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Evaluation of Oral Ketamine for Pain Relief during Normal Labour in Nigerian Parturients

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Abstract

Background: We evaluated the efficacy of oral ketamine for pain relief during normal labour in Nigerian parturients.

Method: A prospective, non-placebo, single blind randomised study was carried out. Two hundred and seventy three (273) booked parturients in active phase of labour were randomly assigned to three treatment groups (A-C). The dosages of oral ketamine that they received were as follows: Group A- 4 mgkg^{-1}; group B- 5 mgkg^{-1}; and group C- 6 mgkg^{-1}. Pain assessment was carried out using both the visual analogue scale (VAS) and verbal rating scale (VRS). The efficacy criterion was provision of adequate analgesia (i.e. no or mild pain/discomfort) defined as VAS ≤3 and/or VRS ≤2 without anaesthesia. Baseline vital signs of the parturients were taken including pulse rate, blood pressure and respiratory rate. Foetal

heart rate was also assessed. Body weight and side effects were recorded. Comparisons of the efficacy and safety of the different dosages of oral ketamine were made.
Results: The minimum sub-anaesthetic dose of oral Ketamine was 4mgkg^{-1} with 93.4% efficacy. The 5mgkg^{-1} and 6mgkg^{-1} gave 95.9% and 98.6% efficacy respectively. Oral Ketamine was associated with a high side effect profile with a statistically significant dose-dependent pattern for dizziness (group A-59.3%, group B-71.4%, group C-75.8%, p=0.04), nausea/vomiting (group A-42.9%, group B-58.2%, group C-60.4%, p=0.03), and hallucination (group A-11%, group B-16.5%, group C-25.3%, p=0.04). Although sedation was commonly reported, it had no impact on pain assessment by VAS or VRS.
Conclusion: The sub-anaesthetic dose of 4 mgkg^{-1} oral ketamine provided effective labour analgesia with more tolerable side effects. The use of lower doses should be explored in order to reduce the side effects to the barest minimum.
Key words: Analgesia, Efficacy, Oral ketamine, Labour, Sub-anaesthetic

INTRODUCTION

Labour and childbirth are painful processes, which occur in all social and ethnic groups.[1] Labour pain is the result of many complex interactions, physiological and psychological, which exert excitatory as well as inhibitory effects. Pain is virtually experienced in all the stages of labour and the severity of pain parallels the duration and intensity of uterine contraction.[2] Pain has adverse effects on labour, the mother and foetus. Pain can lead to maternal hyperventilation and respiratory alkalosis, compensatory metabolic acidosis, hormonal imbalance, and elevated blood pressure. It can further prolong the process of labour and ultimately lead to foetal distress.[3]

The need to make the mother pain-free and comfortable during labour and delivery cannot be overemphasized. The aim of modern obstetrics is a healthy mother and baby with lowest level of morbidity possible and a good experience of birth for the mother and partner. Approach to labour analgesia could be pharmacological or non-pharmacological.[4] Pharmacological agents could be opioid or non-opioid. While the analgesic benefits of the widely used drugs are well-recognised, they have a number of drawbacks that limit their use during labour. Opioid analgesics provide adequate analgesia to the parturients, but may lead to respiratory depression in both the mother and the new born. Moreover, the strong opioids such as morphine and fentanil are not readily available in resource-limited settings. Despite the fact that non-pharmacological techniques obviate the need for chemical analgesia and possibly cause no harm to the mother, the baby or the progress of labour, they all require adequate antenatal preparation that cannot be guaranteed in developing countries. Moreover, a number of women offered these techniques still experience significant labour pain. Epidural analgesia, the internationally acclaimed "gold standard" for pain relief in labour, may be easily administered in developed countries where

expertise, local anaesthetics and availability of epidural kits are no problems. This is not the case in resource-limited settings.

On the other hand, non-opioid analgesics are more readily available and have a better side effect profile compared to opioids. The main problem with their use is that most of the readily available agents are less effective than opioids. However, the non-opioid analgesic ketamine, an N-Methyl-D-Aspartate derivative, has been shown to be effective for labour analgesia when administered parenterally.[3] Despite the wide availability of ketamine, it has not been evaluated for pain relief in labour when administered orally. Considering the convenience of oral drug administration, an effective oral labour analgesic will be a welcome development in resource- limited settings where shortage of qualified anaesthetic manpower cannot support constant use of parenteral labour analgesia. The aim of this study was to evaluate the efficacy of oral ketamine for pain relief during normal labour in parturients accessing care in a resource-limited tertiary health facility in Nigeria.

PATIENTS AND METHODS

Study design and study population

This was a prospective, non-placebo, single blind randomised study conducted from January to December 2008 at the Ebonyi State University Teaching Hospital, Abakaliki. Three different doses of oral ketamine were compared for labour analgesia among booked pregnant women selected for vaginal delivery by their managing obstetricians. Ethical approval was granted by the Research and Ethics Committee of the hospital. Informed consent was obtained from each of the participants. All consenting booked pregnant women whose foetuses presented normally (i.e. lying longitudinally with cephalic presentation) and were in active phase of labour (cervical dilatation ≥ 4cm) were included in the study. Exclusion criteria included trial of labour, scarred uterus, hypertension, preeclampsia/eclampsia, cardiac disease, liver disease, malpresentation, multiple pregnancies, neuropsychiatric disorders, preterm labour(gestational age < 37 weeks by LMP), precious baby, and patients with any contraindication for vaginal delivery. A minimum sample size of 273 subjects was calculated using the Fisher's formula.[5] There were three treatment groups and ninety one participants were enrolled for each group.

Data collection

A pilot study was initially conducted using 12 parturients categorised into 3 treatment groups of 4 parturients each: $6mgkg^{-1}$, $8mgkg^{-1}$ and $10mgkg^{-1}$ oral ketamine. The result of the pilot study was not included in the main study. Due to the very high level of sedation resulting from oral ketamine doses greater than $6mgkg^{-1}$ in the pilot study, a maximum sub-anaesthetic dose of $6mgkg^{-1}$ was adopted. Eligible parturients were assigned into three treatment groups by random balloting using the coded numbering system as follows:

1. Group A-4mgkg-1 of oral ketamine
2. Group B-5mgkg-1 of oral ketamine
3. Group C-6mgkg-1 of oral ketamine

The parturients were made to pick from an envelope containing the coded group A, B, C and the group that a parturient picked was assigned to her. The drug for each group was prepared by a pharmacist. Based on the group to which a participant belonged, ketamine sterile solution (50mg/ml) was prepared according to the patient's weight and diluted with sterile water and 0.5gmml^{-1} of glucose D for oral administration.[6] The glucose D was added to mask the bitter taste of ketamine.[7] The patients were not pre-medicated. An emergency tray containing atropine, diazepam, hydralazine, lidocaine and an Ambu bag was set up and an efficient oxygen delivery system and suction machine were made available. Venous access was established in each patient and connected to 500ml of 5% dextrose water. Baseline vital signs of the paturients were taken including pulse rate, blood pressure, and respiratory rate. Foetal heart rate was assessed using a foetoscope. All the measured parameters were recorded in the proforma.

Patient's pain assessment was carried out using both the Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS). Visual Analogue Scale is a 10 cm, unmarked straight line with the left end of the line representing *"no pain"* and the right end of the line representing "*the worst pain*". Patients were asked to mark on the line where they think their pain was. It was emphasized that the pain in question was pain occurring with contractions. The VAS was interpreted as follows: 0= no pain, 1-3= mild pain, 4-6= moderate pain, 7-10= severe pain.

Verbal Rating Scale (VRS) was carried out in English language or Igbo language (for non-literate participants) based on a 5 point rating scale. The Igbo translation of the VRS was based on the validated translation developed by Ezike and Odiakosa.[7] The English and Igbo equivalents of the VRS are shown in Table 1.

Table 1: Visual Rating Scale (VRS)

VRS	Interpretation in English	Interpretation in Igbo
0	No pain	Ufu adiro
1	Mild pain	Nwantinti ufu
2	Discomforting	Obele ufu
3	Distressing	Nnukwu ufu
4	Horrible	Ajo ufu
5	Excruciating	Nkilika ufu

Rescue analgesia which was half of the initial dose of oral ketamine was administered to patients with VAS ≥ 3, and/or VRS ≥3. Monitoring of the patients' cardio-respiratory parameters was done by the obstetric doctors in the labour ward at fifteen minutes intervals from the time oral ketamine was administered until the delivery of the baby. The efficacy criterion was provision of adequate analgesia (i.e. no or mild pain/discomfort) defined as VAS ≤3 and/or VRS ≤2 without alteration of consciousness.[7]

The proforma for each participant was completed using designated codes each consisting of a serial number, group alphabet, and dose of oral ketamine e.g. code no 1A4 means serial number 1, group A and oral ketamine dose 4mgkg^{-1}. This was explained to the pharmacist to enable him constitute the dose of ketamine. Assessment of safety of oral ketamine was evaluated using the occurrence of adverse/side effects such as hallucination, nausea and vomiting, hypersalivation, dizziness, sedation, headache and nystagmus reported during labour and post delivery. Side effects were recorded according to the reports obtained from the patients.

Data analysis

Data was analysed using the Statistical Product and Service Solutions (SPSS) version 16. Efficacy of the various doses of oral ketamine for labour pain relief was determined using the chi-square test. Statistical significance was set at $p<0.05$.

RESULTS

The characteristics of the study population are shown on Table 2.

Table 2: Characteristics of the study population

Groups	A n=91	B n=91	C n=91	Total 273	p-value
Age (yr) mean/SD	35.3 ± 10.1	37.9 ± 8.2	36.7 ± 9.8	36.6 ± 9.4	0.61
Weight (kg) mean/SD	68.2 ± 12.7	70.6 ± 10.6	70.0 ±11.7	69.6 ± 11.7	0.37
Height (m) mean/SD	1.65 ± 0.7	1.63 ± 0.06	1.64 ± 0.07	1.64 ± 0.1	0.14
BMI (kgm^{-2}) mean/SD	25.1 ± 5.2	26.5 ±3.6	26.1 ± 4.2	25.9 ± 4.4	0.12
Educational status, n (%)					<0.0001
Primary	16 (17.6)	7 (7.7)	40 (44.0)	63	
Secondary	27 (29.7)	54 (59.3)	27 (24)	108	
Tertiary	48 (52.7)	30 (33.0)	24 (26.4)	102	
Parity, n (%)					0.37
Primipara (1)	44 (48.4)	35 (38.5)	42 (46.2)	121	

Multipara (≥2)	47 (51.6)	56 (61.5)	49 (53.8)	152

Group A=4mgkg^{-1}, Group B-5mgkg^{-1} and Group C-6mgkg^{-1} of oral Ketamine .

The age of the parturients ranged from 21 to 40 years with a mean of 36.6 ± 9.4 years. The mean BMI of the study population was 25.9 ± 4.4 kgm^{-2}. There were no significant differences in the age, weight, height and BMI of the parturients in the three groups. The participants were similar in their parity (p=0.54). However, there was a statistically significant difference among the three groups in terms of educational status (p<0.0001). None of the parturients required additional rescue analgesia.

Table 3: Pain assessment using Visual Analogue Scale (VAS)

		VAS at 0min (Baseline value)				
Group	Dosage of ketamine given mgkg^{-1}	No pain	Mild pain	Severe pain	Total	P-value
A	4mg/kg	0	0	91	91	
		0%	0%	100.0%	100.0%	
B	5mg/kg	0	0	91	91	-
		0%	0%	100.0%	100.0%	
C	6mg/kg	0	0	91	91	
		0%	0%	100.0%	100.0%	
	Total	0	0	273	273	
		0%	0%	100.0%	100.0%	
		VAS 30mins after Ketamine administration				
A	4mg/kg	36	39	16	91	
		39.6%	42.9%	17.6%	100.0%	
B	5mg/kg	48	33	10	91	0.000
		52.7%	36.3%	11.0%	100.0%	
C	6mg/kg	71	20	0	91	
		78.0%	22.0%	.0%	100.0%	
	Total	155	94	26	273	

		57.0%	34.4%	9.5%	100.0%	
		VAS 45mins after Ketamine administration				
A	4mg/kg	50	31	10	91	
		55.0%	34.0%	11.0%	100.0%	
B	5mg/kg	60	24	7	91	0.000
		65.9%	26.4%	7.7%	100.0%	
C	6mg/kg	76	15	0	91	
		83.5%	16.5%	0%	100.0%	
	Total	186	70	17	273	
		68.1%	25.6%	6.2%	100.0%	
		VAS 90mins after Ketamine administration				
A	4mg/kg	47	30	14	91	
		51.7%	33.0%	15.4%	100.0%	
B	5mg/kg	55	28	8	91	0.511
		60.4%	30.8%	8.8%	100.0%	
C	6mg/kg	56	30	5	91	
		61.5%	33.0%	5.5%	100.0%	
	Total	158	88	27	273	
		57.9%	32.2%	9.9%	100.0%	

Table 3 shows pain assessment using VAS. The grade *moderate pain* was not included in the table because none of the subjects reported her pain to be "moderate". There was a statistically significant difference in VAS 30 min after administration of oral ketamine in the three groups, with a report of better analgesic effect with higher doses of ketamine ($p<0.0001$). The majority (78%) of the parturients in group C reported no pain compared to 48 (52.7%) for group B and 36 (39.6%) for group A. None of the parturients in group C reported severe pain at 30 minutes compared to 10 (11%) for group B and 16 (17.6%) for group A. At 45 minutes after administration of oral ketamine, the VAS scores showed that the parturients still experienced a statistically significant higher analgesic effect with higher doses of ketamine ($p<0.0001$). Compared to 50 (55%) and 60 (65.9%) who experienced no pain for group A and B

respectively, 76 (83.5%) of those in group C reported no pain. On the other hand, none of participants in group C experienced severe pain at 45 minutes compared to 7 (7.7%) for group A and 10 (11%) for group B. There was no statistically significant difference in VAS 90 minutes after ketamine administration across the three treatment groups (p=0.51). A comparison of the three groups using VRS is shown in Table 4.

Table 4: Pain assessment using Verbal Rating Scale (VRS)

Group	Dosage	No pain	Mild pain	Discomforting	Excruciating	Total	p-value
VRS at 0min (Baseline value)							
A	4mg/kg	0	0	0	91	91	
		0%	0%	0%	100.0%	100.0%	
B	5mg/kg	0	0	0	91	91	
		0%	0%	0%	100.0%	100.0%	-
C	6mg/kg	0	0	0	91	91	
		0%	0%	0%	100.0%	100.0%	
	Total	0	0	0	273	273	
		0%	0%	0%	100.0%	100.0%	
VRS 30mins after Ketamine administration							
A	4mg/kg	27	55	6	3	91	
		29.7%	60.4%	6.6%	3.3%	100.0%	
B	5mg/kg	39	52	0	0	91	
		42.9%	57.1%	0%	0%	100.0%	0.000
C	6mg/kg	66	25	0	0	91	
		72.5%	27.5%	.0%	.0%	100.0%	
	Total	132	132	6		3 273	
		48.4%	48.4%	2.2%	1.1%	100.0%	
VRS 45mins after Ketamine administration							
A	4mg/kg	37	54	0	0	91	
		40.7%	59.3%	0%	0%	100.0%	
B	5mg/kg	53	38	0	0	91	0.000

		58.2%	41.8%	0%	0%	100.0%	
C	6mg/kg	66	25	0	0	91	
		72.5%	27.5%	0%	0%	100.0%	
	Total	156	117	0	0	273	
		57.1%	42.9%	0%	0%	100.0%	
VRS 90mins after Ketamine administration							
A	4mg/kg	37	54	0	0	91	
		40.7%	59.3%	0%	0%	100.0%	
B	5mg/kg	48	43	0	0	91	0.003
		52.7%	47.3%	0%	0%	100.0%	
C	6mg/kg	60	31	0	0	91	
		65.9%	34.1%	0%	0%	100.0%	
	Total	145	128	0	0	273	
		53.1%	46.9%	0%	0%	100.0%	

The pain grades "distressing" and "horrible" were not included in the table because they were not reported by any of the subjects. The VRS 30 minutes after administration of oral ketamine showed a statistically significant higher rate of pain relief for higher doses of oral ketamine (p=0.001). In group A, 27 (29.7%) parturients experienced no labour pain, 55 (60.4%) experienced mild pain while 6 (6.6%) experienced labour as "discomforting" and 3 (3.3%) experienced labour as "excruciating". In group B, 39 (42.9 %) experienced no labour pain, 52 (57.1%) experienced mild labour pain and none of them either reported labour pain as "discomforting" or "excruciating". In group C, 66 (72.5%) of the parturients experienced no labour pain and 25 (27.5%) experienced mild labour pain while none experienced "discomforting" or "excruciating" pain. Although none of the parturients in the three groups reported labour pain to be "discomforting" or "excruciating" at 45 minutes and 90 minutes after ketamine administration, the VRS still showed a statistically significant difference both at 45 minutes (p<0.0001) and 90 minutes (p=0.003).

Based on the combination of results obtained by VAS and VRS at 45 and 90 minutes, 4 $mgkg^{-1}$ of oral ketamine had an overall efficacy of 93.4%, while 5$mgkg^{-1}$ and 6$mgkg^{-1}$ had 95.9% and 98.6% efficacy respectively.

To determine if sedation had any impact on pain assessment, we analyzed the VAS and VRS for non-sedated and sedated parturients separately. The findings showed that sedation had no impact on pain assessment except for VRS at 90 minutes. The VAS for sedated and non-sedated parturients is shown in Tables 5a and 5b respectively.

Table 5a: Pain assessment using Visual Analogue Scale (VAS) for non-sedated parturients

		VAS at 0min (Baseline value)				
Group	Dosage of ketamine given $mgkg^{-1}$	No pain	Mild pain	Severe pain	Total	P-value
A	4mg/kg	0	0	57	57	
		0%	0%	100.0%	100.0%	
B	5mg/kg	0	0	50	50	-
		0%	0%	100.0%	100.0%	
C	6mg/kg	0	0	48	48	
		0%	0%	100.0%	100.0%	
	Total	0	0	155	155	
		0%	0%	100.0%	100.0%	
		VAS 30mins after Ketamine administration				
A	4mg/kg	26	22	9	57	
		45.61%	38.59%	15.79%	100.0%	
B	5mg/kg	23	21	6	50	0.000
		46%	42%	12%	100.0%	
C	6mg/kg	6	42	0	48	
		12.5%	87.5%	.0%	100.0%	
	Total	55	85	15	155	
		VAS 45mins after Ketamine administration				
A	4mg/kg	33	18	6	57	
		57.89%	31.58%	10.53%	100.0%	
B	5mg/kg	27	20	3	50	0.02

		54%	40%	6%	100.0%	
C	6mg/kg	39	9	0	48	
		81.25%	18.75%	0%	100.0%	
	Total	99	47	9	155	
		VAS 90mins after Ketamine administration				
A	4mg/kg	29	16	12	57	
		61.70%	34.0%	25.53%	100.0%	
B	5mg/kg	24	21	5	50	0.08
		48.0%	42.0%	10.0%	100.0%	
C	6mg/kg	26	20	2	48	
		54.2%	41.7%	4.2%	100.0%	
	Total	86	57	19	155	

Table 5b: Pain assessment using Visual Analogue Scale (VAS) for sedated parturients

		VAS at 0min (Baseline value)				
Group	Dosage of ketamine given $mgkg^{-1}$	No pain	Mild pain	Severe pain	Total	P-value
A	4mg/kg	0	0	34	34	
		0%	0%	100.0%	100.0%	
B	5mg/kg	0	0	41	41	
		0%	0%	100.0%	100.0%	
C	6mg/kg	0	0	43	43	
		0%	0%	100.0%	100.0%	
	Total	0	0	118	118	
		0%	0%	100.0%	100.0%	
		VAS 30mins after Ketamine administration				
A	4mg/kg	10	17	7	34	

		29.4%	50%	20.6%	100.0%	
B	5mg/kg	10	27	4	41	0.04
		24.4%	65.9%	9.8%	100.0%	
C	6mg/kg	14	29	0	43	
		32.6%	67.4%	.0%	100.0%	
	Total	34	73	11	118	
		VAS 45mins after Ketamine administration				
A	4mg/kg	17	13	4	34	
		50.0%	38.2%	11.8%	100.0%	
B	5mg/kg	33	4	4	41	0.002
		80.4%	9.8%	9.8%	100.0%	
C	6mg/kg	37	6	0	43	
		86%	14%	0%	100.0%	
	Total	87	23	8	118	
		VAS 90mins after Ketamine administration				
A	4mg/kg	18	14	2	34	
		53%	41.2%	5.8%	100.0%	
B	5mg/kg	25	13	3	41	0.58
		43.9%	31.7%	7.3%	100.0%	
C	6mg/kg	30	10	3	43	
		69.7%	23.3%	7%	100.0%	
	Total	73	37	8	118	

At 30 minutes VAS, the statistically significant difference in pain relief across the 3 doses of oral ketamine remained for both non-sedated ($p<0.0001$) and sedated ($p=0.004$) paturients. The significant difference in pain relief was still seen at 45 minutes VAS: non-sedated ($p=0.02$), sedated ($p=0.002$). As was seen when the parturients were analyzed irrespective of sedation, there was no

statistically significant difference in VAS 90 minutes after ketamine administration across the three treatment groups for both non-sedated (p=0.08) and sedated (p=0.58) parturients.

The VRS for non-sedated and sedated subjects are summarized in Tables 6a and 6b.

Table 6a: Pain assessment using Verbal Rating Scale (VRS) for non-sedated parturients

VRS at 0min (Baseline value)							
Group	Dosage	No pain	Mild pain	Discomforting	Excruciating	Total	p-value
A	4mg/kg	0	0	0	57	57	
		0%	0%	0%	100.0%	100.0%	
B	5mg/kg	0	0	0	50	50	
		0%	0%	0%	100.0%	100.0%	
C	6mg/kg	0	0	0	48	48	
		0%	0%	0%	100.0%	100.0%	
	Total	0	0	0	155	155	
		0%	0%	0%	100.0%	100.0%	
VRS 30mins after Ketamine administration							
A	4mg/kg	18	35	2	2	57	
		31.6%	61.4%	3.5%	3.5%	100.0%	
B	5mg/kg	21	29	0	0	50	0.002
		42%	58%	0%	0%	100.0%	
C	6mg/kg	33	15	0	0	48	
		68.7%	31.3%	.0%	.0%	100.0%	
	Total	72	79	2	2	155	
VRS 45mins after Ketamine administration							
A	4mg/kg	25	32	0	0	57	
		43.9%	56.1%	0%	0%	100.0%	0.0007
B	5mg/kg	25	25	0	0	50	

		50%	50%	0%	0%	100.0%	
C	6mg/kg	38	10	0	0	48	
		79.2%	20.8%	0%	0%	100.0%	
	Total	88	67	0	0	155	
VRS 90mins after Ketamine administration							
A	4mg/kg	23	34	0	0	57	
		40.4%	59.6%	0%	0%	100.0%	
B	5mg/kg	25	25	0	0	50	0.08
		50%	50%	0%	0%	100.0%	
C	6mg/kg	30	18	0	0	48	
		62.5%	37.5%	0%	0%	100.0%	
	Total	78	77	0	0	155	

Table 6b: **Pain assessment using Verbal Rating Scale (VRS) for sedated parturients**

VRS at 0min (Baseline value)							
Group	Dosage	No pain	Mild pain	Discomforting	Excruciating	Total	p-value
A	4mg/kg	0	0	0	34	34	
		0%	0%	0%	100.0%	100.0%	
B	5mg/kg	0	0	0	41	41	
		0%	0%	0%	100.0%	100.0%	
C	6mg/kg	0	0	0	43	43	
		0%	0%	0%	100.0%	100.0%	
		0	0	0	118	118	
		0%	0%	0%	100.0%	100.0%	
VRS 30mins after Ketamine administration							

A	4mg/kg	9	20	4	1	34	
		26.5%	58.8%	11.8%	2.9%	100.0%	
B	5mg/kg	18	23	0	0	41	0.000
		43.9%	56.1%	0%	0%	100.0%	
C	6mg/kg	33	10	0	0	43	
		76.7%	23.3%	.0%	.0%	100.0%	
	Total	50	53	4	1	118	
				VRS 45mins after Ketamine administration			
A	4mg/kg	12	22	0	0	34	
		35.3%	64.7%	0%	0%	100.0%	
B	5mg/kg	28	13	0	0	41	0.007
		68.3%	31.7%	0%	0%	100.0%	
C	6mg/kg	28	15	0	0	43	
		65.1%	34.9%	0%	0%	100.0%	
	Total	68	50	0	0	118	
				VRS 90mins after Ketamine administration			
A	4mg/kg	14	20	0	0	34	
		41.2%	58.8%	0%	0%	100.0%	
B	5mg/kg	23	18	0	0	41	0.04
		34.1%	43.9%	0%	0%	100.0%	
C	6mg/kg	30	13	0	0	43	
		69.8%	30.2%	0%	0%	100.0%	
	Total	67	51	0	0	118	

At 30 minutes VRS, the statistically significant difference in pain relief across the treatment groups was still evident both for non-sedated (p=0.002) and sedated (p<0.0001) parturients. This remained the case at 45 minutes VRS with better analgesic effect at higher doses of oral ketamine: non-sedated (p=0.0007), sedated (p=0.007). However, At 90 minutes VRS only sedated paturients showed a statistically significant difference in pain relief across the three treatment groups (p=0.04). Although better pain relief was still reported by more parturients at higher doses of oral ketamine among non-sedated subjects, the difference in pain relief across the 3 doses did not attain statistical significance (p=0.08).

The mean duration of first stage of labour was 5.81 ± 2.29 hours. The mean duration of labour was shorter in parturients who received 6 $mgkg^{-1}$ oral ketamine (5.37 ± 1.95 hours) compared to those that received 4 $mgkg^{-1}$ (5.93 ± 1.96 hours) and 5 $mgkg^{-1}$ (6.18 ± 2.85 hours) but the difference was not statistically significant (p=0.053).

The adverse effects of oral ketamine reported by the parturients are summarized in Table 7.

Table 7: Comparison of adverse/side effects among the three study groups

Adverse/side effects	Ketamine Dose			p-values
	A (4$mgkg^{-1}$) N=91 n (%)	B (5$mgkg^{-1}$) N-91 n (%)	C (6$mgkg^{-1}$) N=91 n(%)	
Headache	0 (0.0)	1 (1.1)	2 (2.2)	0.36
Dizziness	54 (59.3)	65 (71.4)	69 (75.8)	0.04
Nystagmus	28 (30.8)	30 (33.0)	40 (44.0)	0.14
Hallucinations	10 (11.0)	15 (16.5)	23 (25.3)	0.04
Sedation	34 (37.4)	41 (45.1)	43 (47.3)	0.37
Nausea and vomiting	39 (42.9)	53 (58.2)	55 (60.4)	0.03
Hypersalivation	2 (2.2)	4 (4.4)	5 (5.5)	0.51

Generally, the parturients reported the adverse effects of oral ketamine to be transient. Apart from headache and hypersalivation which were uncommon, most of the adverse effects investigated for were common across the three groups. In each group, dizziness was the most commonly reported adverse effect (59.3% for group A, 71.4% for group B and 75.8% for group C), followed by nausea and vomiting (42.9% for group A, 58.2% for group B and 60.4% for group C), and sedation (37.4 % for group A, 45.1% for group B and 47.3% for group C). The adverse

effects which showed a statistically significantly dose-dependent pattern were dizziness (p=0.04), hallucinations (p=0.04), as well as nausea and vomiting (p=0.03).

Assessment of the newborns based on APGAR score is shown in Table 8.

Table 8: Apgar score in one minute/five minute of the babies according to the treatment groups of the mothers

		Dosage of Ketamine given $mgKg^{-1}$				
		$4mgkg^{-1}$	$5mgkg^{-1}$	$6mgkg^{-1}$	Total	P-value
APGAR Score in 1min	<7	0	0	10	10	0.000
	≥7	91	91	81	261	
APGAR Score in 5mins	<7	0	0	0	0	1.000
	≥7	91	91	91	273	

At one minute APGAR, 10 (11.0%) babies of mothers who received 6 $mgkg^{-1}$ had scores <7 compared to none for the 4$mgkg^{-1}$ and 5$mgkg^{-1}$groups (p<0.001). At 5 minutes APGAR, all the babies of the mothers in the 3 treatment groups had scores of≥ 7.

DISCUSSION

The findings of this study show that oral ketamine provided effective analgesia, regarded as presence of no or mild pain during labour, in an overwhelming majority of our parturients. The three doses of oral ketamine were all effective for labour analgesia. The minimum sub-anaesthetic dose of oral ketamine used for labour analgesia was 4$mgkg^{-1}$ with 93.4% efficacy. The 5$mgkg^{-1}$ and 6$mgkg^{-1}$ gave 95.9% and 98.6% efficacy respectively suggesting a dose-dependent effect. However, we found that the effective analgesia provided by oral ketamine was at the cost of high side effect profile. Despite the considerable proportion of parturients who experienced sedation, pain assessment by VAS and VRS were largely unaffected by sedation.

Ketamine, in sub-anaesthetic doses, has been shown to provide acceptable intra and post-operative analgesia.[8] However, the administration of ketamine via the oral route is not routinely

practised and we did not find any readily available data regarding the use of oral ketamine for labour analgesia. Ezike and Odiakosa[7] in Enugu, South East Nigeria documented the effective analgesic effect of oral ketamine for wound care procedures in adult patients with burns. The minimum sub-anaesthetic dose of oral ketamine for burns dressing was 6mgkg^{-1} with efficacy of 65% with conscious sedation. In agreement with our observation, higher doses of ketamine provided better pain relief with efficacy of 92.5% at 8mgkg^{-1} and 95% at 10mgkg^{-1}. Although the efficacy of 65% obtained using 6mgkg^{-1} oral ketamine in that study appears much less than the 98.6% obtained in our study using 6mgkg^{-1} oral ketamine for labour analgesia, it very much stands to reason that the ketamine analgesic efficacies of both studies should not really be compared since the pains of burns and labour have different mechanisms. It should also be pointed out that unlike our study where the efficacy criterion was based on both VAS and VRS, that of Ezike and Odiakosa[7] was based on VRS alone. The use of oral ketamine for pain relief has also been described in adults for post amputation stump pain, post herpetic neuralgia, phantom limb pain, neuropathic pain, cancer pain, and epidermolysis bullosa.[9-14] While most of these studies documented the efficacy of oral ketamine as monotherapy, Kannan *et al*[10] reported the benefits of oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. Enarson *et al*[9] however observed that the analgesic benefits of ketamine appeared to be most pronounced in patients with pain histories of less than five years.

The analgesic benefit of ketamine when administered parenterally during labour has been documented in a number of studies.[3,12] In the work of Ganla *et al*,[3] 50 term Indian parturient primigravidae were administered intravenous (IV) ketamine for pain relief at an initial bolus dose (0.5mgkg^{-1}) followed by 0.25mgkg^{-1} at an interval of 20 to 30 minutes until full cervical dilatation was achieved. Complete analgesia was achieved in 70% of the parturients while 16% had additional medication for optimal pain relief and only 12% had unsatisfactory pain relief. Although the route of administration and dosage of ketamine in that study differs from that of our study, the analgesic efficacy of oral ketamine used in our study compares favourably with what was achieved using IV ketamine. Similarly, in a previous study in Nigerian paturients, Ayangade[15] reported that carefully controlled IV administration of ketamine produced excellent analgesia in the active phase of labour but with dissociative sleep. Of the 50 patients studied, 49 (98%) were unable to remember if contractions were painful. Compared to the general population, the introduction to delivery interval was significantly shortened in that study (3.6 vs. 6 hours). The ketamine analgesic efficacy of 98% achieved in that study involving Nigerian women is similar to what was obtained using oral ketamine in our study despite the fact that our study involved a larger population of parturients.

The analgesic benefit of sub-anaesthetic doses of parenteral ketamine during labour has also been documented in other studies.[16-18]

Pharmacokinetically, ketamine is well absorbed orally, nasally, rectally, subcutaneously, IV and intramuscularly (IM). Oral bioavailability is 16-20% as opposed to 93% for IM or IV.[19] The compound is metabolized extensively by the hepatic cytochrome p450 system in the liver by N-demethylation and hydroxylation of the cyclohexanone ring. Its primary metabolite norketamine is only one-third to one-fifth as potent as the original compound but may be involved in the prolonged analgesic actions of ketamine.[20]

The comparable analgesic efficacy rates of ketamine for obstetric use between our study and those that employed IV administration means that the convenience of oral administration may make it more desirable. The argument regarding the use of higher doses in our study to achieve effective analgesia compared to the study of Ganla *et al*[3] can be settled by highlighting what constitutes sub-anaesthetic dose ketamine. Sub-anaesthetic dose ketamine is defined as a bolus dose of less than 2mgkg^{-1} when administered IM or less than 1mgkg^{-1} when administered via IV or epidural routes.[21] This definition does not specify the sub-anaesthetic dose for oral route.[21] A number of studies done using oral ketamine have achieved analgesia without anaesthesia at higher doses than the sub-anaesthetic doses of parenteral routes.[7,10-13] The minimum effective sub-anaesthetic dose of oral ketamine in the study by Ezike and Odiakosa[7] was 6mgkg^{-}. At 5mgkg^{-1} dose of oral ketamine, Soyannwo *et al*[6] found that it did not produce psychic phenomenon usually associated with parenteral ketamine.

Apart from effective relief of labour pain, good labour analgesia should be accompanied by early return to normal life style with minimal side effects. A high side effect profile was a major drawback to oral ketamine use in our study and this was also found to be dose-dependent. In descending order, the commonest side effects were dizziness, nausea and vomiting, sedation, nystagmus, and hallucinations. However, it was only dizziness, hallucination, as well as nausea and vomiting that showed a statistically significant dose-dependent side effect profile. As a phencyclidine analogue, ketamine is known for some psychic adverse effects associated with the hallucinogens especially in adults.[6,19] In this study, hallucination was reported in 20.8%, 31.3% and 47.9% for the 4mgkg^{-1}, 5mgkg^{-1} and 6mgkg^{-1} oral ketamine doses respectively. In a previous study involving Nigerian parturients,[15] 80% of patients experienced and narrated dreams. Considering that the total dose of ketamine was not stated in that study, it will be difficult to compare the rate of hallucination they found and the observation made in our study. Sarkar et al[22] used a bolus of 0.2-0.4mgkg^{-1} followed by an infusion of 1mgkg^{-1}h^{-1} and reported hallucination in 14% of their parturients while Ganla *et al*[3] used bolus dose of 0.5mgkg^{-1} followed by an intermittent dose of

0.25mgkg^{-1} at intervals of 20-30 minutes with 54% of their patients reporting hallucinations. Contrarily, Joselyn *et al*[16] used 0.1mgkg^{-1} bolus dose followed by an infusion rate of 0.2mgkg^{-1}h^{-1} and recorded no hallucination or unpleasant dreams. This suggests that further reduction in the dose of oral ketamine below the 4mgkg^{-1} will significantly reduce the rate of hallucination.

The frequency of sedation was also dose dependent. About 28.8% of the patients that received 4mgkg^{-1} oral ketamine had mild to moderate sedation compared to 5mgkg^{-1} and 6mgkg^{-1} that were 34.7% and 36.4% respectively. None of our patients had severe sedation. In the work done by Joselyn *et al*[16] 27% of the women reported feeling drowsy but were rousable. Whereas sedation was desirable in the work of Ezike and Odiakosa,[7] Ayangade[15] and Ganla *et al*[3] did not report the occurrence of sedation in their subjects.

Of the subjects that received 4mgkg^{-1}, 26.5% experienced nausea and vomiting compared to 36.1% that received 5mgkg^{-1} and 37.4% that received 6mgkg^{-1}. In the study in which oral ketamine was used for wound dressing in burns patients,[7] it was noted that patients that received 0.5mgkg^{-1}, experienced more nausea and vomiting than those that received 4mgkg^{-1} and 6mgkg^{-1}. However, subjects that received 2mgkg^{-1}, 8mgkg^{-1} and 10mgkg^{-1} did not experience nausea and vomiting. In another work with low dose IV ketamine,[16] only 7% of the subjects vomited. These discrepancies cannot readily be explained.

The occurrence of dizziness among our patients also demonstrated a statistically significant dose-dependent relationship which contrasts with the finding of Ezike and Odiakosa[7] in which the use of oral ketamine for burns management did not show a significant dose-dependent pattern. Despite the dose-dependent pattern noticed for dizziness, it should also be pointed out that the role of other causes of dizziness such as intra-partum and postpartum haemorrhage in our patients was not ascertained.

In terms of management of these side effects, patients were essentially reassured because the side effects were transient, not severe and the drug was administered only once. It is pertinent to add here that the key to management of these side effects is early recognition through clinical vigilance.

This study was not without limitations. A placebo-controlled trial would have been ideal for this study. However, we considered ethical issues in the selection of the study design. A non-placebo design was adopted to avoid the issue of denying a woman in labour the potential benefits of oral ketamine analgesia. At the centre there is no standarad labour analgesia in routine use. However, pentazocine injection is occasionnally offered to women who find labour pain unbearable but this could have unwanted side

effects on the baby. For this reason we had no standard labour analgesia with which we could readily compare our protocol while ensuring fetal safety as much as possible. The observation that there was a significant difference in educational status accross the three treatment groups could also be perceived as a possible limitation. Although educational status may to some extent influence the outward handling of pain, it still deserves to be said that the pathophysiology of pain whether obstetric or non-obstetric has no bearing on the individual's educational status. Furthermore, randomisation helped to control for confounders. Despite the observation that a significant proportion of parturients experienced sedation, pain assessment by the parturients was largely unaffected by sedation both for VAS and VRS as was shown when the participants were analyzed separately as non-sedated and sedated groups.

In conclusion, this study has shown that oral ketamine in sub-anaesthetic doses provided good analgesia for women in labour. However, the analgesic benefit of oral ketamine was limited by a high rate of side effects. Considering that the minimum sub-anaesthetic dose of $4mgkg^{-1}$ used in this study provided effective analgesia with more tolerable side effects, oral ketamine at a dose of $4mgkg^{-1}$could be offered to women who desire it for labour analgesia. Further clinical studies on the use of oral ketamine for labour analgesia should explore lower doses in order to reduce the side effects to the barest minimum.

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