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Hemodynamic and antiemetic effects of prophylactic hyoscine butyl-bromide during cesarean section under spinal anesthesia: a randomized controlled trial

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Abstract

Background: Abrupt bradycardia and hemodynamic instability during spinal anesthesia for cesarean section are not uncommon and are considered as one of the primary causes of intraoperative nausea and vomiting (IONV). We hypothesized that prophylactic use of hyoscine butyl-bromide (HBB) could improve hemodynamics and reduce IONV in parturients undergoing cesarean section.

Methods: A randomized, double-blind placebo-controlled trial was carried out in a tertiary university hospital, patients scheduled for elective cesarean section were equally randomized to receive either IV HBB 20 mg in 1 ml (Hyoscine group) or the same volume of 0.9% saline (Control group), one minute after spinal anesthesia. The primary endpoint was the incidence of intraoperative bradycardia ($HR < 50 \text{ beats min}^{-1}$). Secondary endpoints included changes in mean arterial blood pressure (MAP), the incidence of Intraoperative and Postoperative nausea or vomiting (IONV & PONV), the fetal heart rate and, Apgar score.

Results: Of the 160 subjects randomized, 80 received HBB and 80 received placebo. There was a significant reduction in the incidence of the primary endpoint of intraoperative bradycardia ($HR < 50 \text{ beats min}^{-1}$) in the Hyoscine group (0% vs 10%; $OR = 0.05$, 95% $CI = [0.003, 0.93]$; $P = 0.004$) compared with placebo. MAP showed an insignificant difference between groups over time. HBB significantly decreased incidences of IONV and PONV ($p = 0.002$ & 0.004) respectively.

Conclusions: In parturients undergoing cesarean section under spinal anesthesia, pretreatment with intravenous HBB was a safe measure for both the mother and the baby to reduce the risk of severe intraoperative bradycardia, but not hypotension. Furthermore, it was associated with less incidence of both IONV and PONV.

Trial registration: <https://clinicaltrials.gov/ct2/show/NCT04069078>

Keywords: Bradycardia, Cesarean section, Hyoscine N-Butylbromide, Spinal anesthesia, Vomiting

Background

In developing countries, anesthetic complications, particularly abrupt bradycardia progressing to sinus arrest, account for about 14% of maternal deaths amongst those undergoing Cesarean section (CS) [1]. Many of

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the reported causes of anesthesia-related deaths can be avoided with proper training and resources [2].

Furthermore, the unopposed vagal activity and maternal hypotension that occurs with sympathetic block associated with spinal anesthesia are one of the primary causes of intraoperative nausea and vomiting (IONV) [3, 4].

Unlike atropine, Hyoscine butyl-bromide (HBB) is an anticholinergic with a quaternary ammonium structure making it unable to cross the blood–brain barrier and has lower placental transfer, so it could be more favorable for use with pregnancy [5, 6]. Furthermore, the similar compound Scopolamine was described before to have antiemetic effects [7]. However, because of the undesirable side effects of scopolamine, its use as an antiemetic prophylaxis becomes questionable [8] and HBB could be a better alternative.

We hypothesized that prophylactic use of HBB could prevent post spinal bradycardia with better hemodynamics and less incidence of IONV in parturients undergoing spinal anesthesia for CS.

Methods

Ethics approval and consent to participate

The current study was a prospective single-center randomized, double-blind placebo-controlled trial registered at www.clinicaltrials.gov (NCT04069078) and first posted on August 28, 2019. The study was carried out in Assiut University Hospital, Egypt, between October 2019 and February 2020. This study was approved by the medical ethics committee of Assiut university with approval number [17300311]. All patients provided written informed consent. All methods were carried out in accordance with the Declaration of Helsinki 2013.

Participants' selection

All patients 18–40 years of age, American Society of Anesthesiologists (ASA) classification class I and II and scheduled for elective or semi-elective surgery (category 3 and 4 Cesarean section) under spinal anesthesia for a Single baby pregnancy of more than 32 weeks were included in this study. Exclusion criteria were Patient's height < 150 or > 180 cm, Body mass index (BMI) > 35 kg m⁻², Contraindication or refusal to undergo regional anesthesia, Baseline bradycardia (HR < 60 beats min⁻¹), or any cardiovascular disease including arrhythmias, Patients on β -adrenergic blockers or any drugs that may alter the normal response to the study drug, Associated medical problem with pregnancy (as hypertension, diabetes mellitus, hepatic impairment or renal impairment).

Blinding and randomization

Patients were allocated in 1: 1 ratio into the two study groups using a web-based randomizer (<https://www.randomizer.org/>) to generate codes placed within sealed, opaque, sequentially numbered envelopes by a research assistant who was not involved in patient care or assessment. This assistant also prepared the study solutions in identical syringes that were labeled "study drug" according to the assigned group as follow:

Hyoscine butyl bromide group (Group H)

Patients received IV study solution, which is hyoscine butyl-bromide 20 mg in 1 ml, one minute after spinal anesthesia.

The control group (Group C)

Patients received 1 ml of IV normal saline as a placebo one minute after spinal anesthesia.

Meanwhile, both patient and the anesthesiologists conducting anesthesia and assessing outcomes were blinded to patient allocation.

Interventions

The preoperative anesthetic assessment was carried out including patients perinatal and general medical history, examination including baseline heart rate (HR), Blood pressure (BP) recording (three readings of HR and BP were averaged to give the baseline value for maternal HR and BP) and review of patients' coagulation profile.

Fasting for 8 h before the operation was acceptable. They were also premedicated with oral sodium citrate (30 mL, 0.3 molar) one hour before the operation as anti-aspiration prophylaxis.

In the operating room in all patients, large-bore intravenous access (18 gauge) was inserted in the left dorsum of the hand, and they were preloaded with 15 mL/kg of Ringer's solution intravenously. The 1st 500 ml was transfused by a pressure bag.

All patients were connected to standard routine monitoring [non-invasive blood pressure (NIBP), electrocardiography, and peripheral oxygen saturation.

With the parturient in a sitting position, spinal anesthesia was conducted using the midline approach after proper antiseptic cleaning and draping in the lumbar vertebral interspace of L3-L4 or a level below using a 25-gauge Quincke needle. After obtaining free flow of cerebrospinal fluids, 3 ml intrathecal solution of hyperbaric bupivacaine 0.5% in a dose of 12.5 mg (2.5 ml) mixed with morphine in a dose of 200 μ g (0.5 ml was withdrawn from a syringe containing 4 mg morphine

sulfate diluted in 10 ml normal saline) were injected intrathecally.

All patients were then made to lie supine, and a wedge was placed below the right hip to give a left lateral tilt. Then the premade study syringe was given IV immediately. Block-level was tested every five minutes using a frozen plastic ampule of sterile water along the midclavicular line to check the response to cold, and the highest sensory level obtained was registered. Surgeons were allowed to proceed with surgery after attaining a block level of at least up to T6.

Data collection

Sociodemographic patient's profile: age, sex, weight, height, and ASA physical status were recorded. HR and the mean arterial blood pressure (MAP) were recorded at 0 (baseline), 1, 3, 6, 9, 15, 20, 25, 30, 40- and 50-min following administration of the study drugs respectively until the end of surgery. And then every two hours for 6 h postoperatively.

Bradycardia ($HR < 50 \text{ beats min}^{-1}$) was treated with intravenous atropine 0.5 mg. Clinically significant hypotension was defined as $MAP < 60 \text{ mmHg}$ or a decrease of $MAP > 20\%$ from the baseline, and if developed, was treated with iv ephedrine sulfate boluses of 6 mg as required. Amount of atropine and ephedrine required, sensory level achieved at 15 min of Spinal anesthesia, the incidence of intraoperative and postoperative nausea or vomiting (PONV), presence of intraoperative chest pain, and intraoperative and postoperative confusion were recorded till six hours postoperative.

Nausea and/or vomiting with stable hemodynamics were treated by iv injection of 4 mg ondansetron. Incidence of postoperative itching was monitored and treated with 25 mg iv diphenhydramine. Respiratory depression (Respiratory rate $< 8 \text{ breaths/min}$ or $SPO_2 < 90\%$) was managed with oxygen therapy, non-invasive or invasive ventilation as appropriate.

Outcome measures

The primary outcome measure was the incidence of maternal bradycardia ($HR < 50 \text{ beats min}^{-1}$). The secondary outcome measures were the changes in MAP, the incidences of IONV and PONV and, the fetal heart rate and Apgar score at one and five minutes after delivery.

Sample size

Data from a previous study reported 17% incidence of bradycardia within controls in parturients undergoing spinal anesthesia for CS [9]. Based on a power of 80% and a confidence level of 95%, the required sample size was calculated as 71 per group (OpenEpi, version 3, open-source calculator) to detect a bradycardia frequency of

less than 3% in the Hyoscine-treated group. Considering of dropouts, 80 patients were recruited in each group.

Statistical analysis

Data were collected and firstly checked for normality of distribution through the Kolmogorov–Smirnov test. Data are presented as mean (SD) or number and ratio. Groups' categorical data were compared through the Chi-square test. Continuous parametric data were compared by unpaired t-test, whereas nonparametric data by Mann Whitney U test (between groups). Changes over time in HR and MAP between and within the study groups and, comparing values at each time point, were analyzed by repeated-measures ANOVA followed by a post hoc Bonferroni test to identify significant differences. Haldane-Anscombe correction was used to calculate OR (odds ratio) when the frequency in one group equals "0". Data were investigated using the computer program IBM, SPSS (Statistical Package for Social Sciences), Version 22, 2015. The P -value < 0.05 was reflected statistical significance.

Results

The recruitment of subjects is shown in Fig. 1. A total of 173 patients were screened for enrollment in this study. Thirteen patients were excluded (five had a body mass index $> 35 \text{ kg m}^{-2}$, two had preeclampsia, two received general anesthesia and, four declined to participate). One hundred sixty parturients completed the study with available data for the final analysis.

Patient characteristics, sensory block level, and operative time were comparable among groups (Table 1).

The incidence of maternal bradycardia ($HR < 50 \text{ beats min}^{-1}$) was calculated to be 0% for the Hyoscine group and 10% for the control group. The relative odds of bradycardia was 95% lower comparing subjects receiving hyoscine to control (OR = 0.05, 95% CI = [0.003, 0.93]; $P = 0.004$).

Moreover, when considering maternal bradycardia as $HR < 60 \text{ beats min}^{-1}$, the incidence was significantly much lower in the hyoscine group in comparison to the control group. (1.3% vs 18.8%; OR = 0.06, 95% CI = [0.007, 0.43]; $P < 0.001$). (Table 2).

Serial changes in heart rate are shown in Fig. 2. Analysis of data showed that heart rate changes over time were significantly different between subjects in both groups [$F(1,158) = 20.8$, $P < 0.001$], with the peak heart rate in the hyoscine group at 3 min after injection then came to baseline within 20 min.

Changes in MAP over time are shown in Fig. 3. MAP showed an insignificant difference between groups over time [$F(1,158) = 1.87$, $P = 0.17$].

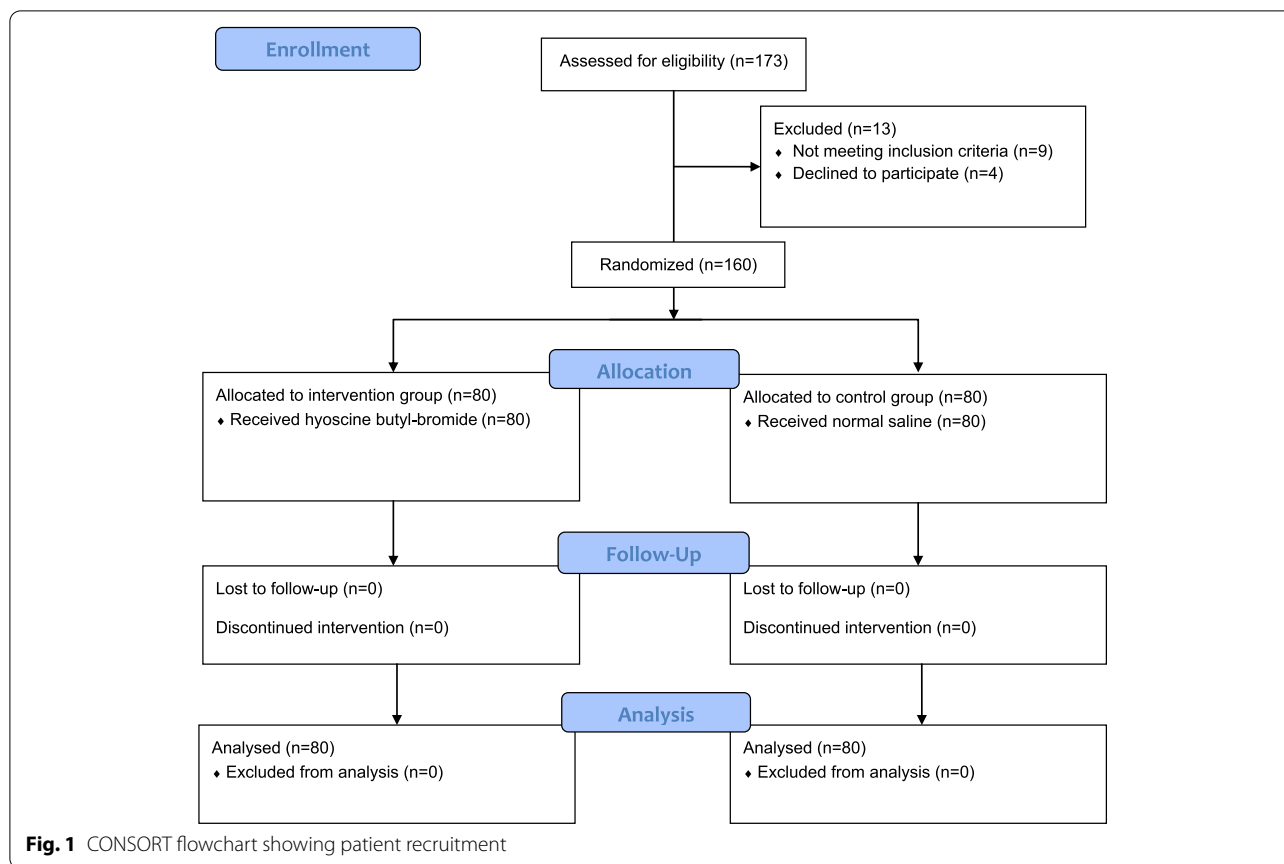


Table 1 Subjects’ characteristics, clinical data, and operative time

	Group C (N = 80)	Group H (N = 80)	P value
Age (years)	27.8 (4.5)	28.0 (4.7)	0.85
Weight (kg)	78.0 (16.9)	77.9 (15.3)	0.98
Height (cm)	166.1 (8.2)	167.4 (8.6)	0.31
BMI (kg m-2)	29.6 (24.2—32.9)	28.0 (23.3—32.9)	0.72
ASA N (%)	ASA 1 80 (100%)	80 (100%)	1
	ASA 2 0 (0)	0 (0)	NS
Sensory level at 15 min (dermatome)	T4 (T3—T4)	T4 (T2 -T 4)	0.21
Operative time (minutes)	30 (26—40)	30 (25—41)	0.62

Data are presented as mean (S.D.), median (25-75th percentiles) or number (%)

BMI Body mass index, NS Not significant, ASA American society of anesthesiologists

P-value < 0.05 was considered statistically significant

Results showed a significantly lower incidences of IONV and PONV in the hyoscine group compared to the control group (13.8% vs 35%; OR = 0.30, 95% CI = [0.14, 0.65]; P = 0.002) and, (28.8% vs 51.3%; OR = 0.38, 95% CI = [0.20, 0.74]; P = 0.004) respectively. (Table 2).

There were no significant differences in the incidences of Intraoperative Chest pain, intraoperative and postoperative confusion between the study groups (Table 2).

Neonatal outcomes were similar between groups (Table 3). Patients required ephedrine or atropine, and the doses used are summarized in Table 4.

Discussion

The present study shows that prophylactic use of I.V. HBB 20 mg with spinal anesthesia prevents intraoperative bradycardia during CS compared with placebo.

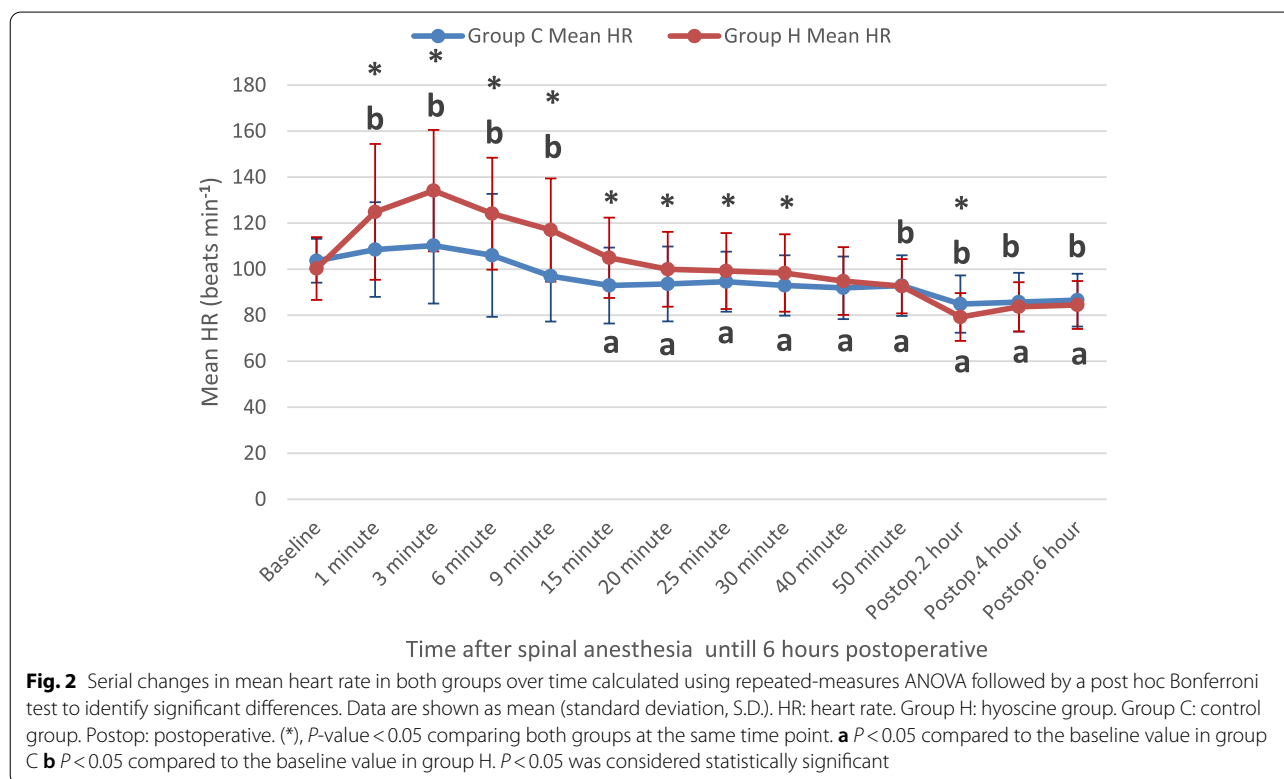
Table 2 Intraoperative and postoperative side effects and interventions

Variables	Group C (N=80)	Group H (N=80)	P value
Bradycardia (HR < 50) N (%)	8 (10)	0 (0)	0.004
Bradycardia (HR < 60) N (%)	15 (18.8)	1 (1.3)	< 0.001
IONV incidence N (%)	28 (35%)	11 (13.8%)	0.002
PONV incidence N (%)	41 (51.3%)	23 (28.8%)	0.004
Patients required Atropine N (%)	11 (13.8%)	0 (0%)	0.001
Patients required Ephedrine N (%)	61 (76.3%)	38 (47.5%)	< 0.001
Total Atropine dose (mg)	0 (0—0)	0 (0—0)	0.001
Total Ephedrine dose (mg)	6 (6—18)	0 (0—6)	< 0.001
Intravenous Fluid volume given (ml)	1000 (1000—1500)	1000 (1000—1437.5)	0.58
Intraoperative Chest Pain N (%)	0 (0%)	2 (2.5%)	0.16
Intra. & Postoperative Confusion N (%)	0 (0%)	0 (0%)	NS

Data are presented as median (25-75th percentiles) or number (%)

IONV Intra-Operative Nausea and Vomiting, PONV Post-Operative Nausea and Vomiting, NS Not significant

P-value < 0.05 was considered statistically significant



The blockade of the preganglionic cardio accelerator fibers originating between T1 to T4 may progress rapidly to complete heart block or asystole, which necessitates intense monitoring and rapid intervention [10]. Furthermore, the reflexes initiated due to hypotension and the decreased preload following spinal anesthesia, might cause sever bradycardia [11].

Despite using ephedrine which was found in a meta-analysis of vasopressor drugs used in CS [12] to be associated with the least incidence of maternal bradycardia, the incidence of bradycardia within controls in our study was found to be 10% (HR < 50 beats min⁻¹).

To our knowledge, few studies investigated bradycardia as a target primary outcome and examined

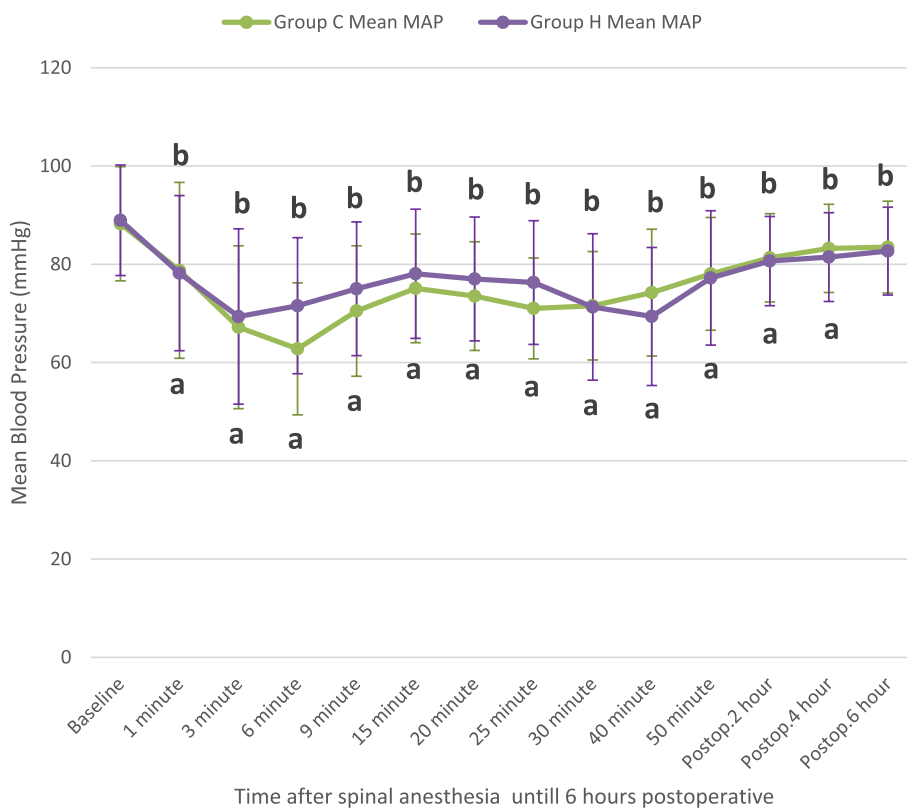


Fig. 3 Serial changes in mean arterial pressure (mmHg) in both groups over time calculated using repeated-measures ANOVA. Data are shown as mean (standard deviation, S.D.). MAP: mean arterial pressure. Group H: hyoscine group. Group C: control group. Postop: postoperative. **a** $P < 0.05$ compared to the baseline value in group C. **b** $P < 0.05$ compared to the baseline value in group H. $P < 0.05$ was considered statistically significant

Table 3 Neonatal outcomes

Variables	Group C (N=80)	Group H (N=80)	P value
Neonatal HR 1 min (bpm)	133.8 (20.1)	134.9 (18.5)	0.70
Neonatal HR 5 min (bpm)	152.3 (14.2)	153.2 (13.9)	0.69
APGAR Score 1 min	8 (7–8.3)	8 (7–9)	0.66
APGAR Score 5 min	9 (9–10)	10 (9–10)	0.77

Data are presented as mean (S.D.) or median (25–75th percentiles)

HR Heart Rate

P-value < 0.05 was considered statistically significant

pharmacological interventions to decrease its incidence. Our results are parallel with a previous report by Chamchad D and others, who stated that prophylactic glycopyrrolate administered before spinal anesthesia prevents bradycardia during Cesarean section ($p = 0.0248$). They found the incidence of bradycardia to be 17% between controls but, they defined bradycardia as $HR < 60 \text{ beats min}^{-1}$ [9].

In contrast to our results, Tarkkila and Kaukinen, found insignificant effect of prophylactic glycopyrrolate on the incidence of bradycardia in an observational cohort of

Table 4 Frequencies of patients required atropine and ephedrine in each group

Groups	Atropine dose (mg)			Ephedrine dose (mg)						
	0	0.5	1	0	6	12	18	20	24	30
Group C (N=80)	69 (86.25%)	9 (11.25%)	2 (2.5%)	19 (23.75%)	23 (28.75%)	17 (21.25%)	13 (16.25%)	3 (3.75%)	4 (5%)	1 (1.25%)
Group H (N=80)	80 (100%)	0 (0%)	0 (0%)	42 (52.5%)	26 (32.5%)	9 (11.25%)	2 (2.25%)	0 (0%)	1 (1.25%)	0 (0%)

Data are presented as number (%)

1,881 patients. However, their study was without randomization or blinding and did not specify the number of patients who received glycopyrrolate or doses given [13]. Also, Kee and co-workers showed no significant effect on the incidence of bradycardia when using glycopyrrolate pretreatment before phenylephrine infusion during spinal anesthesia for CS ($p = 0.50$). Unlike our study, Kee and co-authors calculated the sample size for cardiac output as a primary outcome [14].

The incidence of bradycardia in parturients undergoing spinal anesthesia varied between studies to be as low as 4.2% & 10% in some studies [14, 15] and as high as 46% in other studies [16] according to the definition of bradycardia and the vasopressor used.

Atropine is perhaps the most commonly used anticholinergic drug. However, Hyoscine butyl bromide is a semisynthetic derivative of hyoscine hydrobromide (scopolamine), which has a quaternary ammonium structure that results in lower transfer through the blood–brain barrier causing less incidence of confusion and other central side effects [5, 6]. Our results showed no difference in the incidence of intraoperative and postoperative confusion between the study groups.

While the vagal blockade of glycopyrrolate persists for two to three hours [17], our study found the peak heart rate in the hyoscine group to be at 3 min after injection and came to baseline within 20 min. This makes HBB more preferable than glycopyrrolate to avoid long periods of tachycardia. Regarding the effect on blood pressure, HBB did not show any significant difference in MAP between groups.

Our results showed that HBB reduced the incidence of intraoperative nausea and vomiting significantly. These results were significant in our study because we used ephedrine, which carries a higher incidence of nausea and vomiting than the other vasopressor agents [12].

The exact etiology of intraoperative nausea during spinal anesthesia is unknown. However, it is suggested that the unopposed vagal activity that occurs with sympathetic block during spinal anesthesia is the cause. Supporting this theory is the observation that atropine was more effective in relieving nausea during spinal anesthesia than was the elevation of the blood pressure with vasopressors [18].

Intrathecal opioids are associated with a 30%–70% incidence of postoperative nausea and vomiting [19, 20]. In our study, prophylactic HBB was associated with a significant reduction in the incidence of nausea and vomiting in the first six postoperative hours. Parallel to our results, Harnett and others compared the antiemetic efficacy of transdermal scopolamine, IV ondansetron, and placebo during the first postoperative day. They found scopolamine to significantly reduce the incidence of nausea and vomiting when compared to the placebo group in parturients receiving intrathecal morphine during cesarean

section [7]. However, concerns have been raised regarding the use of scopolamine as antiemetic prophylaxis because of its short duration of action and the undesirable side effects (e.g., visual disturbances, dry mouth, dizziness, agitation, drowsiness) resulting from large peak plasma concentrations [8].

Despite being a quaternary ammonium compound, HBB can target the chemoreceptor trigger zone due to the absence of a well-developed blood–brain barrier in the medulla oblongata. This central effect potentiates the antiemetic effects that it produces through local action on the smooth muscles of the gastrointestinal tract [21].

Regarding neonatal outcome and in accordance with many studies [22–26], our results showed no significant effect of HBB on APGAR score at 1 & 5 min after birth. In a meta-analysis done by Zaynab and colleagues to assess the effectiveness of hyoscine n-butyl bromide in labor progress, analysis of 11 studies involving 1682 participants showed an insignificant difference in the APGAR score at 1 min between HBB and controls (mean difference = -0.04 ; 95% CI: $[-0.09, 0.01]$). Also, the results of seven studies (involving 1453 neonates) showed an insignificant effect of HBB on APGAR score at 5 min after birth (mean difference = -0.03 ; 95% CI: $[-0.08, 0.03]$) [27].

This study is not without limitations; first, we used ephedrine as a vasopressor which appears to be the most likely agent to affect fetal and maternal outcomes adversely, but norepinephrine and phenylephrine are not available in limited-resource areas, in addition to carrying the risk of drug errors in wards outside of Critical Care Units [12]. So that we used ephedrine because of its availability in our community, the ease of its use and, because it has the least effect on the incidence of bradycardia [12]. Second, our results showed an insignificant difference between groups in Side effects like confusion and chest pain, but we did not monitor for dry mouth, constipation, urinary retention, reflux and flushing. However, by data analysis from five studies for the effect of HBB on mouth dryness in a previous meta-analysis [27] the difference between HBB and controls was insignificant.

Conclusions

pretreatment with intravenous HBB 20 mg in parturients undergoing CS under spinal anesthesia is a safe measure for both the mother and the baby to prevent the risk of severe intraoperative bradycardia with no noticeable effect on maternal hypotension. Moreover, it was associated with less incidence of both intraoperative and postoperative nausea and vomiting. Future studies are required to confirm our results, especially the effect on nausea and vomiting as a significant complication of hypotension and intrathecal morphine and as a measure of the quality of recovery after cesarean section.

Abbreviations

CS: Cesarean section; IONV: Intraoperative nausea and vomiting; HBB: Hyoscine butyl-bromide; ASA: American Society of Anesthesiologists; HR: Heart rate; BP: Blood pressure; NIBP: Non-invasive blood pressure; MAP: Mean arterial blood pressure; PONV: Postoperative nausea and vomiting; SD: Standard deviation; OR: Odds ratio; SPSS: Statistical Package for Social Sciences; CI: Confidence interval.

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Authors' contributions

Conception and design: MSA, MMM, Amr MT. Acquisition of data: MSA, Ahmed MT, SAH. Analysis and interpretation of data: MMM, AMAS. Drafting of the manuscript: MSA, MMM, AMAS. All authors participated in the revision of the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the medical ethics committee of Assiut university with approval number [17300311]. All patients provided written informed consent. All methods were carried out in accordance with the Declaration of Helsinki 2013.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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