Intrathecal Fentanyl Versus Intravenous Granisetron for the Prevention of Perioperative Nausea and Vomiting During Cesarean Delivery

Original Article

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ABSTRACT

Introduction: About 66% of cesarean sections (CS) done under intrathecal (IT) anesthesia experience intraoperative nausea and vomiting (IONV). This may increase the aspiration risk, induce discomfort for the patient, and complicate the surgery. Numerous strategies have been employed to diminish the occurrence of perioperative nausea and vomiting; however, they contribute to increased costs and adverse effects.

Objective: To assess the efficacy of IV Granisetron compared to IT fentanyl in reducing Perioperative nausea and vomiting during CS performed under IT anesthesia.

Methods: Ninety patients, aged 18 to 45, with ASA grade I or II scores, were included in the study for CS under spinal anesthesia. 3 groups were involved in the study: the IV Granisetron (1mg) group, the IT fentanyl (20µg) group, and a control group. The frequency of nausea and vomiting was evaluated intraoperatively using the nausea and vomiting evaluation score. Postoperative pain was evaluated using the VAS, and unpleasant symptoms such as headache and pruritus were also noted.

Results: Patients in groups F and G exhibited significantly reduced IONV compared to group C (*P* value <0.05). Moreover, group F had significantly fewer patients (*P* value <0.001) than groups G and C, who got analgesics within one-hour post-surgery, and no severe side effects were seen.

Conclusion: In CS performed under IT anesthesia, fentanyl (20 micrograms) may be more efficacious in mitigating IONV compared to IV Granisetron (1mg).

Key Words: Caesarean delivery; fentanyl; granisetron; nausea and vomiting.

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INTRODUCTION

Perioperative nausea and vomiting impact about 66% of women during CS under IT anesthesia. Mitigating postoperative nausea and vomiting (PONV) is a primary concern for women after CS and is incorporated into the enhanced recovery protocols following CS. Numerous strategies have been employed to diminish the occurrence of perioperative nausea and vomiting; however, they contribute to increased costs and adverse effects[1].

IT lipophilic opioids, such as fentanyl, when combined with bupivacaine as an adjuvant, have demonstrated a reduction in the incidence of IONV and PONV; they are cost-effective and exhibit few significant adverse effects. Therefore, it may serve as an effective option for preventing IONV during CS performed under IT anesthesia[2]. Intravenous 5-HT3 antagonists, such as Granisetron, effectively mitigate perioperative nausea and vomiting with a minimal occurrence of adverse effects; nevertheless, their expense may hinder routine application[3].

This study's main outcome was to compare IT fentanyl versus IV Granisetron in preventing IONV during CS conducted under IT anesthesia. The secondary aim of the study was to evaluate the efficacy of IT fentanyl in providing postoperative analgesia, reducing postoperative analgesic requirements, and its impact on patient hemodynamics.

PATIENTS AND METHODS

We conducted this prospective randomized controlled study following clearance from the local ethical board and the acquisition of informed written consent from all participants. The trial was registered under the clinical trial identifier NCT05474001.

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The study comprised 90 patients classified as ASA grade I or II, aged between 18 and 45 years, who were undergoing cesarean delivery with spinal anesthesia.

Individuals meeting the subsequent criteria were excluded from the study:

- History of nausea and vomiting, including motion sickness, hyperemesis gravidarum, and administration of antiemetic medications during the preceding 2 hours prior to the operation.
- Allergic reaction to the drugs utilized in the trial.
- Complex gestation as placenta previa, preeclampsia, and eclampsia.
- Multiple gestation.
- Fetal distress.
- Patient noncompliance.

Before the surgery, all patients underwent a comprehensive assessment involving a detailed medical history, examination, and investigations, which included a blood count, liver and kidney functions, and coagulation profile tests.

Upon arriving in the operating room, a 20 G IV was established, and the patient was attached to the fundamental anesthetic monitoring. Pre-anesthetic hydration was administered with a 500ml bolus of Ringer's lactate immediately before the procedure.

All patients were given spinal anesthesia using heavy bupivacaine 2ml (10mg) at the L3-L4 lumbar segments and thereafter positioned supine with a fifteen-degree wedge tilt to the left to avoid inferior vena cava compression. They were then randomly allocated into three groups using the closed envelope method.

1. Group (F) Fentanyl group (*n*= 30): IT bupivacaine plus 0.5mL fentanyl (20µg), followed by IV 1mL of normal saline, immediately after spinal anesthesia.

2. Group (G) Granisetron group (*n*= 30): IT bupivacaine plus 0.5mL normal saline, followed by IV 1mL (1mg) Granisetron, immediately after spinal anesthesia.

3. Group (C) Control group (*n*= 30): IT bupivacaine plus 0.5mL normal saline, followed by IV 1mL normal saline, immediately after spinal anesthesia.

We recorded the frequency of the IONV and the frequency of the PONV within the first 24 hours post-surgery, utilizing the nausea and vomiting assessment score.

Nausea assessment score

0	No
1	Mild requiring no medications
2	Requiring medications
3	Resistant to medications

Vomiting assessment score

0	No
1	Single event
2	Repeated requiring medication
3	Resistant to medication

Basic Hemodynamics (HR, BP, RR, SPO2) were documented upon arrival in the operating room before anesthesia and subsequently every 5 minutes after the administration of the IT anesthetic for 40 minutes post-block. Bradycardia (HR <55) was managed using IV 0.5mg atropine. Hypotension (mean arterial pressure below 25% of preoperative value) treated with 5mg of ephedrine intravenously.

Postoperative pain evaluation with the Visual Analog Scale (VAS) every 15 minutes during the initial hour post-surgery, followed by assessments at 3, 6, 9-, 12-, 18-, and 24-hours post-surgery. VAS scores exceeding 3 were treated with a ketorolac IV infusion of 30mg every 8 hours, and the total ketorolac usage within the first 24 hours post-surgery was documented.

Visual analog Scale (VAS)

0	No Pain
1:3	Mild
4:6	Moderate to severe
7:9	Very severe
10	Worst pain

Statistical analysis and Sample size calculation

The sample size calculation was performed using G. power 3.1.9.2 (Universitat Kiel, Germany). The sample size was calculated based on the following considerations: 0.05 α error and 80% power of the study to demonstrate a 21% decrease in the overall cumulative incidences of PONV with intrathecal fentanyl than intravenous granisetron (25% according to a previous study[4]. Four cases were added to overcome dropout. Therefore, 30 patients will be allocated in each group.

Statistical analysis of numerical data was carried out using mean, SD, minimum, and maximum of the range, whereas for categorical data, number and percentage were

used. Analysis for quantitative variables was done using the one-way ANOVA test for parametric data between the two groups and the post-hoc analysis for the two groups. The Paired sample *t*-test was used for parametric data analysis between the two variables in each group. The χ^2-test was used for qualitative data analysis between groups. The level of significance at the *P* value was considered less than 0.05.

RESULTS

Regarding the demographic data and the operative duration, there was no statistically significant difference between the three groups of the study regarding the age, height of the patient, or the duration of surgery. The weight of the patients in group F was significantly lower than in group G (*P* value <0.001). The weight of the patients in group G was significantly higher than in group F and group C. There was no significant difference regarding the patient's weight between groups F and C (Table 1).

When we analyzed the intraoperative hemodynamics of the study population, we found that Systolic and diastolic blood pressure measurements were not significantly different among the three groups at all measurement points (Figure 1, Table 2).

Also, the heart rate was insignificantly different between the three groups of the study before anesthesia and at 5, 10, 15, 20, 30, 35, and 40 minutes after the neuraxial block, however, at 25min. after anesthesia, the heart rate was significantly lower in group C than in group G (*P* value= 0.023) (Table 3).

Regarding the intraoperative complications, intraoperative nausea and vomiting were significantly lower in group F and group G than in group C (*P* value <0.05). Intraoperative hypotension was significantly lower in Group F than in Group G and Group C (*P* value <0.001) (Table 4 and Figure 2).

Table 1: Demographic data and duration of operation of the studied groups:

		Group F (*n*= 30)	Group G (*n*= 30)	Group C (*n*= 30)	*P* value	Post Hoc
Age (years)	Mean±SD	29.8±7.02	32.1±5.39	30.2±4.97	0.288	
Weight (Kg)	Mean±SD	76.3±7.36	83.1±5.88	75.6±6.27	<0.001*	P_1<0.001* P_2= 0.9 P_3<0.001*
Height (cm)	Mean±SD	168.2±3.9	168.5±3.9	167.9±3.56	0.828	
Duration of operation (min)	Mean±SD	37.2±4.29	37±4.66	37.3±4.3	0.958	

*: Significant as *P* value ≤0.05; P_1: *P* value between group F and group G; P_2: *P* value between group F and group C; P_3: *P* value between group G and group C.

Table 2: Intraoperative Diastolic blood pressure of the studied groups:

	Group F (*n*= 30)		Group G (*n*= 30)		Group C (*n*= 30)		*P* value
	Mean	SD	Mean	SD	Mean	SD	
Before induction	72.97	15.09	75.50	8.34	74.67	9.09	0.675
5 min	60.83	9.11	61.33	8.40	64.33	7.74	0.226
10 min	62.17	6.65	65.83	5.88	63.17	7.13	0.089
15 min	67.67	7.51	63.20	13.27	68.33	8.54	0.107
20 min	69.17	5.88	67.17	5.83	89.03	115.85	0.381
25 min	68.83	7.51	70.33	6.56	72.00	9.88	0.322
30 min	72.41	8.62	69.00	7.24	68.39	5.78	0.086
35 min	71.05	7.74	68.95	6.58	72.86	6.99	0.300
40 min	72.86	4.88	69.00	5.68	69.29	8.38	0.439

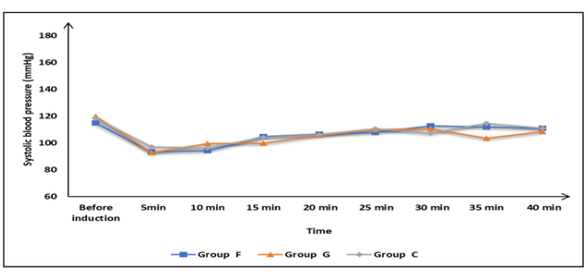

Figure 1: Systolic blood pressure of the studied groups.

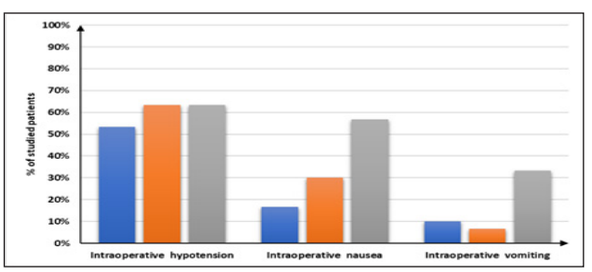

Figure 2: Intraoperative complications of the studied groups.

Table 3: Heart rate measurements of the studied groups:

	Group F (*n*= 30)		Group G (*n*= 30)		Group C (*n*= 30)		*P* value	Post Hoc
	Mean	SD	Mean	SD	Mean	SD		
Before induction	96.50	10.18	102.33	10.21	97.90	12.81	0.112	
5 min	92.33	25.86	89.33	19.82	88.33	16.21	0.746	
10 min	92.17	25.48	84.50	21.11	81.83	18.55	0.171	
15 min	94.73	20.12	87.33	19.11	89.00	21.39	0.336	
20 min	97.83	19.37	95.17	18.07	93.83	21.88	0.730	
25 min	96.17	15.90	101.67	13.22	91.50	14.69	0.031*	P_1= 0.318 P_2= 0.436 P_3= 0.023*
30 min	94.17	12.60	96.33	17.02	91.25	12.14	0.394	
35 min	96.43	10.51	95.79	10.96	95.81	14.14	0.982	
40 min	88.33	16.20	93.33	16.28	96.43	11.07	0. 561	

*: Significant as *P* value <0.001.

Table 4: Intraoperative complications of the studied groups:

	Group F (*n*= 30)	Group G (*n*= 30)	Group C (*n*= 30)	*P* value
Intraoperative hypotension	16(53.33%)	19(63.33%)	19(63.33%)	<0.001*
Intraoperative nausea	5(16.67%)	9(30%)	17(56.67%)	<0.001*
Intraoperative vomiting	3(10%)	2(6.67%)	10(33.33%)	<0.001*

*: Significant as *P* value <0.001.

Regarding the postoperative complications, Postoperative nausea and vomiting did not happen in any patient in groups F and G. However, it happened in 16 patients (53.33%) of group C, which is considered statistically significant (*P*<0.001). Postoperative itching and headache did not occur in any patient of the 3 groups.

At 15min, 30min, and 18 hours postoperative, there was no significant difference in VAS between the three groups. At 45 minutes postoperative, VAS was significantly lower in group F. At 3 and 12 hours postoperative, VAS was significantly higher in group F. At 6 and 12 hours postoperative, VAS was significantly lower in group G. At 9 hours, VAS was significantly lower in groups F and C than in group G. (Figure 3).

Patients who required analgesia within 1hr post-operative, and total analgesic consumption of ketorolac within 24h postoperatively were significantly lower in Group F than Group G and Group C and lower in Group G than Group C (*P* value <0.001) (Table 5).

Table 5: Patients required analgesia and total analgesic consumption of ketorolac in 24h of the studied groups:

		Group F (*n*= 30)	Group G (*n*= 30)	Group C (*n*= 30)	*P* value	Post Hoc
Patients required analgesia within 1h post-operation	Yes	18(60%)	25(83.33%)	30(100%)	<0.001*	
Total analgesic consumption of ketorolac in 24h (mg)	Mean±SD	41±14.7	55±22.4	78±23.1	<0.001*	P_1= 0.025* P_2<0.001* *P3*<0.001

*: Significant as *P* value <0.001.

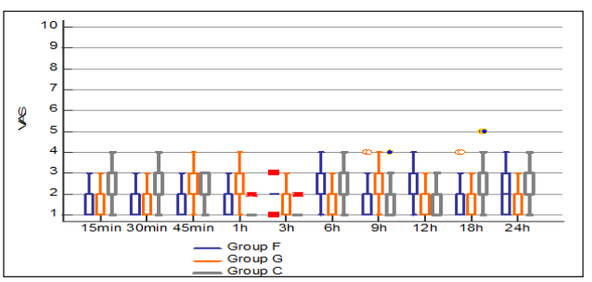

Figure 3: VAS measurements of the studied groups.

DISCUSSION

Perioperative nausea and vomiting in nearly 66% of women during CS under IT anesthesia. Mitigating PONV is crucial for women after CS and is incorporated into the enhanced recovery protocols following CS. Numerous techniques have been employed to diminish the occurrence of perioperative nausea and vomiting; nonetheless, they contribute to increased costs and adverse events[1].

IT opioids, such as fentanyl, when combined with bupivacaine as an adjuvant, have demonstrated a decline in the incidence of nausea and vomiting; they are cost-effective and exhibit minimal severe side effects. Therefore, it may serve as an effective option for the prophylaxis of emetic episodes during CS done under IT anesthesia[2].

Intravenous 5-HT3 antagonists, such as Granisetron, effectively mitigate perioperative nausea and vomiting with few side effects; nevertheless, their expense may hinder routine application[3].

This trial was undertaken to check the efficacy of IT fentanyl compared to intravenous IV Granisetron in preventing perioperative nausea and vomiting during CS under IT anesthesia, as well as to assess the effectiveness of IT fentanyl in improving postoperative analgesia.

This prospective randomized controlled trial involved 90 patients, aged between 18 and 45 years, undergoing CS under IT anesthetic.

This study found no statistical significance concerning demographic characteristics like age, height, ASA physical status score, and surgical procedure time; nonetheless, Group F exhibited a considerably lower weight compared to Group G, while Group G had a higher weight than Group C.

This study showed that the incidence of IONV in groups F and G was significantly less than in group C (*P* value <0.05). This finding aligns with the results of Botea *et al*., (2023), who conducted a study involving 190 patients to evaluate the quality of perioperative analgesia, satisfaction levels, and adverse reactions during elective cesarean sections under IT anesthesia with the addition of fentanyl or morphine to bupivacaine. Pain scores were documented perioperatively for 72 hours (during both rest and movement), along with overall postoperative satisfaction and analgesic-related adverse effects. Fentanyl exhibited markedly fewer adverse events, including severe itching, nausea, vomiting, and disorientation during first mobilization[5].

In contrast, Ghasemloo *et al*., (2021)[6] recommended the administration of Granisetron or Ondansetron. 5-HT3 receptor antagonists appear to be the optimal selection for the management of nausea and vomiting. These medications lack the extrapyramidal adverse effects associated with metoclopramide and are suitable for managing nausea and vomiting in patients undergoing CS with IT anesthesia. They are an efficacious and well-tolerated medication with an improved safety profile, functioning by inhibiting 5-HT 3 receptors on vagal afferent terminals and centrally in the region postrema.

In the present study, intraoperative hypotension was markedly reduced in Group F compared to Group G and Group C (*P* value <0.001). Spinal anesthetic for cesarean delivery frequently induces maternal hypotension. This may result from diminished systemic vascular resistance, leading to hypotension, which is aggravated in pregnant by the inferior vena cava compression, partially offset by elevated stroke volume and HR, as stated by Langesaeter and Dyer (2011)[7]. The current investigation revealed variability in VAS values among groups at various follow-up intervals. At 15 minutes, 30 minutes, and 18 hours postoperatively, there was no significant difference in VAS among the three groups. At 45 minutes postoperatively, the Visual Analog Scale (VAS) was markedly lower in group F compared to groups G and C. At 3 and 12 hours postoperative, the VAS was significantly elevated in group F compared to groups G and C; conversely, at 6 and 12 hours postoperative, the VAS was significantly reduced in group G relative to groups F and C. At 9 hours, the VAS was markedly lower in groups F and C compared to group G. In concurrence with Uppal *et al*., (2020)[8], who performed a comprehensive study to evaluate the efficacy of fentanyl when combined with IT bupivacaine alone and with bupivacaine and morphine for IT anesthesia in cesarean birth. The addition of fentanyl to intrathecal bupivacaine–morphine provided comparable advantages, notably a considerable decrease in the requirement for intraoperative supplementary analgesia.

According to the study findings, postoperative nausea and vomiting were significantly reduced in groups F and G compared to group C (*P* value <0.001). No patient in any of the three groups had itching or headache. This finding aligns with the study by Safiya I and Ganapati (2015)[9], which assessed the clinical efficacy of intrathecal fentanyl and midazolam in preventing nausea and vomiting in a randomized trial involving 90 women aged 18 to 31 years, enrolled for elective CS under IT anesthesia. Participants were randomly allocated into three equal groups, concluding that IT fentanyl 12.5 micrograms or midazolam 2 milligrams both diminish the occurrence and degree of nausea when provided alongside bupivacaine for CS. Furthermore, Iqbal (2019) demonstrated that a low dose of IT fentanyl at 12.5µg, when administered as an adjunct to 0.5% heavy bupivacaine for IT anesthesia in parturients undergoing cesarean sections, reduces the frequency of vomiting during the perioperative period while enhancing analgesic quality without significant adverse effects on either the parturient or the newborn. Our study findings aligned with those of Cooper *et al*., (1997), who noted a significant reduction in nausea and vomiting among patients administered intrathecal fentanyl after cesarean section[10].

CONCLUSION

IT fentanyl may be superior to intravenous Granisetron in reducing IONV during cesarean sections conducted

under IT anesthesia. Intrathecal fentanyl is efficacious in extending postoperative analgesia and reducing the intake of analgesics post-surgery while exhibiting fewer adverse effects such as hypotension, pruritus, and headache.

DECLARATIONS OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study complies with regional and institutional ethical guidelines and with declaration of Helsinki. A written informed consent was obtained from the parents of our case for her participation.

SUBMISSION DECLARATION AND VERIFICATION

All authors of this paper have approved the final version to be submitted; The contents of this manuscript have not been copyrighted or published previously nor under consideration for publication elsewhere; The contents of this manuscript will not be copyrighted, submitted, or published elsewhere, while acceptance by the Journal is under consideration; There are no directly related manuscripts or abstracts, published or unpublished, by any authors of this paper. A written informed consent to publish the clinical data was obtained from the parents of our patient involved in this case report.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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