ORIGINAL ARTICLE

Low-dose ketamine infusion for labor analgesia: A double-blind, randomized, placebo controlled clinical trial

Sam Joel, Anita Joselyn[1], Verghese T Cherian[2], Amar Nandhakumar[3], Nithin Raju[1], Ilamurugu Kaliaperumal[4]

Departments of Surgery, and [1]Anesthesia, Christian Medical College & Hospital, Vellore, Tamil Nadu, India, [2]Department of Anesthesiology, Milton S Hershey Medical Center, PA, USA, [3]Department of Anesthesia and Pain Management, Mount Sinai Hospital, Toronto, Canada, [4]Department of Anesthesia, The Queen Elizabeth Hospital, Adelaide, South Australia

Address for correspondence:
Dr. A. S. Joselyn,
Department of Anesthesia, Christian Medical College & Hospital, Vellore, Tamil Nadu, India.
E-mail: anjeyanth@gmail.com

ABSTRACT

Background: Most primary and secondary level hospitals in developing countries provide inadequate labor analgesia due to various medical, technical and economic reasons. This clinical trial was an effort to study the efficacy, safety and feasibility of intravenous (IV) ketamine to provide labor analgesia. **Materials and Methods:** A total of 70 parturients were consented and randomly assigned to receive either IV ketamine or 0.9% saline. A loading dose of ketamine (0.2 mg/kg) was followed-by an infusion (0.2 mg/kg/h) until the delivery of the neonate. Similar volume of saline was infused in the placebo-group. Intramuscular meperidine was the rescue analgesic in both groups. The pain score, hemodynamic parameters of mother and fetus and the anticipated side-effects of ketamine were observed for. The newborn was assessed by the Neonatologist. **Results:** The pain score showed a decreasing trend in the ketamine group and after the 1st h more than 60% of women in the ketamine group had pain relief, which was statistically significant. There was no significant clinical change in the maternal hemodynamics and fetal heart rate. However, 17 (48.5%) of them had transient light headedness in the ketamine group. All the neonates were breast fed and the umbilical cord blood pH was between 7.1 and 7.2. The overall satisfaction was significantly high in the intervention group ($P = 0.028$). **Conclusion:** A low-dose ketamine infusion (loading dose of 0.2 mg/kg delivered over 30 min, followed-by an infusion at 0.2 mg/kg/h) could provide acceptable analgesia during labor and delivery.

Key words: *Ketamine infusion, labor analgesia, light headedness, low-dose ketamine, meperidine*

INTRODUCTION

In most primary and secondary level hospitals in India and other developing countries, the facility to provide adequate analgesia during labor and delivery is inadequate. The reasons being the non-availability of opioid analgesics, the dread of serious side-effects to opioids like respiratory depression to the mother and the neonate[1] in a poorly staffed labor room, the non-availability of a trained "Anesthesiologist" to manage epidural analgesia and economic constraints. Another reason for epidural not being so popular is because it is known to prolong the second stage and is associated with increased incidence of instrumental delivery.[2]

Access this article online	
Quick Response Code:	Website: www.saudija.org
	DOI: 10.4103/1658-354X.125897

Ketamine is a N-Methyl-D-aspartate receptor antagonist, with excellent analgesic property even in subanesthetic doses.[3] It is readily available and is being used currently, even by non-Anesthesiologists, to provide "sedation" for minor procedures.[4,5] Low-dose ketamine infusion in the perioperative period has shown to produce analgesia and decrease the requirements of opioid analgesics.[6,7] In obstetrics, it is being used as an adjunct to an inadequately functioning spinal anesthesia for caesarean section, as an induction agent for cesarean section and also to provide analgesia during labor in intermittent boluses.[8-13] This clinical trial was an effort to study the efficacy, safety and feasibility of intravenous (IV) ketamine to provide analgesia during labor and also to standardize a technique, with an intention of proposing it as a safe alternative for labor analgesia in a primary or secondary level hospital having a lower level of supervision.

A pilot study was undertaken prior to this clinical trial to observe the safety and efficacy of using ketamine during labor. 30 parturients in active labor were administered low-dose IV ketamine, 0.1 mg/kg as a bolus, when they entered active labor and continued with an infusion at 0.1 mg/kg/h. All women had at least 50% reduction in their pain and none of the newborn had respiratory depression.[14]

MATERIALS AND METHODS

This double-blind, randomized, controlled clinical trial was conducted in a tertiary level hospital after approval of the Institutional Review Board and registered with the clinical trials registry of India (CTRI/2008/091/000264, 03-02-2009). All pregnant women who were in active labor, expected to have normal vaginal delivery, were eligible for the study. Women with cardiac disease, gestational hypertension, epilepsy, known psychiatric disorder, multifetal pregnancy, and cephalopelvic disproportion and those who had a previous caesarean section were excluded from the study. The study plan was explained to the parturient and a written consent was obtained from those who volunteered to participate.

The subjects were randomly assigned to receive either ketamine or 0.9% saline. Subjects in the "ketamine" group were administered ketamine in a loading dose of 0.2 mg/kg over 30 min followed-by an infusion at 0.2 mg/kg/h until the delivery of the baby. The rate of infusion was altered by 1 ml/h (2 mg/ml) to maintain pain relief during uterine contractions. Subjects in the "placebo" group were infused with saline in similar volume. 1 h after starting the infusion, if the relief of pain was inadequate, the obstetrician was allowed to prescribe intramuscular pethidine (meperidine) in a suitable dose for the patient, as per the standard of care.

Randomization and concealment of allotment — a computer-generated randomization list was created prior to commencement of the study and was enclosed in serially numbered, sealed envelopes. When the consented patient entered active labor with regular uterine contractions and requested analgesia, the sealed envelope was opened and the study drug was loaded into a 50 ml syringe by an Anesthesiologist not involved with the study. The concentration of ketamine was 2 mg/ml and the placebo syringe contained normal saline.

Observations

The observations during the study were made by the primary investigator blinded to the randomization. The pain experienced by the parturient was recorded on a 10 point visual analog scale (VAS). This was recorded before and after the administration of the loading dose of the study drug and then every hour. Any reduction in VAS score was used to compare the two groups. Pain score less than or equal to five was accepted as "effective analgesia."

The baseline heart rate, the blood pressure, the pain score, the sedation score and the fetal heart rate were recorded and then at regular intervals during the study period. The anticipated side-effects of ketamine like sedation, occurrence of hallucinations, sleep disturbances, vivid dreams and nystagmus were observed for.

In all the subjects, the fetus was continuously monitored using the external fetal monitor. The newborn was assessed by the Neonatologist, and the Apgar score at 1, 5, and 10 min were noted. The pH of the umbilical cord blood was measured. The mother and the newborn were observed for 48 h after delivery. All parturients were interviewed a couple of hours after the delivery and asked to comment on their perception of overall pain relief and satisfaction with the entire care. This was recorded on a 10 point scale and graded as good, fair, or poor.

Statistics and sample size calculation

Based on the pilot study, the sample size was calculated as 35 subjects in each arm, accepting a difference in pain score of 30% with an error of 5% and a ß error of 20%. Normally, distributed values were summarized as mean and standard deviation (SD) and compared using the Student *t*-test. Non-parametric data were compared by Mann-Whitney U test. Categorical data were compared by Chi-squared test. A $P < 0.05$ was accepted as significant.

RESULTS

Seventy parturients in active labor were randomly assigned to receive either IV ketamine or 0.9% saline. There were no dropouts or loss to follow-up. The demographic details of the two groups were comparable [Table 1]. The duration of labor, the mode of delivery and the estimated blood loss during delivery were comparable between the groups [Table 2].

Relief of pain

The baseline pain score in all the subjects was 10. Immediately after the administration of the loading dose of study drug, 14 parturient in both the groups felt reduction of pain [Table 3]. However, at 1 h, 60% of those who received ketamine and 30% in the placebo group had some relief of pain. More than 60% of women in the ketamine group had some pain relief at 2nd and 3rd h too. By the 4th h, more than 80% of women in the ketamine group had pain relief with VAS scores <5. The pain score showed a decreasing trend in those who received ketamine [Figure 1].

Table 1: The demographic characteristics were comparable between the two groups

Demographics	Group 1 (ketamine)	Group 2 (placebo)
Age (years)	26.1±3.8	24.7±3.9
Weight (kg)	60±10.2	63.9±9.3
Primigravida (%)	19 (54)	25 (71)
Multigravida (%)	16 (46)	10 (29)
Spontaneous labor (%)	20 (57)	17 (49)
Induced labor (%)	15 (43)	18 (51)

Table 2: Comparing the outcomes between the two groups. The duration of labor and mode of delivery were comparable between the two groups. More subjects in the "ketamine" group complained of light headedness when the loading dose of study drug was administered, however more subjects in the "ketamine" group were satisfied with the pain relief and overall care

Outcomes	Group 1 (ketamine)	Group 2 (placebo)	*P* value
Duration of labor (min)	213.29±144.5	234.14±177.39	0.597
Mode of delivery			0.643
Normal	22	25	
Outlet forceps	9	5	
Caesarean section	4	5	
Blood loss (ml)	218±139	199±124	0.599
Rescue analgesia (*n*)	4	7	0.324
Side-effects			0.017*
Light headedness	17	9	
Nystagmus	2	0	
Nausea and vomiting	6	4	
Cord blood pH			0.127
>7.2	23	24	
7.1-7.2	8	10	
≤7.1	0	1	
Patient satisfaction			0.028*
Good	10	7	
Fair	19	9	
poor	6	19	

*significant *P* value < 0.05

Dose of ketamine — the dose of ketamine infused was 0.2 mg/kg/h, which translates to approximately 12 mg/h. The total dose of ketamine used was 45 ± 25 mg.

Rescue analgesia — intramuscular pethidine was administered to four in the ketamine group and seven in the placebo group.

Side-effects

There was no significant clinical change in the maternal blood pressure and heart rate or the fetal heart rate, with the administration of the loading dose of ketamine or

Table 3: The pain scores recorded at baseline and every hour were compared. As the parturient delivered, they were excluded from the analysis. At each stage the number who had some relief of pain among still in labor were compared between the two groups. The ketamine group shows relief of pain in at least 60% of the subjects at each hour

Time (h)	Number (n)	Group 1 (ketamine) (%)	Group 2 (placebo) (%)	*P* value
Pain 0	*n*-in labor	35	35	
	n-no relief	35	35	
	n-relief	0	0	
Pain 0.5	*n*-in labor	35	35	1.00
	n-no relief	21 (60)	21 (60)	
	n-relief	14 (40)	14 (40)	
Pain 1	*n*-in labor	33	31	0.020*
	n-no relief	13 (39)	21 (68)	
	n-relief	20 (61)	14 (40)	
Pain 2	*n*-in labor	25	27	0.029*
	n-no relief	10 (40)	19 (70)	
	n-relief	15 (60)	8 (30)	
Pain 3	*n*-in labor	17	16	0.383
	n-no relief	6 (35)	8(50)	
	n-relief	11 (65)	8 (50)	
Pain 4	*n*-in labor	10	10	0.329
	n-no relief	2 (20)	4 (40)	
	n-relief	8 (80)	6 (60)	
Pain 5	*n*-in labor	7	9	0.381
	n-no relief	1 (14)	3 (33)	
	n-relief	6 (86)	6 (67)	
Pain 6	*n*-in labor	6	6	0.225
	n-no relief	1 (17)	3 (50)	
	n-relief	5 (83)	3 (50)	

n-in labor: Excluding those who had delivered during the previous hour, *n*-no relief: No change in VAS score compared to baseline, *n*-pain relief: decrease in VAS score compared to baseline, *significant

thereafter during the infusion. None of the women who received ketamine complained of psychomimetic side-effects such as hallucinations or vivid dreams. However, 17 (48.5%) of them did complain of light headedness within 10-15 min of starting the loading dose but it subsided by the time the loading dose was completed. In the placebo group, 7 (20%) women complained of short periods of light headedness. This was statistically significant. Nystagmus was seen in two subjects and both had received ketamine. None of the women were overly sedated and all responded coherently throughout their labor. Six in the "ketamine" group and four in the "placebo" group had an episode of vomiting.

Neonatal outcome

Of the 70 neonates delivered, 2 (one from each group and both delivered by caesarean section) were depressed at the 1st min with an Apgar score of <4. The one from

the "ketamine" group improved to an Apgar score of 9 at 5 min, and 10 at 10 min, with administration of oxygen. The one from the "placebo" group had Grade 3 meconium stained amniotic fluid and was transferred to the neonatal intensive care unit. The neurological examination was normal in the rest of the neonates. All the neonates, except the one who needed intensive care, were breast feed. The umbilical cord blood pH was between 7.1 and 7.2 in all the neonates except the two who had a low Apgar score.

Patient satisfaction

The patient's satisfaction with overall pain relief and the entire care was significantly higher in the "ketamine" group when compared with the placebo group (*P* - 0.028).

DISCUSSION

The standard of care for analgesia during labor, in most primary and secondary level hospitals in the developing countries, is an intramuscular injection of pethidine (meperidine) on a p.r.n basis. However, pethidine is not available in many of these centers because of "controlled-drug" regulations. Most obstetricians would avoid administration of pethidine to the parturient, once the cervix is fully dilated and effaced, for fear of neonatal depression at delivery. Therefore, most parturient go through 2nd stage of labor without any analgesia.

The primary objective of this study was to assess the efficacy, safety and feasibility of using low-dose IV ketamine for labor analgesia. This study was conducted in a tertiary level hospital, where the standard of care again is intramuscular pethidine and epidural analgesia is reserved for those who need it for medical reasons, mainly due to socio-economic and logistic reasons such as availability of an anesthesiologist and monitoring.

Prior to this clinical trial, a pilot study was conducted on 30 consented parturient. A bolus dose of 0.1 mg/kg of ketamine was administered, followed by an infusion of 0.2 mg/kg/h. It was observed that the onset of effective analgesia was delayed for up to 3 h of starting the infusion of ketamine and the administration of the bolus dose caused most of women to have nystagmus and a sensation of light headedness. Therefore, it was decided to give a larger loading dose of 0.2 mg/kg, so as to achieve analgesia earlier, but slowly over 30 min, so as to minimize the side-effects.

In the current study, the pain score among the subjects in the "ketamine" group started to show a decreasing trend by 1 h of administration of the loading dose. Table 3 shows that the administration of ketamine provided analgesia in 60% of the parturients compared with 30% in the placebo group. A decreasing trend in pain score in the "ketamine" group is evident in Figure 1. However, as time progressed, the SDs also widened. This is because the subjects who delivered were excluded from the analysis and it did include the pain scores of those who were in the second stage of labor, when the score was highest.

Intramuscular pethidine, as rescue analgesic, was administered to four subjects in the "ketamine" group and seven in the "placebo" group. These patients had no pain relief in the first couple of hours after starting the infusion. Intramuscular pethidine is usually administered in early labor and not repeated before 4 h and is avoided if the delivery of the baby is anticipated in the next couple of hours. This could be the reason why rescue analgesia was not administered to many women in the placebo group, despite having significant pain.

Increasing the dose of ketamine may have provided better pain relief, but studies have shown that the use of a larger dose of ketamine (2 mg/kg) causes emergence phenomena.[3] Sarkar and Sahu[11] used a dose of 0.2-0.4 mg/kg as a bolus followed-by an infusion of 0.5-1 mg/min. This approximated to 1 mg/kg/h and they reported 14% of their study patients to have hallucinations. Ganla *et al*.[12] used 0.5 mg/kg bolus, followed-by 0.25 mg/kg every 20-30 min and reported a high incidence of hallucinations (54%) thereby suggesting that emergence phenomena could be related to peak levels of ketamine. In the current study, none of the subjects complained of hallucinations and this could be due to the fact that the loading dose of ketamine was administered as an IV

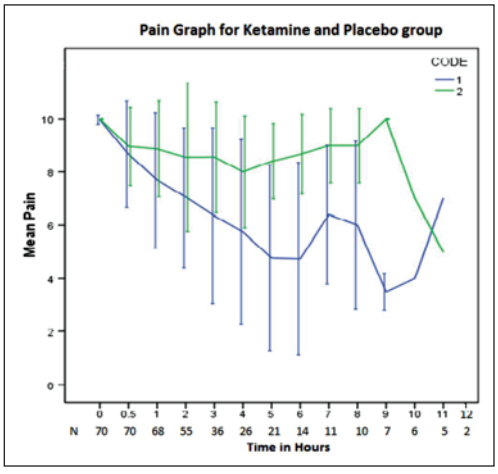

Figure 1: The Y axis shows pain score and the X axis the time in hours after starting the infusion of the study medication. *N* denotes the number of laboring parturient, in both groups, at each hour. Women in second stage of labor are also included in this graph. (1) Blue – ketamine; (2) Green – placebo

infusion and not as bolus. However, 17 women in the ketamine group complained of transient light headedness and 2 of them had nystagmus following the loading dose. This was similar to the observation after the pilot study where these symptoms were observed transiently after the bolus dose. Nine women in the placebo group also had light headedness following the infusion of the study medication. The incidence of nausea and vomiting were similar between the groups. The study intervention did not affect the neonatal outcome. The Apgar score, cord blood pH and the Neonatologist's assessment were within acceptable normal range.

Therefore, this study showed that IV, low-dose ketamine provides satisfactory pain relief during labor and delivery without affecting its progress or the neonatal well-being. A loading dose of ketamine is required to hasten the onset of effective analgesia, however, this need to be administered as a slow infusion so as to minimize the more distressing side-effects of ketamine, such as hallucinations and nystagmus. The transient side-effect of light headedness following the loading dose of ketamine was significant, but was tolerated by the parturient.

Ultimately, the overall perception of the experience of labor and delivery, albeit painful, is biased by the presence of a healthy baby in the mother's arms. However, the difference in patient satisfaction seen between the two groups could possibly be that low-dose ketamine provides analgesia yet does not dissociate the mother from the experience of childbirth.

CONCLUSION

Therefore, ketamine in a loading dose of 0.2 mg/kg delivered over 30 min followed-by an infusion at 0.2 mg/kg/h could provide acceptable analgesia during labor and delivery. Further studies could look at fine tuning the dose especially during the second stage of labor.

REFERENCES

1. Shnider SM, Levinson G. Anesthesia for obstetrics. In: Miller RD, editor. Anesthesia. 4th ed. New York: Churchill Livingstone; 1994. p. 2031-76.
2. Anim-Somuah M, Smyth RMD, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD000331. DOI: 10.1002/14651858.CD000331.pub3.
3. White PF, Way WL, Trevor AJ. Ketamine — Its pharmacology and therapeutic uses. Anesthesiology 1982;56:119-36.
4. Ng KC, Ang SY. Sedation with ketamine for paediatric procedures in the emergency department — A review of 500 cases. Singapore Med J 2002;43:300-4.
5. Newton A, Fitton L. Intravenous ketamine for adult procedural sedation in the emergency department: A prospective cohort study. Emerg Med J 2008;25:498-501.
6. Snijdelaar DG, Cornelisse HB, Schmid RL, Katz J. A randomised, controlled study of peri-operative low dose s(+)-ketamine in combination with postoperative patient-controlled s(+)-ketamine and morphine after radical prostatectomy. Anesthesia 2004;59:222-8.
7. Guignard B, Coste C, Costes H, Sessler DI, Lebrault C, Morris W, *et al*. Supplementing desflurane — Remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesth Analg 2002;95:103-8.
8. Downing JW, Mahomedy MC, Jeal DE, Allen PJ. Anesthesia for caesarean section with ketamine. Anesthesia 1976;31:883-92.
9. Bernstein K, Gisselsson L, Jacobsson L, Ohrlander S. Influence of two different anesthetic agents on the newborn and the correlation between foetal oxygenation and induction-delivery time in elective caesarean section. Acta Anaesthesiol Scand 1985;29:157-60.
10. Dich-Nielsen J, Holasek J. Ketamine as induction agent for caesarean section. Acta Anaesthesiol Scand 1982;26:139-42.
11. Sarkar P, Sahu SP. Ketamine hydrochloride for painless labour. Indian J Anaesth 1992;40:120-3.
12. Ganla KN, Deshmukh S, Bhide A, Desai S. Analgesia in labor by intermittent intravenous bolus ketamine. J Obstet Gynaecol 2000;4:60-2.
13. Galloon S. Ketamine for obstetric delivery. Anesthesiology 1976;44:522-4.
14. Joselyn AS, Cherian VT, Joel S. Ketamine for labour analgesia. Int J Obstet Anesth 2010;19:122-3.

How to cite this article: Joel S, Joselyn A, Cherian VT, Nandhakumar A, Raju N, Kaliaperumal I. Low-dose ketamine infusion for labor analgesia: A double-blind, randomized, placebo controlled clinical trial. Saudi J Anaesth 2014;8:6-10.
Source of Support: Nil, **Conflict of Interest:** None declared.