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Hyoscine butyl-bromide versus ondansetron for nausea and vomiting during caesarean delivery under spinal anaesthesia. A randomized clinical trial

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ABSTRACT

Background: The unopposed vagal activity with sympathetic block and maternal bradycardia that is likely to occur with phenylephrine infusion might be some causes of intraoperative nausea and vomiting (IONV) during spinal anaesthesia. We aimed at comparing hyoscine butyl-bromide (HBB) and ondansetron in reduction of intraoperative bradycardia and thus IONV in women undergoing caesarean delivery (CD).

Methods: In a randomized, double-blind, placebo-controlled trial, women undergoing elective CD were randomly assigned to administer either IV HBB 20 mg, ondansetron 8 mg, or the same volume of 0.9% saline right before spinal anaesthesia. The primary endpoint was the incidence of IONV. Secondary endpoints included intraoperative maternal bradycardia and hypotension and postoperative nausea and vomiting (PONV).

Results: 55 subjects in each group received the assigned intervention. During the intraoperative period, HBB decreased only the incidence of emesis when compared to the control group ($P = 0.046$) while ondansetron statistically decreased the incidence of IONV when compared to the control group ($P = 0.034$). HBB statistically decreased the incidence of intraoperative maternal bradycardia when compared to the controls (1.8% vs 14.5%; OR = 0.1, 95% CI = [0.01, 0.90]; $P < 0.039$). Compared to the control group, ondansetron was superior to HBB in reducing PONV ($P = 0.001$ & 0.57), respectively.

Conclusions: In women scheduled for CD with spinal anaesthesia, prophylactic HBB was as effective as ondansetron in reducing intraoperative emesis, with the added benefit of the less incidence of intraoperative bradycardia than ondansetron. Meanwhile, Ondansetron reduced the incidence of PONV significantly.

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1. Introduction

The total incidence of intraoperative nausea and vomiting (IONV) during regional anaesthesia for caesarean delivery (CD) varies greatly, reaching 80%, according to the anaesthetic technique utilized (spinal, epidural, or combination spinal epidural), as well as the preventive and curative interventions performed [1].

Since spinal anaesthesia is both secure and efficient for CD, it has become the preferred anaesthetic method for elective CDs. One of the main causes of IONV is, however, maternal hypotension related to spinal anaesthesia. This condition (IONV) is thought to be caused by low blood flow to the brain and gut, which stimulates the brainstem's vomiting centre and causes serotonin to be released [2,3].

Although bolus phenylephrine administration efficiently improves hypotension, it does not stop intraoperative nausea in such parturients, which may be linked to preexisting hypotension, and this may negatively impact maternal satisfaction [4,5]. Meanwhile, prophylactic phenylephrine infusion was found to be superior to bolus dosing in reducing intraoperative nausea, on the other hand, there was no significant reduction in intraoperative vomiting [6].

The sympathetic block that allows vagal activity to go unopposed and maternal bradycardia that is likely to occur with phenylephrine infusion might be some causes of IONV during spinal anaesthesia [7,8].

Anticholinergics have been shown to have antiemetic actions via blocking central muscarinic and cholinergic emetic receptors [9,10]. But numerous investigations have produced contradictory results, owing mostly to variations in research design and surgical procedures utilized. Atropine is possibly the most widely used anticholinergic medication. Nevertheless, hyoscine butyl bromide (HBB) is a semisynthetic derivative of scopolamine with a quaternary ammonium composition that leads to less transmission across the blood-brain barrier, resulting in lower incidences of confusion and other central

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adverse effects [11,12]. Because the medulla oblongata lacks a well-developed blood-brain barrier, hyoscine butyl-bromide, a quaternary ammonium, remains able to act on the chemoreceptor trigger zone. This enhances the antiemetic effects it causes by acting locally on the smooth muscle of the gastrointestinal tract [13].

Ondansetron is an antiemetic that is often used during CD which is not without adverse effects, including QT prolongation and Ondansetron-induced extrapyramidal symptoms [14,15].

Therefore, this study aims to compare the efficacy of hyoscine butyl-bromide prophylactic usage on the incidence of intraoperative bradycardia and consequently IONV in women subjected to CD under spinal anaesthesia to that of ondansetron.

2. Materials and methods

The current study was a randomized, double-blind, placebo-controlled trial that was prospectively granted registration at www.clinicaltrials.gov (NCT04785118). The research was conducted at Assiut University Hospital in Egypt between October 2021 and December 2022. The Assiut Medical School Ethical Review Board (Ethical Committee N: 17101500) approved the study protocol in September 2021. Prior to being included in the study, all individuals completed informed consent.

This study included all patients with a single infant pregnancy >32 weeks who were between the ages of 18 and 40, ASA I or II, and scheduled for elective CD under spinal anaesthesia. Patients who met the following criteria were excluded: height between 150 and 180 cm, BMI over 35 kg/m2, contraindication or unwillingness to receive regional anaesthetic. Patients who were taking beta-adrenergic blockers or any other medications that could change the usual reaction to the study treatment, complaining of motion sickness, had recently used antiemetics, or had hyperemesis gravidarum in a previous pregnancy were excluded from the trial.

An online randomizer (https://www.randomizer.org/) was used by a study assistant who did not care for or evaluate patients to create codes that were then enclosed in envelopes that have been sealed and consecutively numbered to randomly assign patients to one of the three study groups. This person also made the solutions used in similar syringes that was labelled "study drug" according to the group they were given to as following:

- **Hyoscine butyl bromide group** (Group H): Just prior to spinal anaesthesia, 20 mg of hyoscine butyl-bromide in 2 ml was administered intravenously.
- **Ondansetron group** (Group O): Just prior to spinal anaesthesia, patients were administered 8 mg of ondansetron intravenously in 2 ml.
- **The control group** (Group C): Just prior to spinal anaesthesia, 2 ml of normal saline was administered intravenously to patients as a placebo.

At that time, both the patient and the anaesthetists administering anaesthesia and evaluating outcomes were unaware of patient allocation.

2.2. Interventions

Preoperative anaesthetic assessment included history, examination, baseline heart rate (HR), and blood pressure (BP) readings (three HR and BP readings were averaged to produce maternal HR and BP baseline values).

All patients received an IV preload of 15 mL/kg of Ringer lactate through a large-bore (18 gauge) intravenous access in the operating room. Transfusion of the first 500 cc was done using a pressure bag.

All parturients had conventional monitoring (NIBP, ECG, and SpO_2). Then the prepared study syringe was given IV just before conduct of the spinal block.

The parturient was seated for midline spinal anaesthesia using a 25-gauge Quincke needle in the vertebral interspace of L3-L4. After ensuring free flow of CSF fluids, started injection of 3 ml solution of 0.5% hyperbaric bupivacaine in dosage of 12.5 mg (2.5 ml) mixed with 25 µg fentanyl (0.5 ml out of a syringe containing 100 µg in 2 ml).

All patients lay supine with a wedge under the right hip to tilt left. Cold sensation was evaluated by applying a frozen sterile water ampule made of plastic along the midclavicular line every 5 min, and the highest sensory level attained was recorded. Surgery was permitted to start after achieving at least a T6 level of block.

Immediately following the subarachnoid injection, a 25 µg/min phenylephrine infusion was started. Subsequently, the rate of phenylephrine infusion was adjusted to maintain a systolic blood pressure (SBP) greater than 80% of the baseline value. However, in cases where the SBP decreased to below 80% of the baseline value despite phenylephrine infusion adjustment, we administered intravenous boluses of 6 mg ephedrine sulphate to treat the hypotension defined as a decrease in SBP to < 80% of the baseline value. Hypertension, defined as a rise in SBP of more than 120% of the baseline value, was treated by discontinuing the phenylephrine infusion, which was then restarted when the SBP returned to < 120% of the baseline value. Bradycardia (HR < 50 beats/min) was treated with 1 mg of intravenous atropine if hypotension existed or withholding the phenylephrine infusion if not. The infusion protocol was maintained until

delivery of the foetus, at which point the attending anaesthesiologist was responsible for the clinical management.

Sociodemographic patient's profile: age, weight, and height were recorded. Heart rate and the SBP were recorded at 5 min before conduction of intrathecal anaesthesia (baseline), 1, 3, 6, 9, 12,15,20, 25, 30, 40- and 50 min, respectively after administering the study drug until the surgery ends.

Postoperative itching was evaluated, and 25 mg iv diphenhydramine was used for treatment.

2.3. Outcome measures

The primary outcome measure was the incidence of IONV. We defined vomiting as emesis with expulsion of gastric contents, retching as emesis without expulsion of gastric contents, and "all emesis" as vomiting, retching, or both. The incidence of nausea and/or all emesis intraoperatively was recorded as a dichotomous variable (yes/no). The secondary outcome measures were the incidence of nausea and/or all emesis in the 24 h after surgery (PONV). The incidence of hypotension was defined as SBP < 80% of the baseline from the time of the subarachnoid injection until delivery. Maternal bradycardia (HR < 50 beats min **−1**) and the foetal heart rate and Apgar score at 1 and 5 min after delivery and the highest sensory level approached at 15 min of spinal anaesthesia were recorded. The presence of intraoperative chest pain, and intraoperative and postoperative confusion were recorded till 6-h postoperative.

2.4. Statistical analysis

On the basis of the results of a previous study showing 56% incidence of IONV in the control group [16]. A sample size of 54 patients in each group was calculated to detect a 50% decrease in the incidence of IONV with $\alpha = 0.05$ and a power of 85%. 55 patients in each group were recruited to compensate for the dropouts.

The data were initially tested for normality of distribution using the Kolmogorov–Smirnov test. The chi-square test compared groups' categorial data. One-way ANOVA examined continuous and ordinal parametric data, while Kruskal-Wallis tested nonparametric data comparing the three groups. IBM SPSS Version 22, 2015, was used to analyse data. P-value <0.05 indicated statistical significance.

3. Results

In this study, 191 individuals were evaluated for eligibility, 18 of whom did not match the criteria, and 8 of whom declined to participate. The other 165 patients were divided randomly into three groups of 55 patients each. All patients (165) were followed up and statistically analysed (Figure 1).

Demographic data, gestational age and sensory block level were comparable between groups (Table 1).

During the intraoperative period, Ondansetron statistically decreased the incidences of nausea, emesis, and both (IONV) when compared to the control group ($P = 0.03$), ($P = 0.009$) and ($P = 0.034$) respectively. Meanwhile, Hyoscine butyl-bromide only decreased the incidence of emesis in comparison to the control group ($P = 0.046$) but, failed to decrease the incidences of nausea and IONV ($P = 0.44$) and ($P = 0.46$), respectively (Table 2).

The incidence of intraoperative maternal bradycardia was decreased significantly by Hyoscine butyl-bromide when compared to the controls (1.8% vs 14.5%; OR = 0.1, 95% CI = [0.01, 0.90]; $P < 0.039$). Also, Hyoscine butyl-bromide was associated with an insignificantly lower incidence of bradycardia than Ondansetron (1.8% vs 7.3%), respectively. The Ondansetron group showed a decreased incidence of intraoperative hypotension when compared to the control group (40% vs 62%; OR = 0.4, 95% CI = [0.19, 0.89]; $P < 0.023$) (Table 2).

The neonatal Apgar scores at 1 and 5 min were insignificantly different between the three groups (Table 3).

As regards the postoperative period, Hyoscine butyl-bromide failed to show a statistically significant reduction in the incidence of postoperative nausea or emesis in comparison to the control group as ondansetron did. The overall 24-h incidences of nausea, emesis and PONV are summarized in (Table 4).

4. Discussion

In this study, we tried to investigate the antiemetic effects of prophylactic intravenous hyoscine butyl-bromide 20 mg, or ondansetron 8 mg on parturients undergoing spinal anaesthesia for CD. We recorded a significantly lower incidence of intraoperative emesis in patients who received hyoscine butyl-bromide. While those who received ondansetron showed lower incidences of intraoperative nausea, emesis, and both (IONV).

The definite cause of IONV during spinal anaesthesia is unknown. However, it has been hypothesized that this is due to the sympathetic block that takes place during spinal anaesthesia, which allows vagal activity to go unopposed. This hypothesis is supported by the observation that atropine was found to be more effective than blood pressure elevation with vasopressors in alleviating nausea during spinal anaesthesia [8]. Ondansetron is an antiemetic acting selectively on 5HT3 receptors at the gastrointestinal tract and centrally at the CTZ

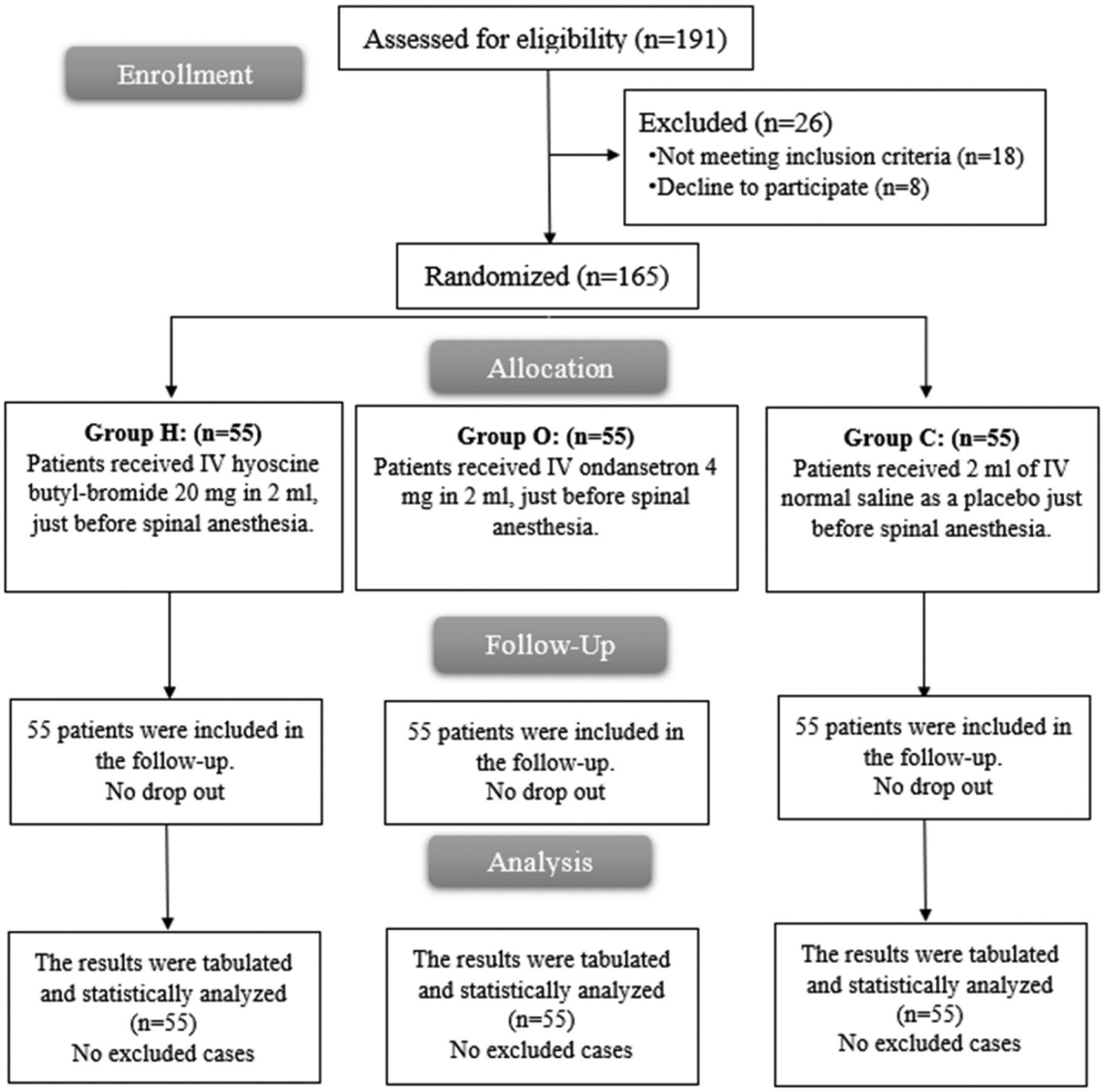

Figure 1. CONSORT flowchart showing patient recruitment.

Table 1. Patient's demographic and clinical data among the three groups.

	Group H ($n = 55$)	Group O ($n = 55$)	Group C ($n = 55$)	P value
Age (years)	27.04 ± 5.17	26.53 ± 5.32	26.82 ± 4.97	0.87
Weight (kg)	70.62 ± 8.18	73.38 ± 9.89	74.07 ± 13.61	0.21
Height (cm)	158.8 ± 3.57	160.24 ± 3.49	158.84 ± 3.67	0.06
BMI (kg/m^2)	28.55 ± 3.52	27.96 ± 2.74	29.31 ± 5.02	0.19
Gestational age (weeks)	37.76 ± 0.94	37.8 ± 0.89	37.67 ± 1.07	0.78
Sensory level at 15 min (dermatome)	T3 (T2 – T4)	T3 (T2 – T4)	T3 (T3 – T5)	0.81

Data are presented as mean±SD, median (25-75th percentiles). BMI = Body mass index.

and vagal nerve terminals [1]. Anticholinergics which are effective in reducing nausea and vomiting act by blocking central muscarinic receptors in the afferent pathways of the vomiting reflex [17].

Hyoscine butyl-bromide can act on the chemoreceptor trigger zone despite being a quaternary ammonium compound since the medulla oblongata has an underdeveloped blood-brain barrier. This central effect enhances its local antiemetic actions on gastrointestinal smooth muscles [13].

To our knowledge, a few studies investigated the antiemetic effects of Hyoscine butyl-bromide. In our study, hyoscine butyl-bromide decreased only intraoperative emesis, unlike Abbas et al. [18] who showed a significantly lower incidence of IONV in the hyoscine butyl-bromide group compared to the control group ($P = 0.002$).

Our results regarding hyoscine butyl-bromide were in line with Quiney and Murphy who compared another anticholinergic (glycopyrrolate) with placebo. They observed that the glycopyrrolate group has

Table 2. Intraoperative complication measurements among the three groups.

	Group H ($n = 55$)	Group O ($n = 55$)	Group C ($n = 55$)	P-value	Effect size[!] (95% CI)
Nausea n (%)	23(42)	16(29)	27(49)	$P_{HC} = 0.44$	0.7 (0.35, 1.6)
				$P_{OC} =$ **0.03**	0.4 (0.19, 0.93)
All emesis n (%)	14(25)	11(20)	24(44)	$P_{HC} =$ **0.046**	0.4 (0.19, 0.98)
				$P_{OC} =$ **0.009**	0.3 (0.14, 0.75)
IONV n (%)	24(44)	17(31)	28(51)	$P_{HC} = 0.46$	0.7 (0.35, 1.58)
				$P_{OC} =$ **0.034**	0.4 (0.19, 0.94)
Bradycardia n (%)	1(1.8)	4(7.3)	8(14.5)	$P_{HC} =$ **0.039**	0.1 (0.01, 0.90)
				$P_{OC} = 0.196$	0.2 (0.02, 2.14)
Hypotension n (%)	28(51)	22(40)	34(62)	$P_{HC} = 0.25$	0.6 (0.30, 1.37)
				$P_{OC} =$ **0.023**	0.4 (0.19, 0.89)
Intraoperative chest pain n (%)	1(1.8)	0 (0%)	0 (0%)	NS	-
Intra. & Postoperative Confusion N (%)	0 (0%)	0 (0%)	0 (0%)	NS	-

[!]Odds ratios are reported for binary variables. IONV = Intraoperative nausea and vomiting.
P_{HC} = P-value comparing Group Metoclopramide (H) vs Group Placebo (C).
P_{OC} = P-value comparing Group Ondansetron (O) vs Group Placebo (C). NS = Non-Significant. p value < 0.05 is considered significant.

Table 3. APGAR score among the three groups.

	Group H ($n = 55$) Mean (SD)	Group O ($n = 55$) Mean (SD)	Group C ($n = 55$) Mean (SD)	P value
1 min	6.91 (1.54)	7.04 (1.54)	6.82 (1.57)	0.760
5 min	8.75 (0.78)	8.69 (0.81)	8.75 (0.84)	0.921

*Significant as p value < 0.05.

Table 4. Postoperative nausea and vomiting among the three groups over the first 24 h.

	Group H ($n = 55$)	Group O ($n = 55$)	Group C ($n = 55$)	P-value	Effect size[!] (95% CI)
Nausea n (%)	24(44)	11(20)	29(53)	$P_{HC} = 0.341$	0.7 (0.3, 1.5)
				P_{OC} <0.001	0.2 (0.1, 0.5)
All emesis n (%)	25(45)	9(16)	29(53)	$P_{HC} = 0.45$	0.7 (0.3, 1.6)
				P_{OC} <0.001	0.2 (0.07, 0.4)
PONV n (%)	28(51)	12(22)	31(56)	$P_{HC} = 0.57$	0.8 (0.4, 1.7)
				P_{OC} <0.001	0.2 (0.1, 0.5)

[!]Odds ratios are reported for binary variables. PONV = postoperative nausea and vomiting.
P_{HC} = P-value comparing Group Metoclopramide (H) vs Group Placebo (C).
P_{OC} = P-value comparing Group Ondansetron (O) vs Group Placebo (C). NS = non-Significant. p value < 0.05 is considered significant.

a reduced frequency of nausea from 68% to 42% and vomiting from 16% to 8%. However, pretreatment with glycopyrrolate worsened hypotension shortly after spinal blockage was established [19].

Our results regarding ondansetron came in line with other studies [20–22] which concluded that ondansetron could efficiently decrease the incidence of IONV during CD under spinal anaesthesia.

The results of our study suggest that Hyoscine butyl-bromide may be an effective medication for reducing the incidence of intraoperative maternal bradycardia, a potentially serious complication that can occur during spinal anaesthesia for CD especially while using phenylephrine infusion.

The statistically significant reduction in the incidence of maternal bradycardia when compared to the control group indicates that Hyoscine butyl-bromide may be a valuable addition to the anaesthesia management plan for patients at risk of this complication.

Furthermore, the study found that patients who received hyoscine butyl-bromide experienced a lower incidence of bradycardia than ondansetron, although the difference was not statistically significant. This suggests that Hyoscine butyl-bromide may be a comparable alternative to ondansetron for reducing the risk of intraoperative maternal bradycardia, with the added benefit of potentially lower incidence.

Our results were in line with Abbas et al. who showed that using I.V. hyoscine butyl-bromide 20 mg to avoid intraoperative bradycardia during CS is more effective than using a placebo [18]. Also, in a meta-analysis conducted by Tubog et al., ondansetron was found to effectively reduce intraoperative maternal bradycardia [23].

Regarding intraoperative hypotension, our results were parallel to other studies [21,23,24] which showed that ondansetron was superior to placebo in attenuating spinal anaesthesia – induced hypotension.

In our study, ondansetron was superior to hyoscine butyl-bromide in minimizing the incidence of post-operative nausea and vomiting (PONV) over the first postoperative day. This was in line with many studies [21,25,26] that proved the preventive effect of ondansetron in context of PONV.

Unlike our results Transdermal scopolamine in a meta-analysis by Apfel et al., was associated with significant reductions in PONV [27]. This might be attributed to the sustained release and the longer duration of action of transdermal scopolamine in comparison to the shorter duration of action of IV hyoscine butyl-bromide that only covered the intraoperative period in this study.

In conclusion, this study found that Hyoscine butyl-bromide reduced the incidences of intraoperative emesis and maternal bradycardia but did not show any significant reduction in the incidences of PONV compared to the control group. So, it could be a good alternative to ondansetron throughout the intraoperative period. It is important to consider the potential side effects and contraindications of Hyoscine butyl-bromide and Ondansetron when selecting an anaesthesia management plan. For example, Hyoscine butyl-bromide may cause dry mouth, blurred vision, and urinary retention, while Ondansetron may increase the risk of QT prolongation and arrhythmias in patients with certain cardiac conditions. Further studies with larger sample sizes monitoring for such side effects might be required.

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