

Pre-Incisional Intravenous Low-Dose Ketamine Does Not Cause Pre-Emptive Analgesic Effect Following Caesarean Section under Spinal Anaesthesia

Ebong EJ*, Mato CN and Fyनेface-Ogan S

Obstetric Anaesthesia Unit, Department of Anaesthesia, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

Abstract

Background: Adequate postoperative pain relief is one of the commonest challenges faced by women who deliver by caesarean section.

Aim: This study was aimed at finding out the effect of pre-incisional administration of low dose intravenous ketamine on the post-operative analgesia demand time.

Patients and Methods: Following approval from the Hospital's Ethical Committee, a prospective, randomised double-blind study was carried out to evaluate the pre-emptive effect of low-dose ketamine on women undergoing elective caesarean section under plain bupivacaine/fentanyl spinal anaesthesia.

Results: Eighty women completed (83.33%) the study. The results were comparable in both groups for maternal age, weight, height, gestational age and parity. There was no statistical difference in the patient characteristics between the two groups under study.

The mean time taken to achieve a maximal sensory level was 9.3 ± 0.91 mins in Group-A and in Group-B 8.35 ± 1.49 mins, $p=0.260$. The regression time to two segments was also the same in the two groups of women. The mean in the Group-A was 28.1 ± 1.52 mins while the Group-B had 27.6 ± 2.10 mins, $p=0.161$.

The time to first analgesic request in the Ketamine Group was 193.44 ± 26.53 mins while that for the Placebo group was 140.14 ± 22.34 mins. The difference in the duration was statistically significant, $p=0.0001$.

Conclusion: It is concluded that the pre-incisional administration of low-dose intravenous ketamine only demonstrated a delayed time to first analgesic request in the women who had plain bupivacaine/fentanyl spinal anaesthesia and not a pre-emptive analgesic effect.

Keywords: A low-dose ketamine; Spinal anaesthesia; Plain bupivacaine; Fentanyl; Pre-emptive analgesia

Introduction

Pain is a subjective and multidimensional experience that is often inadequately managed in clinical practice [1]. Effective control of postoperative pain is important after anaesthesia and surgery. It can both be unpleasant and harmful to the patient. Good postoperative pain relief improves patient's satisfaction and decreases morbidity [2,3]. Inadequately controlled pain is often overlooked [4] and has undesirable physiological and psychological consequences.

Inadequate pain relief following a caesarean delivery may impair the mother's ability to optimally care for her infant in the immediate postpartum period and adversely affect early interactions between mother and infant [2]. Pain and anxiety may also reduce the ability of a mother to breast-feed effectively [5,6]. It is necessary that pain relief be safe and effective, that it does not interfere with the mother's ability to move around and care for her infant, and that it results in no adverse neonatal effects in breast-feeding women [3].

The role of ketamine as an agent for pre-emptive analgesia is yet to be fully elucidated. While some workers confirm the pre-emptive effect of ketamine [7,8] others claim that it only delays time to request for supplemental analgesic [9,10]. Our study was to evaluate the effect of low dose intravenous ketamine as a pre-emptive analgesic in patients undergoing caesarean section under spinal anaesthesia. Pre-emptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by that procedure.

Owing to this 'protective' effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented [10].

Patients and Methods

Following approval by the University of Port Harcourt Teaching Hospital's Ethics and Research Committee, a prospective, randomised, double blind, placebo-controlled study was carried out on parturients undergoing elective caesarean section under spinal anaesthesia.

Patients excluded from the study include those that are more than American Society of Anesthesiologists (ASA) physical status Classification II, refusal to participate in the study, history of drug abuse

***Corresponding author:** Dr. Emmanuel J Ebong, Obstetric Anaesthesia Unit, Department of Anaesthesia, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria, Tel: +234-803-342-6236; **E-mail:** dremmanuelebong@yahoo.com

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and allergy to study drugs, Psychiatric disorder, bleeding disorders and, evidence of foetal compromise

Each parturient was reviewed by the researchers the night before the scheduled operation during which the use of a 10-cm visual analogue scale (VAS) for scoring pain was explained to the patient. None of the patients in this study received premedication. Informed consent was obtained from all the patients and they were recruited by convenient sampling. The recruited patients were categorized into 2 groups, (Group-A, (Ketamine) and Group-B, (placebo)) by a research assistant using the simple randomization technique of consecutive numbers. Patients who had odd numbers were categorized under Group A and received low-dose intravenous ketamine while those who had even numbers were Group B and received placebo. The patients were all instructed to request analgesia when they feel pain postoperatively. On arrival in the operating room, all the patients had their baseline vital signs (pulse, blood pressure and oxygen saturation) measured and recorded.

All the patients for the study received the same intravenous fluid preload - 20ml/kg normal saline over 10-15 mins through an 18-G intravenous cannula sited in the non-dominant hand. The anaesthetic machine was checked and prepared for possible use should the spinal anaesthesia failed. Two adult laryngoscopes with long and short blades and, three cuffed endotracheal tubes (appropriate size, one smaller and one larger) were prepared. Thiopentone sodium 4mg/kg, suxamethonium 2 mg/kg and atracurium 0.4 mg/kg were drawn up and labelled for possible conversion to general anaesthesia.

Following adequate preloading with normal saline, each patient was placed in the sitting position with the feet resting on a stool and an assistant supporting her shoulders at the front. The administrator was appropriately gowned and observing aseptic technique; the skin of the patient's back was prepared with chlorhexidine and alcohol, and draped. The area of puncture (L₃/L₄ interspace) was infiltrated with 2 ml 1% lidocaine plain. Using a size needle as a guide, the spinal puncture was performed with a 25-gauge pencil point spinal needle.

For all the patients, correct placement of the spinal needle in the subarachnoid space was confirmed by a back-flow of the cerebrospinal fluid. Both groups of the study population received a combination of bupivacaine 10 mg with fentanyl 20µg as the agent injected into the subarachnoid space. At the end of the subarachnoid injection, both the size and spinal needles were withdrawn and a light sterile dressing placed over the puncture site. The patients were returned to the supine position and adjusted to a 15° left lateral tilt to ensure left displacement of the gravid uterus.

The maternal blood pressure and pulse rate were monitored and recorded at 5-minute intervals during the intraoperative period using an automated, non-invasive device (Ajour Huntleigh® multiparameter monitor). Peripheral oxygen saturation (SpO₂) was also monitored continuously and recorded. The intraoperative fluid requirement was administered according to the patient's need by the attending anaesthetist. No additional drug was administered to any of the patients.

A blinded attending anaesthetist administered the prepared drug A (ketamine 0.25mg/kg diluted to 10 ml with sterile water) or B (10ml normal saline) 5 minutes before the surgical incision was made.

A fall in maternal systolic blood pressure more than 20% below baseline value was regarded as hypotension. Ephedrine hydrochloride 5 mg bolus (and occasionally a repeat dose) and additional 10 ml/kg normal saline were administered to treat the hypotension until the

blood pressure returned to normal level. Patients with a decrease in heart rate to less than 50 beats per minute were treated with 0.5 mg intravenous atropine. Oxygen was routinely administered through a face mask at the rate of 4 l/min to all patients. At delivery of the baby, APGAR scores were assessed at one and five minutes. Cord blood pH was measured using a pH Meter (Hanna Instruments HI98130 Combo Waterproof pH Tester, Transcat, Inc. Rochester, NY). Within the intraoperative period, patients in both groups were assessed using the RAMSAY sedation score scale.

The spread of sensory block was determined by pinprick in the mid-clavicular line every minute until block reached the T₆ dermatome. Motor block was also assessed according to Bromage scale. Return of motor function during the postoperative period was assessed every 30 minutes until complete recovery. The first request for analgesia was measured as the time from subarachnoid injection of bupivacaine plus fentanyl combination to the first analgesia administration after caesarean section. The severity of postoperative pain was quantified using the 10-cm VAS (0 = no pain; 10 = worst pain imaginable). The VAS was evaluated every 30 minutes during until the time of request for analgesic. The time of first request for analgesia and side effects were assessed at 30-minute interval and recorded by an investigator who was blinded to the group allocation. Intravenous pentazocine (a Benzomorphan derivative) 30 mg and intramuscular diclofenac sodium 75 mg were injected as stat doses as soon as the pain score was higher than 4. This was regarded as the first request for analgesia. Subsequently, Pentazocine was administered on requests with a minimum of a 4 hourly interval while diclofenac was given 12 hourly.

The severity of nausea (mild, moderate and severe), pruritus, and sedation (Ramsay Sedation Scale) was recorded during the intraoperative and postoperative periods. Nausea and vomiting was treated with intravenous 10 mg metoclopramide. Post dural puncture headache (PDPH) was regarded as headache which is relieved on lying down. The patients were observed for PDPH until discharge from hospital and were requested to grade the severity as mild, moderate and severe. Initial treatment was with the use of bed rest, intravenous fluid therapy and intravenous acetaminophen. The end point of follow-up of these patients was at their discharge from the hospital.

Sample size determination

Following a computer generated sample size determination, a total of 96 patients were recruited and randomly allocated into two groups of patients each.

Comparative statistical tests

All data collected obtained were fed into a spreadsheet and analyzed using the Statistical Package for Social Sciences (SPSS) 15.0 software (SPSS, Chicago, IL, USA) for windows. Interval or ratio measurements, for example, time for first request for analgesia was analyzed using t-test. Proportion measurement, for example, incidence of hypotension, sedation, bradycardia, was analyzed using the z-test. Summary statistics were done for baseline parameters using tables. The confidence interval of 95% ($p=0.05$) was accepted for the study.

Results

A total of 96 women were approached for this study. Out of this, only eighty (83.33%) women participated throughout the study. Sixteen women were excluded from the study. Nine women were excluded following a patchy block from spinal anaesthesia and were converted to general anaesthesia. While 6 women requested for some sedation

after the delivery of their babies and were excluded from the study, one woman had massive maternal haemorrhage due to placenta accreta and was also not included into the study.

In this study, Group-A received pre-incisional intravenous low-dose ketamine 0.25 mg/kg while Group-B also received pre-incisional intravenous 10 ml placebo (normal saline) and became the control. Both groups had Caesarean section with subarachnoid bupivacaine 10 mg and fentanyl 20µg.

Thirty nine women completed the study in the Group-B while 41 women completed it in the Group-A. In both groups, the same standard technique of surgery – Pfannestil incision, exteriorization of the uterus and repair, and repair of layers were performed.

Table 1 shows the Patients’ characteristics. The results were comparable in both groups for the maternal age, weight, height, gestational age and parity. The mean maternal age in Group-A was 33.0±1.59 years while it was 31.05±1.71 years in the Group-B. There was no statistical difference between them, p=0.166.

The result also shows that the mean maternal weight for Group-A was 84.83±6.90 kg while that for the Group-B was 80.45±6.12 kg, p=0.339. There was no statistical significance in the maternal weights. The two groups were also comparable in maternal height. The Group-A had a mean maternal height of 164.48±2.06 cm while the Group-B had 163.43±2.18 cm, p=0.499. There was no significant difference statistically.

The ASA risk assessment between the two groups was the same. The Group-A had 1.30±0.22 while Group-B had 1.35±0.29, p=0.745. There was no statistical difference between them. The gestational

Variable	Group-A	Group-B	t-Value	p (2-tailed)
Age (years)	33.0±1.59	31.05±1.71	1.44	0.166
Weight (kg)	84.83±6.90	80.45±6.12	0.98	0.339
Height (cm)	164.48±2.06	163.43±2.18	0.69	0.499
ASA	1.30±0.22	1.35±0.29	0.33	0.745
Gestational age (weeks)	39.55±0.54	39.45±0.44	0.33	0.745
Parity	1.90±0.40	2.15±0.31	1.04	0.311

mean ± standard deviation

Table 1: Patients Characteristics.

	Group-A	Group-B	t-Value	p (2-Tailed)
Mean spinal puncture to incision interval (mins)	5.22±0.46	5.30±0.46	0.42	0.753
Mean incision-delivery interval (mins)	4.15±0.57	4.25±0.50	0.33	0.745
Mean Apgar scores at one minute	8.45±0.239	8.60±0.235	0.90	0.379
Mean Apgar Scores at five minute	9.45±0.239	9.60±0.235	0.72	0.480
Mean umbilical cord pH				
Venous blood	7.35 ± 0.05	7.39 ± 0.05	0.41	0.724
Arterial blood	7.28 ± 0.05	7.30 ± 0.05	0.44	0.811
Mean duration of surgery (mins)	55.45±5.61	57.90±5.40	0.55	0.589

mean ± standard deviation

Table 2: Patients Surgical Condition.

Variable	Group-A	Group-B	t-Value	p (2-tailed)
Time of maximal sensory level (mins)	9.3±0.91	8.35±1.49	1.16	0.260
Regression to two segments (mins)	28.1±1.52	27.6±2.10	1.46	0.161
First analgesia request (mins)	193.24±26.53	140.14±22.34	5.12	0.0001
Duration of motor block (mins)	159.15± 21.51	138.40±25.16	1.35	0.193
Total pentazocine consumption in first 24 hrs (mg)	84.0±9.76	106.5±7.16	3.68	0.002
Total diclofenac consumption in first 24 hrs (mg)	150.0	150.0		

mean ± standard deviation

Table 3: Subarachnoid Block Characteristics And Analgesia Data.

ages between the groups were the same. Group-A had a mean GA of 39.55±0.54 weeks while it was 39.45±0.44 weeks in the Group-B, p=0.745. There was no statistical difference. The level of parity between the two groups was also the same. While Group-A had a mean parity of 1.90±0.40, Group-B had 2.15±0.31, p=0.311. There was also no statistical difference between the parity levels in the two groups.

Table 2 shows the surgical conditions in the two groups. Both groups were comparable in the surgical condition. The mean spinal puncture-surgical incision interval in Group-A was 5.22±0.46 mins while it was 5.30±0.46 mins in Group-B, p=0.753; there was no statistically significant difference between them. The incision-delivery (I-D) interval was also the same in the two groups. While Group-A had a mean I-D interval of 4.15±0.57 mins, Group-B had 4.25±0.50 mins, p=0.745.

The Apgar scores were recorded in first and the fifth minutes. The mean Apgar scores in the first minute of the babies delivered in the Group-A was 8.45±0.239 and that in Group-B was 8.60±0.235. There was no significant difference, p=0.379. At five minutes, the Apgar scores of the babies delivered in the Group-A was 9.45±0.239 while in the Group-B was 9.60±0.235. There was also no statistical difference between the two groups, p=0.480. The cord venous and arterial blood (p=0.41 and p=0.44 respectively) were not significantly different between the two groups of the newborns.

The mean duration of surgery was found to be the same. While Group-A had a mean duration of 55.45±5.61 mins, Group-B had 57.90±5.40 mins. There was also no difference between them, p=0.589.

Table 3 shows the subarachnoid block characteristics and the analgesia data. All the patients achieved a T6 dermatomal sensory block height. The mean time taken to achieve a maximal sensory level was 9.3±0.91 mins in Group-A, and in Group-B 8.35±1.49 mins. There was no statistically significant difference in the time to achieve the maximal sensory level between the two groups, p=0.260. The regression time to two segments was also the same in the two groups of women. The mean in the Group-A was 28.1±1.52 mins while the Group-B had 27.6±2.10 mins, p=0.161.

The time for first analgesia request (time from institution of subarachnoid block to when patient requests for pain relief) is shown in Table 3. The women in Group-A had a mean analgesia request time of 193.44±26.53 mins while that in Group-B was 140.14±22.34 mins.

Time	Group-A	Group-B
0 min	2	0
5 mins	2	0
10 mins	2	0
20 mins	2	0
30 mins	2	0

Table 4: Intraoperative Ramsay Sedation Score.

Complications	Group-A n=41	Group-B n= 39
Hypotension	2 (4.88)	3 (7.69)
Shivering	0	4 (10.26)
Nausea and vomiting	4 (9.76)	3 (7.69)
Bradycardia	0	2 (5.13)
Post dural puncture headache	3 (7.31)	2 (5.13)
Chest Pain	4 (9.76)	6 (15.39)
	13 (31.71)	20 (51.28)

n=number number (percentage)

Table 5: Incidence of Complications.

The difference in the mean analgesia request time was statistically significant, $p=0.0001$. The ketamine group had a more prolonged analgesia time than those who had the placebo. The women in Group-A had a more prolonged time of motor blockade, 159.15 ± 21.51 mins than those in the Group-B 138.40 ± 25.16 mins, although the difference was not statistically significant $p=0.193$.

The analgesic consumption is also shown in Table 3. Although both groups received the same amount of diclofenac (150mg) in 24 hours, the use of opioid was less in the Group-A than Group-B. There was more rescue analgesic administration in the Group-B. The mean total dose of pentazocine administered in Group-A was 84.0 ± 9.76 mg while it was 106.5 ± 7.16 mg in Group-B. The difference was significant, $p=0.002$.

Table 4 shows the intraoperative Ramsay sedation scores. The maximum sedation score attained in the Group-A was 2 (cooperative, oriented and tranquil) while it was zero in the Group-B.

Table 5 shows the various complications that occurred both intra- and postoperatively. It shows that there were more complications in the Group-B than the Group-A. However, the commonest complication in the two groups was chest pain. The incidence of this complication was 9.76% and 15.39% in Group-A and Group-B respectively. This probably may have been due to the exteriorisation of the uterus during repairs. The patients who had this complaint were reassured.

Nausea and vomiting was also one of the complications in the two groups. Four (9.76%) women in the ketamine group and 3 (7.69%) women in the placebo experienced nausea and vomiting. This may also be attributed to the exteriorisation of the uterus during repairs. Some of the patients with mild nausea were reassured while others who had severe nausea and vomiting were treated with 10 mg intravenous metoclopramide.

Hypotension was common in both groups. The incidence of hypotension in Group-A was 4.88% (2 patients) while Group-B had 7.69% (3 patients). This complication was treated with rapid intravenous fluid administration and bolus doses of intravenous 5 mg ephedrine hydrochloride.

Post dural puncture headache (PDPH) was one of the complications but the incidence was low. The PDPH occurred within the first 24-48 hour postoperative period. The incidence was 7.31% in Group-A and 5.13% in Group-B. These patients were reassured and managed with intravenous fluid and bed rest.

However, 4 (10.26%) of the women in the Group-B had intraoperative post spinal shivering and none in the Group-A. Patients with post-spinal shivering were covered with warm blankets.

Bradycardia was not a complication in the Group-A while it occurred in 2 (5.13%) women in the Group-B. The patients who had this complication were given intravenous 0.6 mg atropine.

Discussion

Multimodal therapy for postoperative pain control is now widely practiced due to the advantage it provides in blocking multiple pain pathways while minimizing side effects of each individual pain medication [10]. The research work studied the effect of low dose intravenous ketamine as a pre-emptive analgesic in patients undergoing caesarean section under spinal anaesthesia. Pre-emptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by that procedure.

Although the literatures on the effect of ketamine on preemptive analgesia are conflicting, however some observations were made from the results of this study. Firstly, it was noted that the time to first request for postoperative analgesic (TFA) was significantly delayed in the ketamine group than the control group. The difference in the time to first request of analgesic was about 53 minutes. This finding corroborates with that of Amanor-Boadu et al in which ketamine prolonged the TFA [11]. It has been demonstrated in other studies that ketamine delayed the first request for analgesia by approximately 10–30 mins compared to control group [10,11].

One important factor that could influence the effect of ketamine used could be the injecting dose. While in this study, 0.25 mg/kg of ketamine was used, Amanor-Boadu et al [11] in their study used a relatively higher dose (0.5mg/kg) of the agent resulting to a prolonged TFA also observed in their study. The efficacy of ketamine is frequently linked to the activation of NMDA receptors of the dorsal horn of the spinal cord. In case of adequate perioperative analgesia, NMDA receptors activation is likely to be suppressed and ketamine administration is useless. In other studies that have documented a preemptive effects of ketamine [10] the perioperative opioid analgesia is questionable and likely to have induced intraoperative activation of NMDA receptors. In this study, no other intravenous analgesic was administered which could have influenced an activation of the NMDA receptors.

Evidence has shown that postoperative pain is a product of both peripheral and central sensitization [12]. Following the stimulation of free nerve endings by incision, cutting and traction, chemical mediators of pain such as bradykinnin and prostaglandin maintain the pain longer with resultant primary hyperalgesia. The development of secondary hyperalgesia is facilitated when A-alpha and A-beta nerve fibres, which do not normally mediate pain, are so induced when peripheral sensitization occurs.12

To achieve a sustained preemptive analgesia, pain of initial injury must be blocked and since chemical mediators continue to be released for longer than the initial insult, their effects must be prevented for a longer time than the duration of action of the single dose of analgesia administered. Unfortunately, our study could not demonstrate the sustained preemptive effect thought to be exhibited by ketamine at the dose used. The study did demonstrate that the TFA was more significantly prolonged in the group that had low dose ketamine.

It has been stated that preemptive analgesia may be difficult to demonstrate due to some other reasons such as the effect of other

anaesthetic agents used during anaesthesia and surgery [13]. In our study although plain bupivacaine/fentanyl spinal anaesthesia were conducted for all the patients, none of the participating patients received any other form of analgesics during and after anaesthesia. Any other analgesic administered was at the first time the patients requested for it. Intraoperative use of any other analgesic may exert a partial preemptive effect, a situation which may modify the result. Dermot et al proposed that a sustained preemptive effect should include neuraxial block prior to the noxious surgical stimulation and continuation of analgesia throughout the intraoperative period to block the nociceptive input [14]. The single-shot low dose ketamine used in this present study however may have reduced pain and delayed the onset of central sensitization. Central sensitization being a phenomenon whereby repeated painful stimulus leads to more severe pain perception over time despite no change in the intensity of the painful stimulus.

Secondly, it was also observed that postoperative analgesic consumption was significantly lower in ketamine group at first 24 h compared to the other group. This result was comparable with other studies [15,16] which showed that small doses of ketamine reduced opioid requirements for postoperative pain. Although this effect of ketamine may be due to antagonism of spinal NMDA receptor sites, it can act on several receptor systems such as opioidergic and cholinergic [17].

Ketamine also activates the monoaminergic descending inhibitory pathway at supraspinal sites resulting in antinociception [18]. Although in this research work, there was no clear distinction in the opioid requirements between the two groups, but the ketamine group showed an apparent lower dose of opioid needs in 24 hours. It has been demonstrated that ketamine can induce consistent and statistically significant decrease pain intensity at rest compared with control and delays the time to first request of rescue analgesic [10]. But the study could not demonstrate any evidence of a relationship between the dose of ketamine and analgesic efficacy [10].

N-methyl-D-aspartate (NMDA)-receptor antagonism is the most important neuro-pharmacological mechanism for the analgesic effects of ketamine [19]. The same mechanism may be involved in the supposed neuro-protective potency of the substance. Effects on opiate receptors may contribute to the analgesic state as well as to dysphoric reactions. Sympathomimetic properties are mediated by enhanced central and peripheral mono-aminergic transmission.

The women's request for analgesia was monitored with the VAS for 24 hours. The result showed that the average VAS score in the placebo group had risen to 3 at the 90th minute postoperative period. At the 120 minutes, the placebo group had received a dose of pentazocine on attaining an average VAS score of 4 or more. But this was not the case with the ketamine group which experienced a delay in time to request for analgesic. This finding further strengthens the benefit of ketamine as a potent analgesic even in low doses.

Psychomimetic responses to small ketamine doses have not been found troublesome [16]. The absence of characteristic sedations, dreams and hallucinations of ketamine observed in this study is similar to another report [11]. None of the patients who had low dose ketamine scored more than zero on the ramsey sedation scale. This could be due to the small doses used during the study [20,21]. Ketamine however, can be administered to pregnant women, but the patients should be informed about the potential risks such as hallucinations or nightmares.

The administration of the local anaesthetic agents into the subarachnoid space has been associated with haemodynamic changes

[22]. One of the haemodynamic changes observed during this study was hypotension. It is commonly associated with spinal anaesthesia either due to the cephalad spread of the anaesthetic agent or poor venous return as a result of the weight of the gravid uterus on the vena cava especially as the pregnant woman assumes a supine position for the surgery. The few cases of hypotension observed in the study may have been due to optimum care – ensuring proper left lateral tilt of the gravid uterus, administration of intravenous fluid and intravenous ephedrine. Other measures that can be used to prevent hypotension due to spinal anaesthesia include the use of compressed stockings, prophylactic administration of vasopressors, and administration of colloids [23]. The incidence of hypotension in the ketamine group was less probably due to the sympathomimetic effect of the agent. But the patients that developed hypotension were treated with rapid fluid administration and the use of ephedrine.

Bradycardia could be a complication of spinal anaesthesia for caesarean section following neural blockade of the accelerator fibres of the T₂ to T₄ which supply the heart. When blocked, decreased cardiac contractility and hence bradycardia follow due to unopposed vagal activity. A block as high as T₁ completely removes the body's ability to compensate for circulatory changes in addition to producing generalized vasodilatation - the total spinal phenomenon. However in this study, only 5.13% of the women in the placebo group developed some bradycardia and none in the ketamine group. Ketamine is well known to cause a rise in blood pressure and heart rate due to its sympathomimetic activity. This could be the reason for the less incidence of bradycardia observed in the group that received low dose ketamine.

Postspinal shivering was a complication that was prominent amongst the placebo group. None of the women in the ketamine group developed shivering. Ketamine, a competitive NMDA receptor antagonist, also inhibits postoperative shivering [24]. It is likely that NMDA receptor antagonists modulate thermoregulation at a number of levels. In rats, neurones in the preoptic-anterior hypothalamus have been shown to increase their firing rate by application of NMDA. Furthermore, NMDA receptors modulate noradrenergic and serotonergic neurones in the locus coeruleus. In the dorsal raphe nucleus, serotonin acts as a neuromodulator to enhance the effects of NMDA receptors. Finally, NMDA receptors at the dorsal horn of spinal cord modulate ascending nociceptive transmission. In addition to being a competitive NMDA receptor antagonist, ketamine has several other pharmacological properties; these include being a κ opioid agonist, blocking amine uptake in the descending inhibitory monoaminergic pain pathways, having a local anaesthetic action and interacting with muscarinic receptors. Therefore it probably controls shivering by non-shivering thermogenesis either by action on the hypothalamus or by the β -adrenergic effect of norepinephrine [25].

The incidence of PDPH in this study was 7.31% in the ketamine group and 5.13% in the placebo group. Post dural puncture headache occurring after spinal anaesthesia for caesarean section has reduced due to the development of newer bevel designs and smaller gauge needles. Fyeface-Ogan et al, [26] found that the incidence of PDPH was 6% with 25G Whitacre needle but 0% with 26G needle. In our study, the incidence rates were observed to be about the same even though size 25 whitacre needles were used. The management of PDPH in the patients in our study included bed rest, liberal fluid administration and analgesics. The use of epidural blood patch is also frequently used as the definitive treatment [27].

While analysis of umbilical cord blood gases remains the gold

standard for assessment of the newborn, [28] assessment of all the newborn in this study was also carried out using the Apgar [29] scoring system. In our study, the mean umbilical cord venous blood pH was 7.35 ± 0.05 and that of the arterial blood pH was 7.28 ± 0.05 . These pH values correlated well with the high Apgar scores observed in all the newborn in our study.

Conclusion

This study shows that the pre-incisional administration of low dose intravenous ketamine delayed the time to first analgesic request in women who had caesarean section under bupivacaine/fentanyl spinal anaesthesia. The study could not substantially demonstrate the preemptive analgesic property of ketamine. The failure of this study to clearly show this desired effect of ketamine may increase the on-going controversy regarding the concept of preemptive analgesia thought to be exhibited by ketamine.

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