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Neonatal and Maternal Safety Profile of Low-Dose Ketamine Analgesia as an Adjuvant to Subarachnoid Anaesthesia in Caesarean Section

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Abstract

Background: This study investigated the effect of low-dose ketamine on neonatal and maternal well-being with a view to assessing neonatal and maternal safety profile of low-dose ketamine-induced analgesia as an adjuvant to subarachnoid block in caesarean section.

Methods: After obtaining ethical approval, spinal anaesthesia was performed in 120 healthy pregnant women scheduled for caesarean section 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 to 5 mL, as a bolus dose 2 minutes before surgical incision, K2 received 0.3 mg/kg ketamine also made up to 5 mL with sterile water, as a bolus dose 2 minutes after delivery of baby, while groups NK1 and NK2 received equivalent volumes of normal saline (5 mL) 2 minutes before surgical incision and 2 minutes after baby extraction respectively. Incidence of maternal side effects and neonatal well-being were assessed after surgery. Results were analysed using ANOVA, and chi-square statistics. Student Newman-Keuls tests was used for post hoc analysis as appropriate. P value of < 0.05 was considered statistically significant.

Results: The demographic characteristics and The American Society of Anaesthesiologists (ASA) Score of Physical Health Status of the participants were comparable across all groups. The indices of maternal well-being including pulse rate, incidence of chest pain and shivering were not significantly different in low-dose ketamine group relative to the non-ketamine group. Similarly, the incidence of hypertension was not significantly affected by low-dose ketamine, however incidence of hypotension was significantly elevated in the non-ketamine group relative to the ketamine group (p = 0.047). There was no incidence of hallucination, nightmares and confusion among the mothers across all groups. The duration of surgery was significantly increased in K1 relative to NK1, but was not when K2 was compared to NK2. The neonatal Apgar score at 1 minute after birth was not significantly different across all groups.

Conclusion: This study indicated that the administration of intravenous low dose (0.3 mg/kg) ketamine during caesarean did not result in statistically significant maternal and neonatal adverse effects, suggestive that low-dose

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ketamine has a good safety profile for use perioperatively as an analgesic adjuvant to subarachnoid block in caesarean section.

Keywords: Ketamine; Safety; Caesarean-section

Abbreviations: ASA: American Society of Anaesthesiologists; SPSS: Statistical Package for Social Sciences.

Introduction

Provision of adequate analgesia after surgery remains topical globally with particular challenge in developing countries due to issues of availability of drugs and adequacy of facilities. Non-availability of opioid analgesics coupled with associated side effects including tolerance, dependence, hyperalgesia, allodynia, nausea, vomiting and central nevous system depression have necessitated the search for more effective and safer means of providing perioperative analgesia [1,2]. Caesarean section is a Grade 3 (major) surgery that results in severe pain for mothers often requiring adequate postoperative analgesia. 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 especially from deep vein thrombosis, reduced hospital costs and increased participant satisfaction [3].

Ketamine is a N-Methyl-D-Aspartate receptor antagonist is a dissociative anaesthetic with excellent analgesic property even at subanesthetic moderate doses, though with serious side effects including psychotomimetic and neurotoxicity [4-6], thus limiting its widespread use in pain management. However recent studies have reported that low-dose ketamine infusion in the perioperative period produced analgesia and decreased the requirements for opioid analgesics [7,8]. Low-dose ketamine has being suggested as an effective adjunct to spinal anaesthesia for pain management in caesarean section [9]. In order to validate the use of low-dose ketamine for perioperative pain management in caesarean section, it is expedient to assess its safety profile on foetal and maternal well-being, hence this study.

Methodology

This study was undertaken as a prospective, placebo-controlled, double-blind, randomised 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 and written 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 Anesthesiologists (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). No pre-medication was given to any of the participants. 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 participants for the study received the same intravenous fluid preload of 20 ml/kg normal saline over 10-15 minutes via an 18-G intravenous cannula sited in the non-dominant hand before receiving spinal anaesthesia at a sitting position.

All groups received heavy bupivacaine 10 mg injected over 30 seconds into the subarachnoid space after confirming correct placement of the spinal needle in the L_3-L_4 inter-space. Thereafter, each participant had caesarean section under spinal anaesthesia, using the same standard technique of surgery- Pfannenstiel incision, extraction of baby, exteriorization of the uterus and repair, and repair of layers. Group K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 minutes before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose via the vein 2 minutes after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 minutes before surgical incision, and 2 minutes after delivery of baby respectively. Maternal indices of

well-being including blood pressure, pulse rate, incidence of shivering, chest pain and hallucination was observed and recorded for 36 hours after subarachnoid block. An increase in maximum systolic blood pressure by > 30 % above the baseline systolic blood pressure or > 15 % rise of maximun diastolic pressure above the baseline diastolic blood pressure was considered hypertension. Similarly, a difference in the minimum systolic blood pressure relative to baseline blood pressure by > 30% or > 15 % drop in the minimum diastolic blood pressure relative to the baseline blood pressure was considered hypotension. A heart rate > 100 beats per minute was considered tachycardia, while a heart rate below 60 beats per minute was considered bradycardia. Neonatal well-being was assessed using Apgar score at 1 and 5 minutes after birth.

Post-operative analgesia which comprised intravenous pentazocine 30 mg 6 hourly, intramuscular diclofenac 75 mg 8 hourly, and intramuscular paracetamol 600 mg 8 hourly was initiated from the time participant first requested for analgesia as scheduled in the protocol of the hospital.

Data was obtained using a designed data collection proforma form. Data collected was analyzed using the Statistical Package for Social Sciences (SPSS) IBM 20.0 software (SPSS, Chicago, IL, USA) for windows. Results were analyzed using ANOVA and Chi-square statistics. Student Newman-Keuls test was used for post hoc analysis as appropriate. P value of < 0.05 was considered statistically significant.

Results

Demographic characteristics of the study groups

One-Way 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 (in years)	29.97 ± 5.78	28.77 ± 5.56	29.97 ± 4.97	31.33 ± 7.09	0.420
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+ SD. No statistical difference across all groups (ANOVA).

K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 minutes before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose via the vein 2 minutes after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 minutes before surgical incision, and 2 minutes after delivery of baby respectively.

Influence of Health Status on Pattern of Distribution of Participants into groups

The distribution of the participants into the treatment groups is independent of their health status according to ASA score (χ^2 = 2.805, p-value = 0.423). In other words, the composition of the participants by ASA score of physical health status across all treatments groups is comparable (Table 2).

Participant's Physical Health Status (ASA)						
	K1 (n = 30)	**K2** (n = 30)	**NK1** (n = 30)	**NK2** (n = 30)	**Total**	**Statistic**
Healthy (ASA 1)	19	17	13	18	67	χ^2 = 2.805
Mild Systemic condition (ASA II)	11	13	17	12	53	p = 0.423
Total	30	30	30	30	120	

Table 2: American Society of Anaesthesiologists (ASA) Score of Physical Health Status of the Participants.

K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 minutes before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose via the vein 2 minutes after delivery of baby, while groups NK1 and NK2 received equivalent volumes

of intravenous normal saline 2 minutes before surgical incision, and 2 minutes after delivery of baby respectively.

Effect of low dose intravenous ketamine (3 mg/kg) on duration of surgery

One-Way ANOVA revealed significant difference (p = 0.035) in the means of duration of surgery across the groups (Table 3a). The post-hoc analysis revealed that the duration of surgery was significantly prolonged in group K1 when compared with 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 3).

Duration of Surgery					
	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

Table 3: Effect of Low Dose Intravenous Ketamine (3 mg/kg) on Duration of Surgery. Values are expressed in Mean + SEM. * = p < 0.05 relative to K1, Duration of Surgery (DOS).

K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 minutes before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose via the vein 2 minutes after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 minutes before surgical incision, and 2 minutes after delivery of baby respectively.

Effect of low dose ketamine (3 mg/kg) on neonatal outcome score at 1 min after birth

The distribution of the neonatal Apgar score at I minute after birth across groups was independent (χ^2 = 2.805, p-value = 0.423) of the pattern and quality of drug administration to the groups (Table 4).

	K1 (n = 30)	**K2** (n = 30)	**NK1** (n = 30)	**NK2** (n = 30)	**Total**	**Statistic**
Apgar Score at 1 min < 7	7	1	5	5	18	χ^2 = 4.967
Apgar Score at 1 min > 7	23	29	25	25	102	p = 0.232
Total	30	30	30	30	120	

Table 4: Effect of Low Dose Intravenous Ketamine (3 mg/kg) on Neonatal Outcome Score at 1 minute after birth.

Values are expressed in Mean + SEM. K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2minutes before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose via the vein 2 minutes after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 minutes before surgical incision, and 2 minutes after delivery of baby respectively.

Effect of administration of Low Dose Ketamine (3 mg/kg) on Maternal Condition

There was no significant effect of low-dose ketamine on incidence of hypertension, tachycardia, chest pain and shivering among participants, however the incidence of hypotension is significantly lower in the ketamine group relative to the non-ketamine group (Table 5).

Maternal Condition	**K1+K2**	**NK1+NK2**	**Total**	**Statistics**
No of Hypotension	3	11*	14	χ^2 = 3.962
Absence of Hypotension	57	49	106	p = **0.047**
	K1+K2	**NK1+NK2**	**Total**	
No of Hypertension	1	1	2	χ^2 = 0.058
Absence of Hypertension	59	59	128	p = 0.476
	K1+K2	**NK1+NK2**	**Total**	
Presence of Tachycardia	2	1	3	χ^2 = 0.4
Absence of Tachycardia	58	59	117	p = 0.527

	K1+K2	NK1+NK2	Total	
Presence of Chest Pain	3	7	10	$\chi^2 = 0.982$
Absence of Chest Pain	57	53	110	p = 1.0
	K1+K2	**NK1+NK2**	**Total**	
Presence of Shivering	4	7	11	$\chi^2 = 0.4$
Absence of Shivering	56	53	109	p = 0.527

Table 5: Effect of Low Dose Intravenous Ketamine (3 mg/kg) on Maternal Condition.

Values are expressed in Mean + SEM. * $p < 0.05$ relative to KI+K2 (ketamine group) group. NK1+NK2 are the non-Ketamine group. (K1 received 0.3 mg/kg ketamine as a bolus dose intravenously 2 minutes before surgical incision (after subarachnoid block); K2 received 0.3 mg/kg ketamine as a bolus dose via the vein 2 minutes after delivery of baby, while groups NK1 and NK2 received equivalent volumes of intravenous normal saline 2 minutes before surgical incision, and 2 minutes after delivery of baby respectively.

Discussion

In the quest to address the inadequacies of perioperative analgesia, several modalities including the use of ketamine as an adjuvant to augment surgical pain management has been suggested [10]. Moderate doses of ketamine administration in humans have been reported to be associated with psychotomimetic and cytotoxic effects-major drawbacks in the justification of ketamine as appropriate analgesic drugs [5,11]. However several studies have reported that ketamine retains the analgesic property even at such low doses devoid of these major side effects [9,12]. Consequently, recent studies have explored and reported the significant beneficial effect of ketamine at subpsychotomimetic doses at augmenting analgesia of subrachnoid block in a number of major surgeries [13, 2]. Considering the peculiarity of caesarean section, the outcome of which is judged not only by factors come to other surgeries, but also by the well-being of mother and the newborn after surgery, this study assessed the safety profile of the reported low-dose ketamine analgesia on mothers and newborns post caesarean section surgery.

The demographic characteristics and The American Society of Anaesthesiologists (ASA) score of physical health status of the participants in this study were comparable across all groups. This indicates that the demographic characteristics and pre-surgery health status of the participants had no influence on the outcome of this study. The indices of maternal well-being including pulse rate, incidence of chest pain and shivering were not significantly different when low-dose ketamine group was compared to the non-ketamine group. Similarly, the incidence of hypertension was not significantly affected by low-dose ketamine, although incidence of hypotension was significantly elevated in the non-ketamine group relative to the ketamine group ($p = 0.047$). This is suggestive of a beneficial effect of ketamine on hypotension. This is agreement with previous studies that ketamine (though at higher doses than that employed in this study) is the only anaesthetic with sympathomimetic action, which produces stimulation at cardiac level and in the peripheral resistances [14,15]. There was no incidence of hallucination, nightmares and confusion among the mothers across all groups indicative of the subpchytomimetic, hence safety of the dose of ketamine employed in this study [5,9,16,17]. A prominent unwanted effect of most anaesthetic agents and opioid analgesic employed in perioperative management of pain in newborns is respiratory depression [18] and cytotoxity on brain cells [6], hence this study employed the safety profile of low-dose ketamine on central nervous function of the neonates using Apgar score at 1 min. it was reported that the neonatal Apgar score at 1 minute after birth was not significantly affected across all groups in this study.

Conclusion

Taken together, the results of this study indicated that administration of intravenous low dose (0.3 mg/kg) ketamine during caesarean did not result in statistically significant maternal and neonatal adverse effects. This indicates that low-dose ketamine has a satisfactory short term safety profile for use perioperatively as an analgesic adjuvant to subarachnoid block in caesarean section. It is recommended that the long term consequence of early exposure of neonates to low-dose ketamine should be explored.

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