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Augmenting Subarachnoid Block Analgesia in Caesarean Section Delivery with Sub-Psychotomimetic Dose of Ketamine

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Abstract

This study investigated the effect of low sub-psychotomimetic dose (0.3 mg/kg) of ketamine on subarachnoid block-induced analgesia with a view to assessing the analgesic effectiveness of combination of low dose ketamine with subarachnoid block in management of post caesarean section pain.

Spinal anaesthesia was performed in 120 healthy pregnant women scheduled for elective caesarean delivery using 10 mg hyperbaric bupivacaine. Parturient mothers were randomly selected into four groups (n=30) consisting of K1, K2, NK1 and NK2. K1 received 0.3 mg/kg intravenous ketamine diluted with sterile water for injection to 5 mL, as a bolus dose 2 min before surgical incision; K2 was treated as K1 but at 2 minutes after delivery of baby, while NK1 and NK2 received equivalent volumes of normal saline 2 min before surgical incision and 2 min after baby extraction respectively. Age, weight, duration of surgery (DOS) and the time of first request for analgesia (TFA) for all participants were recorded. Post-operative pain intensity was assessed using a visual analogue scale (VASPI) at 2, 4, 8, 12, 24 and 36 h after spinal anaesthesia induction. Results were analyzed using ANOVA and Kruskal-Wallis tests. Student Newman-Keuls and Man-Whitney rank sum tests were used for post hoc analysis as appropriate. P value<0.05 was considered statistically significant.

There was no significant difference in age and weight across groups, but duration of surgery was statistically prolonged in K1 group relative to NK1 group. Low dose ketamine significantly augmented the analgesic effect of spinal block anaesthesia, especially when given at two minutes before surgical incision.

Keywords: Ketamine; Bupivacaine; Analgesia; Spinal block; Caesarean section

Introduction

Millions of caesarean deliveries are performed globally on daily basis, many of which are due to indications ranging from emergency situations (e.g. foetal distress) to maternal request [1]. However, despite a growing trend in acute pain management, there still exist deficiencies in post-operative pain management, and participants continue to receive inadequate care of algesia post-operatively. Post-operative pain following caesarean section often leads to both physiological and psychological consequences; including inability of the mother to give adequate care to the neonate immediately after birth. Benefits of adequate post-operative analgesia include early mobilization and less hospital stay, reduced morbidity, reduced risk of deep vein thrombosis, reduced hospital costs and increased participant satisfaction.

Ketamine, a dissociative anaesthetic agent commonly used for minor surgical procedures in many developing countries has been reported to have analgesic properties [2-4]. The widespread use of ketamine has been limited by the psychotomimetic side effects it produces at moderate doses [5]. Although previous studies have reported the analgesic potential of low dose ketamine [6,7], the relevance of time of administration during the peri-operative period and the time profile of the augmented analgesia produced by low dose ketamine have not been extensively assessed.

This study set out to determine whether intravenous ketamine, at a dose of 0.3 mg/kg, would be effective for improving post-operative analgesia after caesarean section under subarachnoid block and examines the time profile of the resulting analgesia at different moments during the peri-operative period.

Materials and Methods

This study was undertaken as a prospective, placebo-controlled, double-blind, randomized study using 120 parturient mothers. Ethical approval was obtained from the Ethical Research Committees of the Obafemi Awolowo University, Ile-Ife, Nigeria and Mother and Child Hospital, Ondo, Nigeria. Informed consent was obtained from each participant whose physical status belonged to class ≤ II according to the American Society of Anesthesiology (ASA) physical status, and was scheduled for elective caesarean section.

The criteria for exclusion in this study included parturient mothers with known cardiac disease, gestational hypertension (>Class II in American Society of Anaesthesiologists (ASA) Classification of Physical Health Status), epilepsy, psychiatric disorder, and bleeding disorders. Others are parturient mothers with multiple gestations,

parity greater than one, previous caesarean section, history of allergy to ketamine and heavy bupivacaine and evidence of foetal compromise or distress.

Each parturient mother was reviewed by the investigator the night before the scheduled surgery (preoperative assessment) during which every participant was trained on the use of a 10 cm Visual Analogue Scale for scoring pain intensity (VASPI) [8]. No pre-medication was given to any of the participants. All participants for the study received the same intravenous fluid preload of 20 ml/kg normal saline over 10-15 min *via* an 18-G intravenous cannula sited in the non-dominant hand before receiving spinal anaesthesia at a sitting position.

The parturient mothers were divided into 4 groups of 30 each by simple randomization technique of consecutive numbers. The four groups consisted of K1, K2, NK1 and NK2. All groups received heavy bupivacaine 10 mg injected over 30 sec into the subarachnoid space after confirming correct placement of the spinal needle in the L3-L4 inter-space. Thereafter, each participant had caesarean section under spinal anaesthesia, using the standard technique of surgery-Pfannenstiel incision, extraction of baby, exteriorization of the uterus and repair of layers.

Group K1 received 0.3 mg/kg ketamine [9,10] as a bolus dose intravenously 2 min before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose *via* the vein 2 min after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 min before surgical incision, and 2 min after delivery of baby respectively. The post-operative pain intensity experienced by the participant, assessed based on the participant's feedback on the Visual Analogue Scale was taken at 2, 4, 8, 12, 24 and 36 h after spinal anaesthesia was instituted [11-13]. Data was obtained using a designed data collection proforma form. Data collected was analyzed using Primer of Biostatistics by Stanton A. Glantz, Version 3.01. Results were analyzed using ANOVA and Kruskal-Wallis tests. Student Newman-Keuls and Man-Whitney rank sum tests were used for post hoc analysis. P value<0.05 was considered statistically significant.

Results

Demographic characteristics of the study groups

ANOVA statistics showed no significant difference (p=0.420) in mean maternal age and mean maternal weights (p=0.262) across the all groups in this study (Table 1).

Demographic Characteristics of the Study Groups					
	K1 (n=30)	K2 (n=30)	NK1 (n=30)	NK2 (n=30)	ANOVA p-value
Age (years)	29.97 ± 5.78	28.77 ± 5.56	29.97 ± 4.97	31.33 ± 7.09	0.42
Weight (kg)	73.20 ± 7.17	72.33 ± 8.19	75.57 ± 7.96	75.23 ± 6.06	0.262

Table 1: Demographic characteristics of the study groups.

Values expressed in mean ± SEM. No statistical difference across all groups (ANOVA). K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 min before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose *via* the vein 2 min after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 min before surgical incision, and 2 min after delivery of baby respectively.

Effect of low dose intravenous ketamine (0.3 mg/kg) on duration of surgery and time of first request for analgesia

One-Way ANOVA revealed significant difference ($F_{(29,119)}$=2.92; p=0.035) in the means of duration of surgery across the groups. The post-hoc analysis revealed that surgery duration in group K1 was significantly longer than NK1 (p=0.033) while there was no significant difference when the following groups were compared: K1/K2, p=0.936; K1/NK2, p=0.926; K2/NK1, p=0.134; K2/NK2, p=1.000; and NK1/NK2, p=0.143 (Table 2).

Similarly, there was significant difference in of TFA ($F_{(29,119)}$=69.5; p<0.0001) across the groups (Table 2). The post-hoc analysis revealed that TFA was significantly smaller in group NK1 compared with group K1; TFA was significantly smaller in group NK2 compared with K2; TFA was significantly smaller in group K2 compared with K1 (Table 2).

Duration of Surgery and Time of First Request for Analgesia					
	K1 (n=30)	K2 (n=30)	NK1 (n=30)	NK2 (n=30)	ANOVA p-value
DOS (mins)	46.83 ± 8.06	45.60 ± 7.18	41.0 ± 10.40*	45.53 ± 6.44	0.035
TFA (mins)	204.2 ± 42.6	164.4 ± 33.3*	99.0 ± 24.8*	112.4 ± 22.9#	<0.0001

Table 2: Effect of low dose intravenous ketamine (0.3 mg/kg) on time of first request for analgesia and duration of surgery.

Values are expressed in Mean ± SEM. *=p<0.05 relative to K1, #=p<0.05 relative to K2, Duration of Surgery (DOS), Time of First Request for Analgesia (TFA). K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 min before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose *via* the vein 2 min after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 min before surgical incision, and 2 min after delivery of baby respectively.

Effect of intravenous low dose ketamine (0.3 mg/kg) on post-caesarean section pain intensity following subarachnoid block using visual analogue score

Krusal-Wallis statistics revealed significantly (p<0.05) lower visual analogue score of pain intensity (VASPI) in the combined ketamine group (K1+K2) when compared with the combined non-ketamine group (NK1+NK2) at all assessment points within 36 h after spinal anaesthesia (Figure 1a). Similarly, there was significantly (p<0.05) lower VASPI in K1 relative to NK1 at all points of assessment (Figure 1c). The VASPI was lower in K1 group relative to K2 group at 4, 8, 12 and 36 h, though the difference did not get to a level of significance (Figure 1b), but the pain intensity at the points of assessment was significantly lower in K2 when compared with NK2 except at the 12th h mark where the difference was not statistically significant (Figure 1d).

Values are expressed in Mean ± SEM. *=p<0.05 relative to non-ketamine group. Visual Analogue Score (VAS) n=30. Ketamine group comprised K1+K2 (K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 min before surgical incision (after subarachnoid

block); K2 received 0.3 mg/kg ketamine as a bolus dose *via* the vein 2 min after delivery of baby). Non-ketamine comprised NK1+NK2 (NK1 and NK2 received equivalent volumes of intravenous normal saline 2 min before surgical incision, and 2 min after delivery of baby respectively).

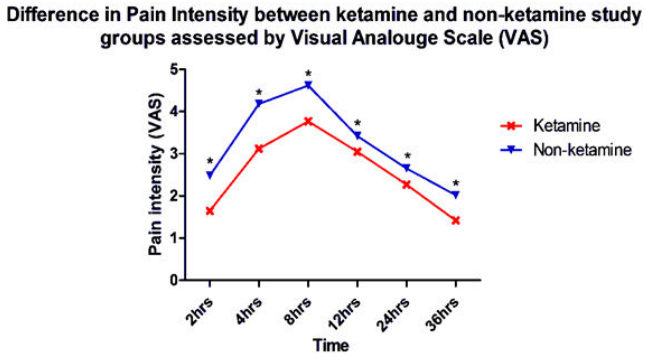

Figure 1a: Effect of intravenous low dose ketamine (0.3 mg/kg) on post-caesarean section pain intensity following subarachnoid block using visual analogue score.

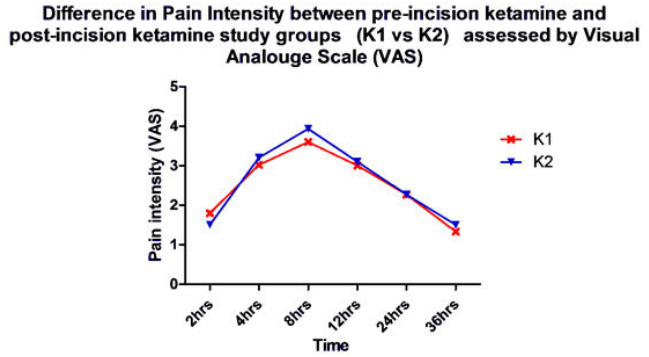

Figure 1b: Effect of intravenous low dose ketamine (0.3 mg/kg) on post-caesarean section pain intensity following subarachnoid block using visual analogue score.

Values are expressed in Mean ± SEM. No significant difference between the groups throughout post-surgery duration of observation 36 h Visual Analogue Score (VAS). n=30, K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 min before surgical incision, K2 received 0.3 mg/kg ketamine as a bolus dose *via* the vein 2 min after delivery of baby.

Values are expressed in Mean ± SEM. *=p<0.05 relative to NK1 group. Visual Analogue Score (VAS). n=30. K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 min before surgical incision (after subarachnoid block); NK1 received saline as a bolus dose intravenously 2 min before surgical incision.

Values are expressed in Mean ± SEM. *= p<0.05 relative to NK2 group. Visual Analogue Score (VAS). n=30. K2 group received 0.3 mg/kg ketamine as a bolus dose intravenously 2 min after baby extraction while NK2 group received saline as a bolus dose intravenously 2 min after baby extraction.

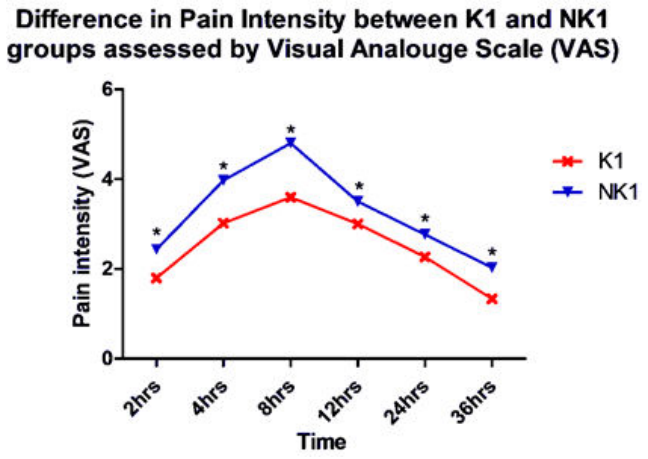

Figure 1c: Effect of intravenous low dose ketamine (0.3 mg/kg) on post-caesarean section pain intensity following subarachnoid block using visual analogue score.

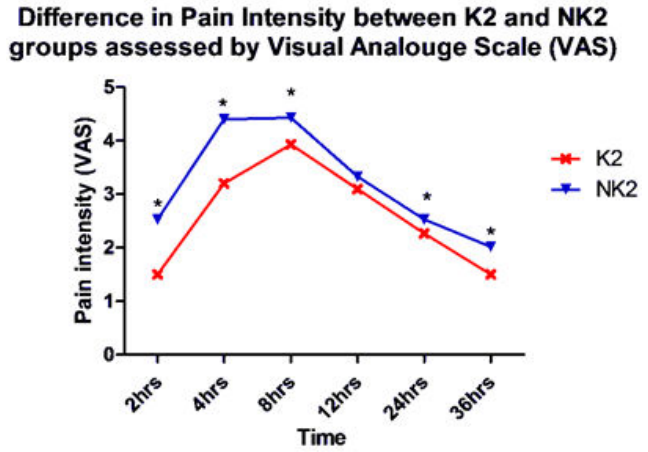

Figure 1d: Effect of intravenous low dose ketamine (0.3 mg/kg) on post-caesarean section pain intensity following subarachnoid block using visual analogue score.

Discussion

Nowadays, satisfactory post-operative pain control is one of the most important as-yet unresolved challenges in the surgical setting and has a major impact on patients and on the health system in general [14]. Ketamine is a well-established drug that has been in use for around 50 years [15] and is increasingly more consolidated in modern clinical practice [14]. It produces a spectrum of biological effects summed up as dissociative anaesthesia which comprises hypnosis, psychotomimetic effects, sedation and unconsciousness at higher doses; intense analgesia (or more accurately anti-nociception); increased sympathetic activity; and maintenance of airway tone and respiration [16]. The widespread use of analgesic effect of ketamine has been limited because of various side effects including psychotomimetic at moderate doses [17]. Hence this study explored the effect of a low-

dose ketamine, earlier reported to be devoid of psychotomimetic effects in preclinical and clinical studies [18-20], on analgesia of subarachnoid anaesthesia in post caesarean section mothers.

Findings of this study indicated that the participants were comparable in age and weight. Previous studies reported the influence of age and weight on perception of pain in humans [21,22] hence the possible bias of age and weight on perception of pain is ruled out in this study.

The significant increase in the time to first request for analgesia (TFA) in the ketamine groups relative to the non-ketamine groups and the significant reduction in the visual analogue score of pain intensity (VASPI) at all assessment points for the ketamine groups relative to the corresponding non-ketamine groups are suggestive of significant enhancement of analgesia by low-dose ketamine administration. This is also supported by the absence of any significant change in TFA and VASPI when NK1 was compared with NK2. These are consistent with previous findings of significant delay in the time for first request for analgesics in participants who had intravenous low dose ketamine peri-operatively relative to participants who did not [7,23]. Administration of low-dose ketamine 2 min (K1) before incision produced significant delay in TFA when compared with administration of same drug at the same dose 2 min after the birth of baby (K2). Similarly, VASPI scores for the K1 group at 4. 8, 12 and 36 h are lower when compared to K2, albeit the difference was not statistically significant. Altogether, these findings point to augmentation of analgesia following administration of low-dose ketamine preoperatively, and the pre-incision administration of low-dose ketamine produced better enhancement of analgesia than that produced by administration after birth of baby. Moreover, the enhanced analgesia lasted for the whole period of observation 36 h in this study.

The analgesic enhancement reported for ketamine in this study can be explained by the pharmacological properties of this drug. NMDA receptor has been reported to play an important role in the sensitization of peripheral nociceptive receptors and conduction of nociceptive impulses in the central nervous system [2]. It is generally considered that ketamine-induced supraspinal blockade of the NR2B NMDA sub-unit has the most important anti-nociceptive influence [24], however ketamine is also reputed for acting to augment opioid mu-receptor function [25-27], albeit its analgesia has been reported not to be reduced by naloxone; which negates a primary opioid-mediated mechanism of action. In support of the non-opioid mechanisms of analgesia hypothesis, recent studies have suggested that ketamine analgesia seems to be largely associated with increased dopamine activity in mice. Ketamine also augments endogenous anti-nociceptive systems–presumably, in part, *via* its aminergic (serotonergic and noradrenergic) activation and inhibition of re-uptake [28]. The activation of the aminergic systems have also been widely reported for classical and novel antidepressants. Hence, another plausible explanation of ketamine-induced potentiation of analgesia as reported in this study is a corollary of its antidepressant effect [29-31] which is rapid in development and endures well after the drug has been eliminated (more than 36 h after administration in this study), judging from the T1/2 of ketamine [32]. Pain and depression have been reported to be often closely linked [33], although the direction of the causative relationship between the two is less clear. This association is often explored in the use of antidepressants in pain management. Alternatively, ketamine may set in chain of cell signaling cascades that interrupt the gradual propagation of pathophysiological changes associated with pain mediation [34]. As outlined in previous studies, ketamine regulates a number of gene expression pathways potentially linked to pain mediation, including NMDA receptor expression, astrocytic activation and synaptic structure and function. Of course all of these different systems do not act in isolation, but are themselves part of the integrated nervous system with a myriad of interactions occurring at all levels [34], ultimately resulting in inhibition of pain mediation by low dose ketamine as reported in this study.

Conclusion

In view of these findings of this study, which are suggestive that low-dose ketamine is a valuable adjuvant in perioperative management of pain in women undergoing caesarean section, it is recommended that the safety on this drug at the dose employed in this study be assessed on maternal and foetal well-being in the peri and postoperative periods.

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