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Research Article

Effect of ketamine on intraoperative nausea and vomiting during elective caesarean section under spinal anaesthesia: A placebo-controlled prospective randomized double blinded study

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Abstract *Purpose:* The well documented maternal and fetal safety following spinal anaesthesia in caesarean section (CS) makes it the preferred anaesthetic technique. Intraoperative nausea and vomiting in parturients subjected to CS under spinal anaesthesia is a major drawback of the technique. Post-spinal hypotension, the sympathetic blockade and associated relative vagal hyperactivity in addition to intraoperative visceral pain are the most important underlying factors behind the high rate of IONV during spinal anaesthesia. Ketamine has a unique sympathomimetic and vagolytic criteria that may help in reducing the incidence of IONV secondary to spinal-induced hypotension. This study was an attempt to evaluate the effect of ketamine on the IONV in parturients subjected to elective CS under spinal anaesthesia.

Patients and methods: Two hundred twenty-nine patients were randomly allocated into two equal groups: the ketamine group; in which 0.5 mg/kg was infused intravenously in 20 min and the placebo group; in which normal saline was infused. The two groups were given subarachnoid block with local anaesthetic hyperbaric 0.5% bupivacaine and intrathecal fentanyl.

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Results: IV infusion of ketamine was associated with significant reduction in the incidence of intraoperative nausea and hypotensive episodes.
Conclusion: This study demonstrated a beneficial effect of IV infusion of ketamine on IONV in parturients subjected to elective CS under spinal anaesthesia.

1. Introduction

Intraoperative nausea and vomiting (IONV) during caesarean section (CS) under spinal anaesthesia is a common complication with an incidence ranging from 40% to 60% [1–4]. Many factors may contribute to this high rate of IONV during CS; sympathetic block and the resultant hypotension secondary to spinal anaesthesia, visceral pain and vagal stimulation during CS are probably the most important factors [5]. Ketamine has unique central sympatho-mimetic, vagolytic and analgesic properties [6]. These properties of ketamine are assumed to reduce the incidence of spinal induced hypotension. In this study, we hypothesized that an IV infusion of ketamine would lower the incidence of intraoperative nausea and vomiting secondary to spinal-induced hypotension. This placebo-controlled prospective randomized double-blinded study was designed to evaluate the impact of ketamine on prevention of intra-operative nausea and vomiting as a primary outcome in parturients subjected to elective CS under spinal anaesthesia. Maternal and fetal side effects were considered as a secondary outcome.

2. Patients and methods

After approval by an ethical committee at Mansoura University Hospitals and obtaining a written informed consent from eligible parturients scheduled for elective caesarean section under spinal anaesthesia, ASA1 and 2 parturients having singleton pregnancy were included. Exclusion criteria included history of motion sickness, post-operative nausea and vomiting, gastrointestinal disease, allergy to (bupivacaine, fentanyl or metoclopropamide), pregnancy induced hypertension, history of non-gestational diabetes and history of smoking. Obese patients (body weight >90 kg), epileptic patients, patients given antiemetics or corticosteroids within 24 h before CS, patients who was heavy sedated (with Ramsy sedation score more than 3), and patients having any absolute contraindications to spinal anaesthesia were excluded. Included patients were randomly (using computer generated randomization table) allocated into two equal groups: the ketamine group ($n = 110$) and the control group ($n = 110$).

In the ketamine group, ketamine was diluted to a total volume of 20 ml via normal saline. Using an infusion pump (Graseby 3100-waltford, Herts-UK), ketamine was given at a dose of 0.5 mg kg^{-1} over 20 min started while patient back was being cleaned and scrubbed for spinal anaesthesia before intrathecal injection. In the control group, a similar volume of normal saline was given using the same technique used in the ketamine group. In order to achieve blindness of the study, one researcher was involved only in drug preparation according to patient's randomization and group assignment. The other researcher (anaesthesia provider) gave spinal block, managed the patient according to the study protocol and recorded the intraoperative data.

Patients started NPO midnight of the surgery, Ringer lactate infusion in a rate of 1.5 ml/kg^{-1} h^{-1} commenced at 6 am on the day of surgery through an 18-G peripheral IV cannula, a 20 ml of 0.3 M sodium citrate given orally 15 min before shifting the patient to the main operating theatre.

In the waiting area of the operating room, patients were monitored with ECG, automated noninvasive arterial blood pressure and pulse oximetry. An average of two readings of the mean arterial blood pressure (MABP) and heart rate (HR) were taken 5 min apart and considered the basal readings. Preloading with 10 ml Kg^{-1} of hydoxyethyl starch solution (6% HES 200/0.5 Braun Melsungen AG-Germany) was completed within 15–20 min, after which patient was shifted to the operating room (OR) where the standard monitoring of ECG, HR, BP and SpO2 was extended.

In the OR, we performed spinal anaesthesia in the sitting position under complete aseptic technique and skin infiltration with 0.5 ml of 1% lidocaine at site (L3-4 or L4-5) of spinal needle insertion. We used a spinal needle 25-G pencil point type, once free flow of clear CSF was obtained a 15 μg fentanyl loaded in 2 ml syringe was injected intrathecally followed by a hyperbaric bupivacaine 0.5%. The dose of bupivacaine was adjusted according to parturients height, 2 ml (10 mg) was given to those having a height <155 cm and 2.2 ml (12 mg) was given if the height was $\geqslant 155$ cm. After intrathecal injection, patients were immediately returned supine with left uterine displacement and supplemented with oxygen 4 L min^{-1} via clear facemask. Dermatomal level of sensory block was assessed by pinprick method; T5 was the minimum acceptable level before surgical incision. Both groups were given the same anaesthetic management by well-trained anaesthetists having an experience more than 10 years in the anaesthesia practice.

Mean arterial blood pressure (MABP) was measured every 1 min for the first 10 min then every 2 min until the end of ketamine or placebo infusion. Intraoperative hypotension-defined by MABP less than 20% of the basal reading-was managed by increasing the infusion rate of Ringer lactate solution concomitant with administration increments of 3 mg ephedrine hydrochloride. Arterial blood pressure was measured 1 min after ephedrine injection and if hypotension persists another ephedrine bolus was given, atropine sulphate (0.5 mg) was given when hypotension was associated with bradycardia (HR <50 beats min^{-1}). At the end of CS the incidence of hypotension (percentage per each group), hypotensive episodes (number of hypotensive episodes per each group) and increments of ephedrine hydrochloride in mg. were recorded.

Ramsay Sedation Scale (RSS; 1 = anxious and agitated, 2 = co-operative and tranquil, 3 = drowsy but responsive to command, 4 = asleep but responsive to glabellar tap, 5 = asleep with a sluggish response to tactile stimulation, 6 = asleep and no response). It was used to measure sedation level at 5, 10, 15, 20, 25, and 30 min after surgical incision, patients having RSS 4 or more were rejected.

Oxytocin was given immediately after baby delivery and clamping of the umbilical cord. Using a 10 ml syringe, a 10 units of oxytocin diluted into 10 ml of normal saline was given incrementally starting by an IV bolus dose of 2 ml (2 units) followed by increments of 2 units according to uterine contractility as per the obstetrician opinion. At the end of surgery; the total amount of oxytocin units administered, the technique of uterine repair (Either exteriorized or insitu) and duration was recorded. Patients given uterotonics other than oxytocin were rejected from the study. We replaced rejected patients from the study according to group assignment.

During surgery; intraoperative pain was managed by administration of 20 μg fentanyl given as IV bolus. At time of consent and again before the administration of spinal anaesthesia, patients were reminded to report any side effect or discomfort including nausea. Leading questions about nausea were avoided. Intraoperative nausea was recorded as follow (no nausea = 0, nausea only = 1, nausea and retching = 2), also the timing of IONV (during infusion or after) was recorded. Nausea with retching or vomiting were managed by a rescue dose of 10 mg metoclopramide diluted in a 10 ml of normal saline and given IV slowly, while nausea only was managed by assurance. Maternal side effects (such as desaturation, hallucinations) as well as fetal well-being (assessed with the Apgar scoring) were recorded.

Upon completion of the CS, parturients were transported to the post-anaesthesia care unit (PACU) where routine monitoring of BP, ECG, and SpO2 in addition to oxygen supplementation were applied to all patients under the care of PACU nurses then all patients were discharged and shifted uneventfully to the ward.

3. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17). Based on previous investigations [1–4] which reported an incidence between 40% and 60% of intraoperative nausea of parturients operated for CS under neuraxial anaesthesia, assuming 30% is the predicted incidence in the control group, to achieve 50% reduction in the incidence of intraoperative nausea (the primary outcome) at two-sided significance level 0.050% and 80% power, it was calculated that a minimum of 110 patients were required in each group. Normally distributed numerical data were presented by its mean and standard deviation (SD), while in-between group differences were compared parametrically using the independent-samples Student *t* test. Non-normally distributed numerical data were presented as absolute number (percent or range), while inter-group differences were compared non-parametrically using the Mann–Whitney *U* test. Significance level was set at $P < 0.050$.

4. Results

A total number of 229 patients were enroled in this study, 9 patients were rejected, 2 patients required general anaesthesia one because of failed block and the second because of inadequate block, 5 patients given methyl-ergometrine according to the obstetrician opinion, 1 patient had RSS = 4, and 1 patient was given midazoalm immediately after delivery as she was very anxious.

Table 1 Demographic and haemodynamic data in the ketamine and control groups.

Data	Ketamine group	Control group	*P* value
Age (yr)	29.1 ± 5.6	29.6 ± 6.2	0.569
Weight (Kg)	79.8 ± 8	77.8 ± 8.4	0.077
Height (cm)	161 ± 5.1	160.1 ± 5.9	0.549
Basal MABP mmHg	86.1 ± 8.2	86.3 ± 7.4	0.809
Basal HR; bpm	74.2 ± 9.4	75.7 ± 11.8	0.330

Data are expressed by mean ± SD or absolute number (%), MABP = mean arterial blood pressure, HR = heart rate, bpm = beats per min. *P* value <0.050 is considered significant.

There was neither maternal, fetal mortality, nor serious regional complications in the form of total spinal, paraplegia, epidural abscess, haematoma. All patients maintained a Spo2 level above 94%.

There was no significant difference in patient's data including age, weight, height, basal MABP and basal heart rate with *P* values 0.569, 0.077, 0.549, 0.809, and 0.330 respectively, (Table 1). Obstetric data including sensory block, bupivacaine dose, uterine exteriorization, number of parturients underwent bilateral tubal ligation (BTL), duration from skin incision to uterine repair, operative time, oxytocin requirements showed no significant statistical difference between the two groups: *P* values 0.531, 0.199, 0.440, 0.801, 0.531, 0.585, and 0.277 respectively, (Table 2). Apgar scores at 1 and 5 min did not show significant changes with *P* values 0.196 and 0.229 respectively (Table 2).

The lower incidence of intraoperative hypotension (35.5% vs 45.5%) was not significant (*P* value 0.214), however the number of hypotensive episodes and ephedrine requirements increased significantly in the placebo group compared with ketamine group *P* values 0.018 and 0.016 respectively. Five patients (4 in the placebo group and 1 in the ketamine group) recorded concomitant hypotension and bradycardia and were given IV bolus 0.5 mg atropine sulphate.

The incidence of intraoperative nausea was 20.9% in the ketamine group compared with 40.9% in the placebo group, which was statistically significant (*P* value 0.004). Both vomiting episodes and number of patients who required rescue antiemetics in the ketamine group compared with placebo one (2.3% vs 4.6% and 6 vs 11 respectively) were not statistically significant *P* values 0.702 and 0.423 Table 3. The majority of hypotensive episodes occurred during first 20 min of operation (infusion period) in both ketamine and placebo groups (85.7% and 84.3% respectively), similarly incidence of nausea during infusion period in both ketamine and placebo groups was 73.9% and 75.6% respectively.

There was no significant reduction in the incidence of pain, RSS, hallucinations between the two groups (Tables 3 and 4).

5. Discussion

The use of ketamine in the current study was associated with significant reduction in the incidence of intra-operative nausea and hypotensive episodes in parturients subjected to elective CS under spinal anaesthesia; however, the reduction in the incidence of intraoperative vomiting and rescue antiemetic requirements was not statistically significant.

Table 2 Anaesthetic and obstetric data in the ketamine and control groups.

Data	Ketamine group	Control group	*P* value
Sensory block	T4(T2–T6)	T4(T2–T5)	0.531
Bupivacaine dose	11.8 ± 0.7	11.6 ± 0.8	0.199
Exteriorization of uterus; n	39 (45.9)	42 (40)	0.440
BTL; n	8(7.1)	7(5.9)	0.801
Time from skin incision to closure of uterine incision time	17.7 ± 4.7	17.3 ± 4.8	0.533
Operative time; min	52.6 ± 7.7	52 ± 8.1	0.585
Oxytocin dose; U	12.6 ± 3.4	13.1 ± 3.6	0.277
Apgar score 1st min	7.9 ± 0.9	7.8 ± 0.9	0.196
Apgar score 5th min	8.5 ± 0.7	8.7 ± 0.7	0.229

Data are expressed by mean ± SD or absolute number (%) BTL = bilateral tubal ligation, *P* value <0.050 is considered significant.

Table 3 Intraoperative hypotension and ephedrine requirements, pain and rescue fentanyl increments, episodes of intraoperative nausea and vomiting, and rescue antiemetic requirements and incidence of hallucinations and nystagmus in the two groups.

Data		Ketamine group (*n* = 110)	Control group (*n* = 110)	*P* value
Intraoperative hypotension		39 (35.5)	50 (45.5)	0.214
hypotensive episodes	Total no	77	133	0.018
	during 1st 20 min	64	118	–
	After 1st 20 min	13	15	–
Ephedrine dose in mg		2.1 (0–9)	4.03 (0–15)	0.016
Intraoperative nausea	Total no	23 (20.9)	45 (40.9)	0.004
	during 1st 20 min	17	34	–
	After the 1st 20 min	6	11	–
Intraoperative vomiting		3 (2.7)	5 (4.5)	0.702
Rescue antiemetics		6 (5.5)	9 (8.2)	0.423
pain		3 (2.7)	4 (3.6)	1.000
Hallucinations		1 (0.9)	0 (0)	0.317

Data are expressed by mean ± SD, median (range) or absolute number (%), No = number of patients, min = minutes, value <0.050 is considered significant.

Table 4 Ramsey sedation score (RSS) in both ketamine and control groups.

	Ketamine group (*n* = 85)						Control group (*n* = 85)						*P* value
	1	2	3	4	5	6	1	2	3	4	5	6	
5 min	0	82	3	0	0	0	0	85	0	0	0	0	0.081
10 min	0	83	2	0	0	0	0	85	0	0	0	0	0.156
15 min	0	82	3	0	0	0	0	85	0	0	0	0	0.081
20 min	0	82	3	0	0	0	0	85	0	0	0	0	0.081
25 min	0	83	2	0	0	0	0	85	0	0	0	0	0.156
30 min	0	84	1	0	0	0	0	85	0	0	0	0	0.371

Data are expressed by absolute number of patients under each RSS, *P* value <0.050 is considered significant.

The well-documented maternal and fetal safety of spinal anaesthesia compared to general anaesthesia encouraged anaesthetists to use it as the gold standard for the anaesthetic management of parturient subjected to CS. Unfortunately intraoperative hypotension, and IONV are significant and irritating drawback of spinal anaesthesia [1–4].

IONV is an uncomfortable feeling for patients, upsets obstetricians, distresses anaesthetists, and may increases the risk of visceral injury during surgery because of the involuntary uncontrolled abdominal movements.

Spinal hypotension and gastrointestinal hyperactivity resulted from relative vagal hyperactivity secondary to spinal anaesthesia plays a significant role [5,7], Datta et al. found avoidance of spinal hypotension during CS reduced emetic episodes by 6–7 folds [7].

Several investigators studied different medications to reduce IONV in parturients undergoing CS under spinal anaesthesia; Santos and Datta [1], and Mandell et al. [2] used droperidol in an IV dose of 2.5 mg and 0.5 mg – respectively-vs placebo and they found droperidol caused a significant reduction in the incidence of nausea compared to the placebo groups (*P* value 0.024 and 0.001). Fuji and his colleagues [3] investigated the preventive effect of IV granisteron 3 mg, metoclopropamide 10 mg, droperidol 1.25 mg against placebo; they found that the three drugs were similarly effective in reduction of intraoperative nausea compared to placebo

effect (*P* value 0.001). In contrast to Fujii et al. [3] result, Balki and his colleagues [4] found grnisteron ineffective in prevention of intraoperative nausea in parturients given spinal anaesthesia for CS and they postulated this difference to the use of more strict control of the causative factors of IONV specially hypotension. Glycopyrrolate was studied in prevention of intraoperative nausea during CS because of its vagolytic effect and it reduced the incidence of IONV from 68% in the placebo group to 42% in the study group [8]. Fujii and Numazaki [9] used the IV anaesthetic agent propofol in different sub-hypnotic doses; they reported that a dose of 1 and 2 mg kg^{-1} h^{-1} reduced intraoperative nausea significantly compared to placebo, whereas a dose of 0.5 mg kg^{-1} h^{-1} was not effective compared with placebo.

Despite ketamine is a very known, old and established drug, we are not aware of any study that has specifically looked at the effect of a ketamine infusion on the incidence of nausea and vomiting secondary to spinal anaesthesia induced IONV secondary to spinal-induced hypotension in elective caesarean section. Ketamine is an intravenous dissociative anaesthetic agent related to phencyclidine group which works by antagonizing *N*-methyle D-aspartate (NMDA) receptors [6]. Because of its unique analgesic and dissociative criteria in addition to the distinct symatho-mimetic, vagolytic pharmacological properties, ketamine is used frequently in anaesthesia practice for purposes of analgesia, sedation and induction of anaesthesia many years ago (9). These criteria especially sympatho-mimetic and vagolytic properties encouraged us to conduct this study.

In our study the incidence of hypotension in the control group was less compared to previous reports [10,11]. This can be explained by the use of prehydration with colloid fluid that was reported by Ngan Kee et al.; found that colloid in the form of gelfusine or heastril preloading was associated with less incidence and severity of hypotension during CS under regional anaesthesia [12,13]. Titrating bupivacaine dose according to the patient height and maintaining left uterine displacement are other factors.

The use of ketamine as IV induction agent in haemodynamically-compromised patients subjected to emergent surgical interventions was shown to increase mean arterial blood pressure by a mean of 10% when compared to basal readings as reported by White PF [14].

In our study, the frequency of hypotensive episodes during infusion period was nearly twice in the placebo group compared with ketamine group (118 vs 64) with significant statistical difference in the total hyptensive episodes between the two groups; this could be explained by the sympatho-mimetic effect as well as vagolytic effect of ketamine.

Compared to other studies [1–4], the incidence of intraoperative nausea was less and this can be explained by the less incidence of hypotension. The use of intrathecal fentanyl and its related analgesia as reported by Manullang et al. [15], and the use of ketamine in the current study had an additional effect in reducing intraoperative nausea significantly compared with placebo group. The marked reduction in the incidence of hypotensive episodes during infusion-nearly to half-in ketamine group compared to placebo group could explain a strong relation to the significant reduction in the incidence of intraoperative nausea during spinal anaesthesia for CS. This effect was confirmed by other studies that have shown that if intraoperative hypotension is eliminated, the incidence of nausea and vomiting can be reduced to less than 5% [16]. Low dose of IV ketamine was shown to reduce the incidence of postoperative nausea/vomiting score in another types of surgeries as reported by Yamauchi et al. [17]. They found that administration of a low-dose ketamine infusion at skin incision and continues post-operatively not only improved the analgesic effects, but also it reduced postoperative nausea and vomiting. This finding is agree with the result of our study despite different explanation.

Both maternal and fetal safety of ketamine in CS is documented; Ngan Kee et al. [18] compared the effect of ketamine induction vs thiopental induction on postoperative analgesia in elective CS, they found that patients in the ketamine group required less analgesic drugs in the first 24 h compared with thiopental group and the neonatal apgar score was comparable without inter-group significant changes In another study Nielsen and Holasek [19] studied ketamine as an induction agent in CS and found an excellent Apgar scores (mean 9.1 at 1 min and 9.9 at 5 min) associated with ketamine induction. These studies agree with our results that did not detect any significant changes in the apgar scores between the two groups at both 1 and 5 min Apgar scores (*P* values 0.195, and 0.229).

The non-significant difference in the sedation level measured by RSS between the two groups (Table 4) disagrees with the result of Saricalouge et al. study [20] which investigated the impact of intravenous ketamine on ischaemia-reperfusion injury in patients subjected to knee arthroscopy under spinal anaesthesia and found significantly higher RSS in the ketamine group. This difference could be explained by the higher ketamine dose and the use of midazoalm in their study [20], although a higher sedation score was reported in their study [20], it was not associated with increased incidence of either respiratory depression or hallucinations in the ketamine group which agrees with the result of the our study.

We speculate that; despite the reduction in the incidence of hypotension was insignificant however the frequency of hypotensive episodes was significantly less in the ketamine group, hence the ephedrine requirements, compared with placebo group could explain the statistically significant reduction in the incidence of intraoperative nausea in ketamine group compared to the placebo one.

In this study, we used a single dose of ketamine which could be considered one of the limitations of the study, further study may be required to study the effect of different ketamine doses. We excluded psychologically disturbed patients without formal assessment by a more psychiatrist, which is considered another limitation?

In conclusion, the current study demonstrated that IV ketamine infusion in parturients subjected to elective CS under spinal anaesthesia effectively reduced intraoperative nausea which was associated with the marked reduction in the incidence of hypotensive episodes compared to placebo group.

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