anesthesia and Perinatology

Table 4: SOAP statement

In accordance with this, we administer 0.1 mg morphine in the subarachnoid spinal cord and 1000 mg acetaminophen 6 hourly for post-cesarean pain. Although morphine-induced nausea and vomiting has been reported in some patients, a dose of 0.1 mg administered in the spinal cord has demonstrated good analgesia with no greater risk of PONV in the 12-24 h period post-surgery [9]. Additionally, regular acetaminophen administration is known to reduce PONV while maintaining analgesia [10]. Dexamethasone at a dose of 4-8 mg has also been shown to be efficacious in the prevention of post-cesarean section PONV [11], leading to its adoption as one of the three drugs included in the SOAP statement. However, while GS and OND were approved for insurance coverage as treatments for PONV in Japan in August 2021, dexamethasone was not. Dasgupta M et al. reported a CR rate of 82.5% in patients treated with GS versus a rate of 45% in patients administered a placebo in a study conducted on 80 patients who underwent cesarean sections at 0–4 h post spinal anesthesia [2]. The high CR rate in our study may be accounted for by the fact that apart from adhering to the SOAP statement, we also provide postoperative pain management as described above. We observed no statistically significant differences in the CR and CC rates at 0-6 hours and 6-24 h post spinal anesthesia, which may be a consequence of the persistence of the antiemetic effect of GS for 24 h, along with the proper implementation of the aforementioned SOAP guidelines and postoperative pain management, all of which in conjunction may have resulted in suppression of PONV. While none of the patients in this study experienced grade 3 or higher AEs due to GS administration, Grade 1 AST and ALT elevations were observed in two patients who improved after 3 days. Thus, the AEs associated with GS administration were found to be mild and manageable. PONV is known to occur more frequently and acutely in cases of severe hyperemesis [12]. One patient of several episodes of vomiting and requiring metoclopramide administration was observed. We considered this patient to be at high risk for PONV because of had severe hyperemesis in early pregnancy. The present study is limited by the fact that it is a single-institute retrospective cohort study. Secondly, the results of this 1-arm study were not compared with those of patients who did not undergo GS. We, therefore, intend to validate these preliminary findings in a multicenter phase II trial, and a subsequent randomized phase III trial. Thirdly, the quality of evaluations may be compromised since they were not conducted via questionnaires. Finally, appropriate risk assessment and selection of high-risk patients requiring GS administration are considerable challenges. This is the first retrospective cohort study on Japanese patients that evaluated the efficacy of GS administration post-cesarean section. Our findings support the aggressive administration of this drug in cesarean sections on account of high CR and CC rates and manageable AEs.

Conclusions

This retrospective study on the usefulness of GS administration for PONV post-cesarean section under spinal anesthesia revealed high CR and CC rates. Thus, the administration of GS safely prevented PONV, with no incidence of grade 3 or higher AEs. These results imply that GS administration in conjunction with appropriate perioperative management may be useful in the prevention of PONV.

Conflicts of interest: All authors declared that there are no conflicts of interest.

Authors' contributions

Conceptualization: Jonai N, Shoji T

Literature Search and date collection: Kanasugi T, Takeshita R, Yodogawa Y, Ito R, Abe M

Writing-Original Draft Preparation: Jonai N

Writing-Review and Editing: Shoji T

All authors have read and agreed to the published version of the manuscript.

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