"SAFETY AND EFFICACY OF LOW DOSE INTRAVENOUS KETAMINE IN LABOUR ANALGESIA,A SINGLE BLINDED RANDOMIZED CONTROLLED TRIAL "

By

Dr. CHITTA.SREELAKSHMI

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UNDER THE GUIDANCE

DR. VIJAYALAKSHMI GOBBUR$_{MD,}$

PROFESSOR,

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY,

BLDE UNIVERSITY'S, SHRI B.M. PATIL MEDICAL COLLEGE,

HOSPITAL & RESEARCH CENTRE, VIJAYAPUR,

KARNATAKA.

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B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL

& RESEARCH CENTRE, VIJAYAPUR- 586103

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Date: **Dr. CHITTA.SREELAKSHMI**

Place: Vijayapur

B.L.D.E UNIVERSITY'S

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Date:

Place: Vijayapur

DR.VIJAYA LAKSHMI GOBBUR M.D,
Professor,
Department of Obstetrics and Gynaecology,
BLDEU Shri B.M.Patil Medical College,
Hospital & Research Centre,
Vijayapur, Karnataka.

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL

& RESEARCH CENTRE, VIJAYAPUR

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Date:

Place: Vijayapur

Dr. R.H.GOBBUR$_{M.D}$,
Professor,
Department Of Pediatrics,
BLDEU Shri B.M.Patil Medical College, Hospital & Research Centre,
Vijayapur, Karnataka.

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL

& RESEARCH CENTRE, VIJAYAPUR - 586103

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Date:

Place: Vijayapur

DR. P.B.JAJU$_{\textbf{M.D}}$,

Professor and H.O.D,

Department of Obstetrics and Gynaecology,

BLDEU Shri B.M. Patil Medical College,

Hospital & Research Centre,

Vijayapur, Karnataka.

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL

& RESEARCH CENTRE, VIJAYAPUR- 586103

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Date:

Place: Vijayapur

DR.S. P. GUGGARIGOUDAR

Principal,

BLDEU Shri B.M. Patil

Medical College, Hospital &

Research Centre, Vijayapur,

Karnataka.

B.L.D.E UNIVERSITY'S

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Place: Vijayapura

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Place : Vijayapur **Dr. C.SREELAKSHMI**

Date

ABSTRACT

INTRODUCTION-

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 low dose intravenous ketamine in labor analgesia. The phencyclide derivative Ketamine is widely used as IV and IM anesthetic agent and is mediated through opiate receptor and N-methyl D-asparate receptors. A systemic administration of ketamine produce a obvious advantage over nacrotics in which major drawback is respiratory depression.

AIM AND OBJECTIVES-

To study the efficacy of Ketamine in labor analgesia in following parameters.

1.Maternal outcome in form of duration & mode of delivery, complication of 3rd stage of labor.

2.Fetal outcome inform of APGAR score.

3.To evaluate patient satisfaction about this method.

MATERIALS AND METHODS-

A total of 120 parturients were consented and randomly assigned to receive either IV ketamine or 0.9%NS. A loading dose of 0.2mg/kg over 30mins following by an infusion of 0.2mg/kg/hr until delivery of the baby. The control group will be infused with NS with similar volumes.

RESULT-

The duration of active phase was shortened in study group than control group. 53% women delivered in 4hrs compared to only 20% in control group. 41.7% women delivered in 5hrs compared to only 45% in control group. 93% delivered vaginally, 3.3% instrumental delivery, 3.3% LSCS. No significant hemodynamic changes seen 13.3% had headache, 8.3% nausea, 11%had minimal rise in PR & BP, 3.3% had irrelevant speech. Mean VAS score in Ketamine group is 4 and in control group is 6.8($p<0.001$).Study group had no marked change in APGAR score when compared to control group.

CONCLUSION-

A low dose ketamine infusion provide acceptable analgesia during labor with out significant maternal and fetal complications, with no inhibition of bearing down reflex.

LIST OF ABBREVATIONS

NMDAR	-	N-Methyl-D-Asparate Receptors.
IV	-	Intravenous.
IM	-	Intramuscular.
5%	-	5% Dextrose.
NS	-	Normal Saline.
APGAR	-	Appearance Pulse Grimace Activity Respiration.
VAS	-	Visual Analogue Scale.
RASS	-	Richmond Agitation Sedation Scale.
LSCS	-	Lower Segment Caesarean Section.
CRH	-	Cortico Releasing Hormone.
ACTH	-	Adreno-cortico Tropic Hormone.
DHEA-S	-	Di hydro Epi Androsterone- Sulphate.
GABA R	-	Gamma Amino Butyric Acid.
TENS	-	Transcutaneous Electrical Nerve Hormone.
PCA	-	Patient controlled Analgesia.
CEI	-	Continuous Epidural Infusion.
CSEA	-	Continued Spinal Epidural Analgesia.
CSA	-	Continuous Spinal Analgesia.
LSB	-	Lumbar Sympathetic Block.
PNB	-	Pudendal Nerve Block.
PCB	-	Para Cervical Block.
CVS	-	Cardio Vascular System.
CNS	-	Central Nervous System.

ICP	-	Intra Cranial Pressure.
NSAID	-	Non Steroidal Anti-Inflammatory Drugs.
IHD	-	Ischemic Heart Disease.
ANC	-	Antenatal Care.
IUGR	-	Intra Uterine Growth Retardation.
PROM	-	Pre mature Rupture of Membranes.
CPD	-	Cephalo Pelvic Disproportion.
SD	-	Standard Deviation.
NPOL	-	Non Progression of Labour.
MSL	-	Meconium Stained Liquor.
FD	-	Fetal Distress.
PPH	-	Post Partum Hemorrhage.
NICU	-	Neonatal Intensive Care Unit.
RD	-	Respiratory Distress.
MAS	-	Meconium Aspiration Syndrome.
IPPV	-	Intermittent Positive Pressure Ventilator.
LMP	-	Last Menstrual Period.
EDD	-	Expected Date of Delivery.
POG	-	Period of Gestation.
USG	-	Ultra Sonography.

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INTRODUCTION

Labour is defined as physiological process by which the products of conception (fetus, amniotic fluid, placenta, and membranes) are separated and expelled from the uterus through the vagina into the outside world. It is defined by the presence of regular uterine contractions accompanied by cervical effacement and dilatation and fetal descent[1]. Labour is physiological but painful event. The anxiety, fear and stress a women suffers is beyond description.

Labour analgesia ensures pain relief, controls alteration of placental circulation thereby safe guarding the fetus against hypoxia[2].

Programmed labour concept:

1.Providing optimum pain relief.

2.Ensuring adequate uterine contractions.

3.Close clinical monitoring of labour events.

Most of the primary and secondary level hospitals in developing countries provide inadequate labour analgesia due to various medical, technical and economic reasons. This clinical trial is an effort to study the efficacy, safety, and feasibility of low dose intravenous (IV) ketamine to provide safe yet effective labour analgesia.[3]

The phencyclidine derivative Ketamine is widely used as intra-muscular and intra-venous anaesthetic agent. Studies indicate that analgesia produced by Ketamine is mediated through opiate receptors and NMDA receptors, monoaminergic receptors, muscarinic receptors and voltage sensitive Ca^{2+} channels. As systematically administered Ketamine is unlikely to produce respiratory depression, it seemed to offer an obvious advantage over the Opiods analgesics in which major drawback is respiratory depression[4].

Ketamine is a NMDA receptor antagonist with excellent analgesic property even in sub anaesthetic doses, to provide “sedation” for minor procedures[3,4]. Low-dose Ketamine infusion provide adequate analgesia during labour and does not lead to dreadful side-effects like respiratory depression to the mother and the neonate in a poorly staffed labour room[5]. Although it proved to be a good analgesic agent because of its abuse, hallucinogenic and dissociative properties it is used limitedly in the area of labour as compared to the peri-operative pain management and cachexial pain management[3,4].

So, this study is intended to evaluate the role and safety of the low dose intra-venous Ketamine administration in labour analgesia , and its effects in mother and the baby.

OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

1. To study the low dose effectiveness of Ketamine as labour analgesic.

SECONDARY OBJECTIVE

1. To assess the maternal outcome in the form of duration of labour, mode of delivery, complications of third stage of labour.

2. Fetal outcome in the form of APGAR score at 1min and 5min, early initiation of breast feeding after(< 30min).

REVIEW OF LITERATURE

Most women suffer unbearable pain and distress during labour and thought of impending labour pains makes them nervous and dampens their morale. In 1813 in york, england, queen victoria was given chloroform by Dr. John Snow for birth of 8th child and popularized the use of pain relief in labour[6].

Obstetric anaesthesia has always had an uneasy relationship with systemic Opioids. sedation, nausea and vomiting, respiratory and neonatal depression combined with doubtful efficacy as a labour analgesia have limited their uses[7]. In 1966 Chodoff and Stella were first to report Ketamine(1.5-2mg/kg/hr) in relieving labour pain along with Nitrous oxide inhalation with which had significant number of depressed newborns requiring resuscitation so they concluded that Ketamine could be effective in lower doses[8].

In a study done by Gregory Janeczko, Loyola university stritch school of medicine, Maywood, Illinois in 1974 Ketamine was found generally satisfactory for anesthesia in 370 normal vaginal deliveries. Although APGAR scores with low dose Ketamine (0.3mg/lb) for delivery were comparable to a normal dose of Ketamine (1 mg/ lb) resulted in lower APGAR scores($p<0.001$) and comparing the results of high dose Ketamine to other general anesthetics were borderline significant($p<0.05$).[9]

In a study done by Ayangade.O in 1979, In general population 50 pregnant were taken in study and administration of Ketamine at rate of 50-60mg loading dose stat and 50-60mg in 5%D at controlled infusion, induction delivery interval reduced to 3.6hrs from 3 hrs. 78% described total experience as pleasant, while the rest found it unpleasant or uncertain. The one minute APGAR score of 6.8 was not significantly different from general population.[10]

Ketamine was used in continuous intravenous infusion to relive pain in 55pregnant women by Paul Sarkar, S.P.Sahu in 1991 an initial dose of 0.2 to 0.4mg/kg body weight followed by a continuous infusion of 0.5 to 1 mg/min and increased to double if needed and resulted in excellent analgesia in 35 women, fair analgesia in 13 women and in 2 women's it was unsatisfactory. No significant maternal complications were noticed 5cases had unpleasant dreams, 2 cases had hallucinations subsided by inj Lorezepam 4mg i.v, 5 cases had nausea and vomiting. Mean APGAR score at 1min is 8.26 and at 5mins is 9.62.[11]

In a study done by Maroof, J.N medical college, Aligargh India in 1998, which was done on 30, 2nd gravida patients belonging to 21 - 30 age group having a history of normal delivery and with no risk factors. Three patients were excluded from study as they underwent caesarean section due to in co-ordinate uterine contractions. mean duration of delivery was 3.2+/-1.1 hr and mean dose of Ketamine required was 87.2+/-9.7mg. Four patients required supplemental analgesic techniques and were withdrawn from study consider as a failures. pain score of the patient were 2.3+/-1.6(with Ketamine n=23) and 8.10+/-0.8 (with out Ketamine n =27) respectively, this was statistically significant, p= 0.0001. All 23 patients on Ketamine infusion were willing to accept the same form of treatment for labour in future.[12]

The study was under taken to assess the effect of intermittent intravenous bolus Ketamine labour analgesia in 50 patients by Kedar N. Ganla, in 2000. It reveals excellent results 82% of patients required only 200mg of this drug, 84% of the patients delivered normally, 6% had forceps delivery, 4% had vacuum assisted vaginal delivery, 6% had LSCS. APGAR score was >8 at the 5mins. 36 cases had complete relief, 8 cases had moderate pain, 6 cases had mild pain.[13]

A study conducted by Krishna J in NHL municipal medical college in 2010- 2012, states that the duration of 1st and 2nd stage was remarkably shortened in study group. 64% of parturient in study group delivered with in 3 hours of entering the active phase of labour compared to only 10% in control group. In study group 98% delivered vaginally only 2% required instrumental delivery. There is no inhibition of bearing down reflex by Ketamine, no maternal exhaustion in study group. In present study Ketamine had no effects on APGAR score at 1min and 5min. 30% had marginal rise in pulse rate of 10- 15 beats/min. 16% had rise in B.P not beyond 15-20 mm of Hg. 10% cases had nausea but no vomiting. 90% had excellent pain relief and 8% had satisfactory pain relief, while 2% had no pain at all.[14]

In a study done by Sam Joel, Anitha Joselyn, from dept. of anesthesia in Christian medical college &hospital, Vellore, TN in 2008-2009, which was done on 70 parturient who were randomly selected and given Ketamine and 0.9%saline and it states that the pain score showed a decreasing trend in the Ketamine group and after the 1st hour more than 60% had pain relief , which was statistically significant. there was no significant clinical changes in the maternal hemodynamic and fetal heart rate. however, 17(48.5%) of them had transient light headedness in Ketamine group .All the neonates were breast fed and the umbilical cord pH was between 7.1 and 7.2. The over all satisfaction was significantly high in the intervention group ($p = 0.028$).[15]

OTHER ANALGESIC WITH KETAMINE -

In a study done by Shirish N Daftary, V Desai in 2008. study is done to asses and develop an indigenous protocol to optimize labor outcome, as programmed labor. Ketamine is administered once cervix is almost 7 - 8cms dilated, at rate of 0.25 to 0.5mg/kg body weight in 10ml normal saline as slow bolus. Top up dose is repeated at half of the initial dose rate and last dose is given after the delivery. study group had mean

shorter duration of active phase as 3.5hrs compared to controls of 5.2hrs. Excellent pain relief was of 24% and 62% of substantial relief in comparison to 32% only in other group. second stage of labor was reduced by half and lesser blood loss.[16]

In a study done by Duggal geethika, Maharaja Agresen medical college, Agroha, in 2012- 2014, which done on 50 parturient and were divided into two group. In group A Ketamine 0.2mg/kg as bolus was given and for maintenance continues infusion of Ketamine 50mg in 500ml of 5% dextrose was given. In group B an additional dose of intravenous Tramodol 1.5mg/kg was given after bolus dose of Ketamine and half dose given earlier was repeated when cervix was fully dilated. Average induction delivery time is 162.16 in group A and 170.87 in group B and p valve is 0.797 (not significant). 28% in group had excellent pain relief and 48% in group B which is significant. Mean APGAR score at 5mins is 9.92 in group A and 10.0 in group B, p valve 1 (highly insignificant). Maternal side effects were less in group b than group A and study concluded that addition of Tramodol to Ketamine analgesia is very effective and reduces the maternal and neonatal complications.[17]

OTHER ANALGESICS-

In a study done by Kumud gupta, NIMS medical college and hospital, Jaipur, Rajasthan in 2015, which done on 100 primigravida pregnant women randomly enrolled in study group for programmed labour and control group for traditional management of labour. In study group inj.Tramadol 1mg/kg and inj.Drotaverine 40mg i.m given in active labour and 2mg of Diazepam + 6mg Pentazocine given 2nd hourly along Oxytocin. In control group only Tramadol is used for pain relief. Mean duration of active labour in study group is 3.45 and 4.78 in control group which is significant($p < 0.0004$). 86% had excellent pain relief in study group and only 22% in control group which is statistically

significant. No significant neonatal complications. study group had significant drug related side effects like nausea, vomiting, drowsiness, that subsided after 12 hours.[18]

Comparison of analgesia efficacy of Paracetamol and Tramodol for pain relief in active labour by Jeetinder Kaur Makkar, Kajal Jain in 2013. Its a prospective , randomized, double blinded study, 60 parturient were randomized to 2 groups and received 1mg/kg of Tramodol i.m and 1g of Paracetamol i.v same doses received after 4hours of initial dose. Duration of first stage of labour was shortened in Parecetamol group, 340±111 in T group, 248±98 in P group p value- 0.003. No difference in neonatal outcome Mean APGAR score of Tramadol group at 1min is 7.93±0.25 and at 5mins is 8.93±0.25(p valve-1), and in Paracetamol group at 1min is 7.93±0.24 and at 5mins is 8.98±0.25(p valve-1).[19]

LABOUR

DEFINATION- Series of events that take place in the genital organs in an effort to expel the viable products of conception (fetus, placenta and the membranes) out of the womb through vagina into outer world.[20]

It is characterized by regular, painful uterine contractions that increase in frequency and intensity and are associated with progressive cervical effacement and dilatation.

Normal labour term should full fill the criteria-

i. spontaneous onset,

ii. at term,

iii. singleton,

iv. with vertex presentation,

v. with out undue prolongation,

vi. natural termination with minimal aids,

vii. with out any complication to mother and the baby.[20,21]

Causes of onset of labour-[21]

i. Uterine distension:

Stretching effect on myometrium by the growing fetus, liquor increases gap junction proteins, receptors for Oxytocins and specific contraction associated proteins.

ii. Fetoplacental contribution:

Fetal hypothalamic-pituitary-adrenal axis -> increases CRH -> increased release of ACTH -> fetal adrenals -> increased cortisol secretion -> accelerated production of estrogen and prostaglandins from the placenta.

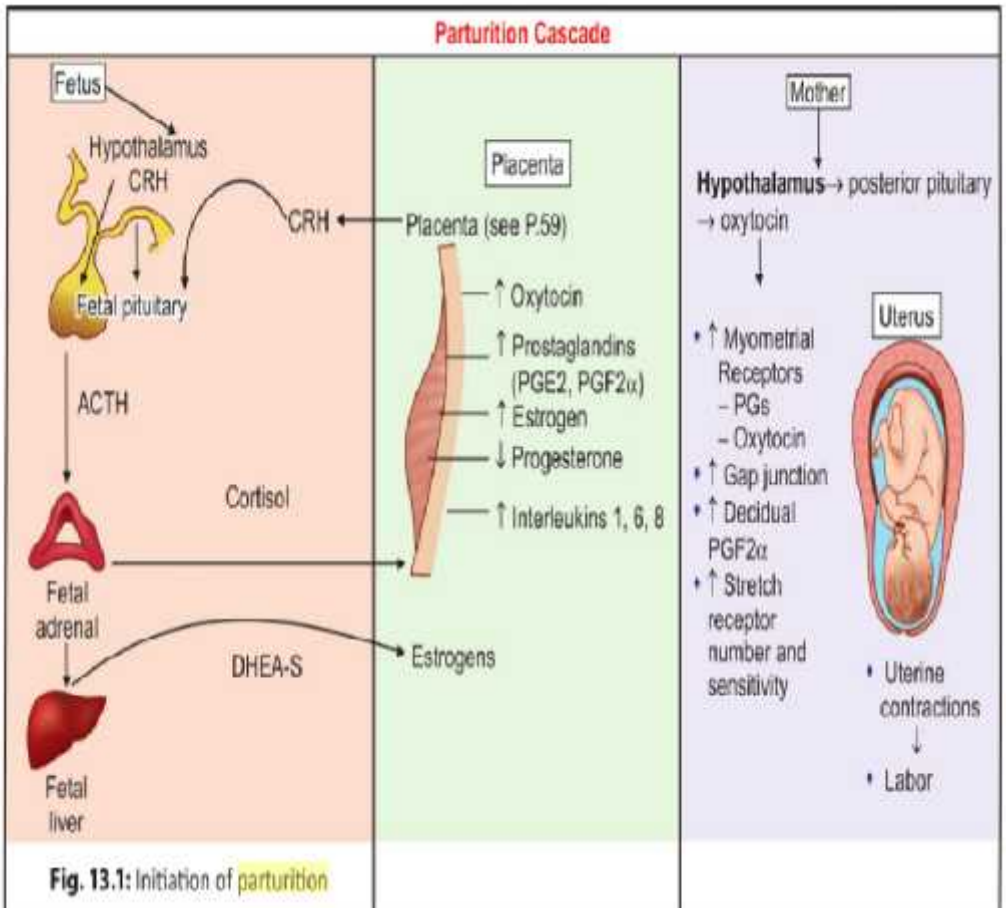


Figure 1: Initiation of Parturition

iii. Estrogens-

Increases the release of Oxytocin from maternal pituitary.

Promotes the synthesis of myometrial receptors for Oxytocin, prostagandins and increase in gap junction in myometrial cells.

Accelerates lysosomal disintegration in the decidual and amnion cells resulting in increased $PGF_{2\alpha}$ synthesis.

Stimulates the synthesis of myometrial contractile proteins.

Increases the excitability of the myometrial cell membranes.

iv. Progesterone- increased fetal production of DHEA-S and cortisol inhibits the conversion of fetal pregnenolone to progesterone.

v. Prostaglandins- synthesis is triggered by rise in estrogen level, glucocorticoids, mechanical stretching in late pregnancy, increase in cytokines, infection, vaginal examination, and rupture of the membranes. prostaglandins enhance the gap junction formation.

STAGES OF LABOUR-

1. **First stage -** Onset of true labour pains to fully dilatation of cervix, Cervical stage of labour. It takes 12 hours in primipara and 6 hours in multiparae. First stage consists of latent phase(up to 3cms) and active phase (up to 10cms). This stage is chiefly concerned with dilatation and effacement of the cervix and ultimate rupture of the membranes.
2. **Second stage-** Occurs from full cervical dilatation (10 cm) and end with expulsion of the fetus from birth canal. Normally the second stage lasts for 2 hrs in primipara and 30mins in a multipara. This stage concerns with the descent and delivery of the fetus through the birth canal. It has two phase
    i. The propulsive phase- starts from full dilation up to the descent of the presenting part to the pelvic floor.
    ii. The expulsive phase is distinguished by maternal bearing down effort and ends with delivery of the baby.
3. **Third stage-** It begins after expulsion of the fetus and ends with expulsion of placenta and membranes. This stage is concerns with placental separation and its expulsion. The separation is achieved by marked reduction in the uterine surface area of placental site following delivery due to retraction. Two ways of placental separation - central(Schultze) and marginal (mathews-Duncan).[21]

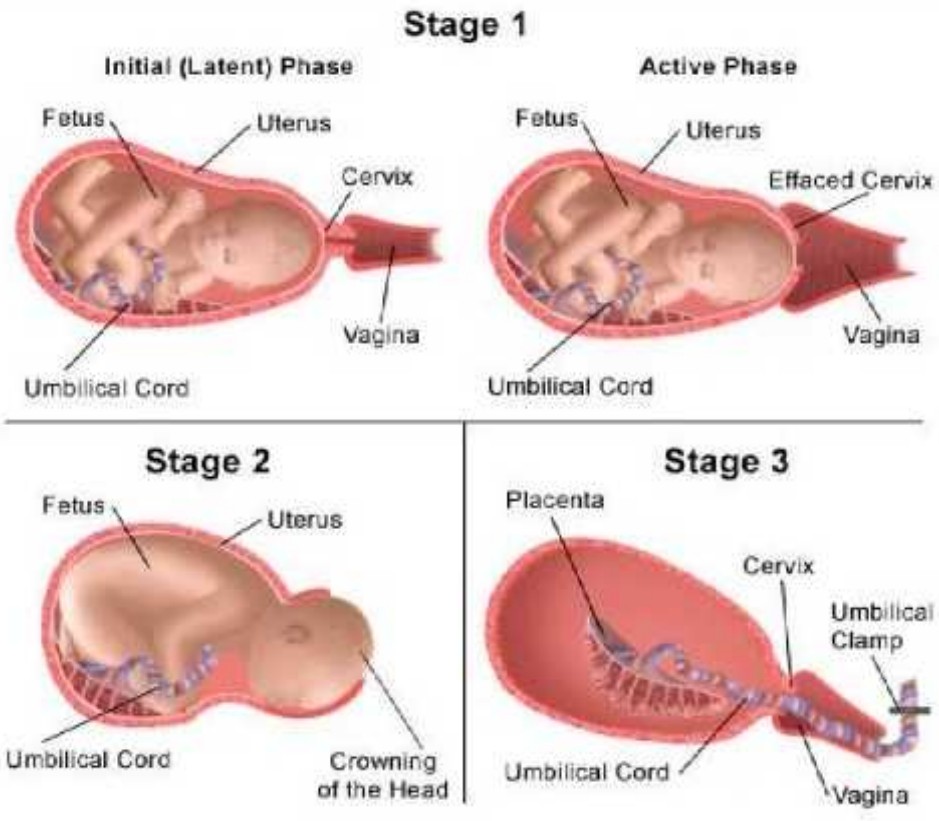


Figure 2 : Stages of Labour.[21]

PHYSIOLOGY OF LABOUR PAIN

Mechanism of labour pain-

Perception of pain during the first stage of labour begins with nociceptive stimuli arising in the mechanical and chemoreceptor's in the uterus and cervix.[22] High threshold mechanoreceptors get stimulated due to intense pressure generated during contractions of the uterus. Myocellular injury due to repeated contractions in later stages, release bradykinin, histamine, serotonin, acetylcholine and potassium ions which activate chemical nociceptors.[23]

TABLE I - Labour pain : Pathways and Mechanisms[23]

Labour pain : pathways and mechanism			
Site of origin	Mechanism	Pathway	Site of action
Uterus, cervix	Distortion, stretching, tearing of fibres	Afferents which accompany sympathetic pathway to T10-L1 refer to cutaneous branches of posterior divisions	Upper abdomen &groin, mid-back.
Peri uterine tissues , Lumbo sacral region	Pressure often in association with fetal mal position or platypelloid pelvis	Lumbosacral plexus L5-S1 (? Pelvic splanchnic nerves)	Low back, Thigh.
Bladder, Urethra, Rectum	Pressure by presenting part	S2-S4	Referred to perineum and sacral area.
Vagina	Distension, Tearing	Somatic S2-4	Not referred.
Perineum	Distension, Tearing	Pudendal (S2-S4); Genitofemoral(L1-2); Ilioinguinal(L1); Posterior cutaneous nerve of thigh(S2-3)	Not referred.
Bladder	Over distension	Afferents which accompany sympathetic pathway to T11-L1	Supra pubic.

a. Peripheral pathways

First stage of labour : Pain of the first stage of labour is due to uterine contractions and stretching of the cervix. It is cramping and visceral in nature, diffuse and poorly localized. Sensations are carried through Ad and C primary afferent fibres which pass sequentially through the inferior, middle and superior hypogastric plexus, the lumbar and lower thoracic sympathetic chain and end in rami communicants associated with T10-L1 spinal nerves(fig 3). It is predominantly carried by the C fibres.[22]

Second stage labour : During the late first and second stage of labour, somatic pain predominates, as a result of distension and traction on the pelvic structures, the pelvic floor and the perineum and is carried via the pudendal nerve through the anterior rami of S2 through S4. Unlike visceral pain of first stage, it is sharp and well localised, due mainly to less arborisation and the faster conduction velocity in the sacral pathways. It is predominantly carried by the Ad fibres.[24]

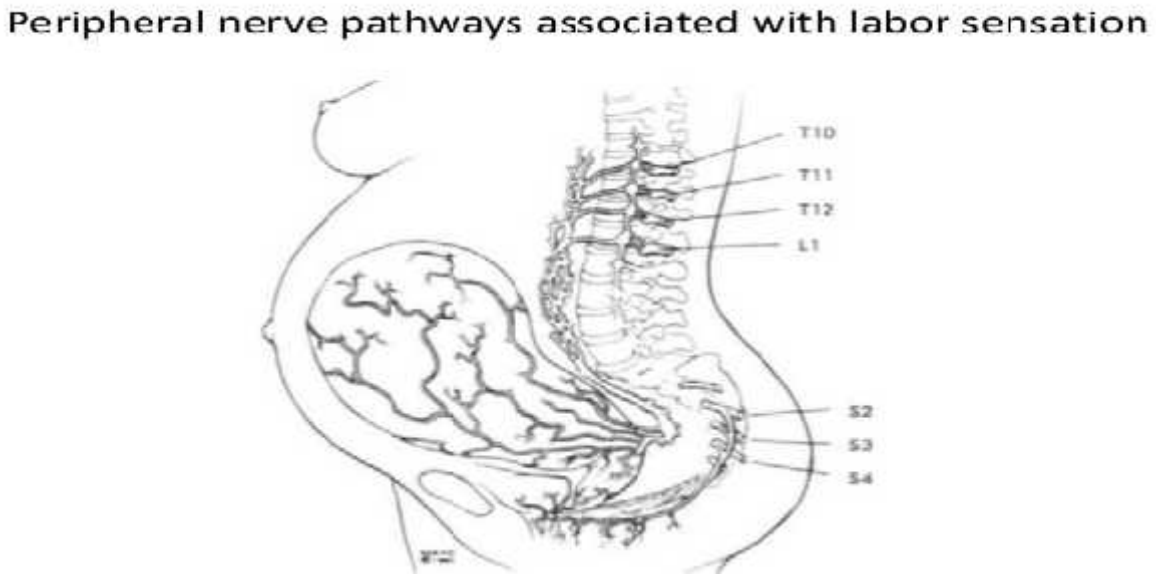


Figure 3: peripheral pathway of labour pain.[22]

b. Central pathways

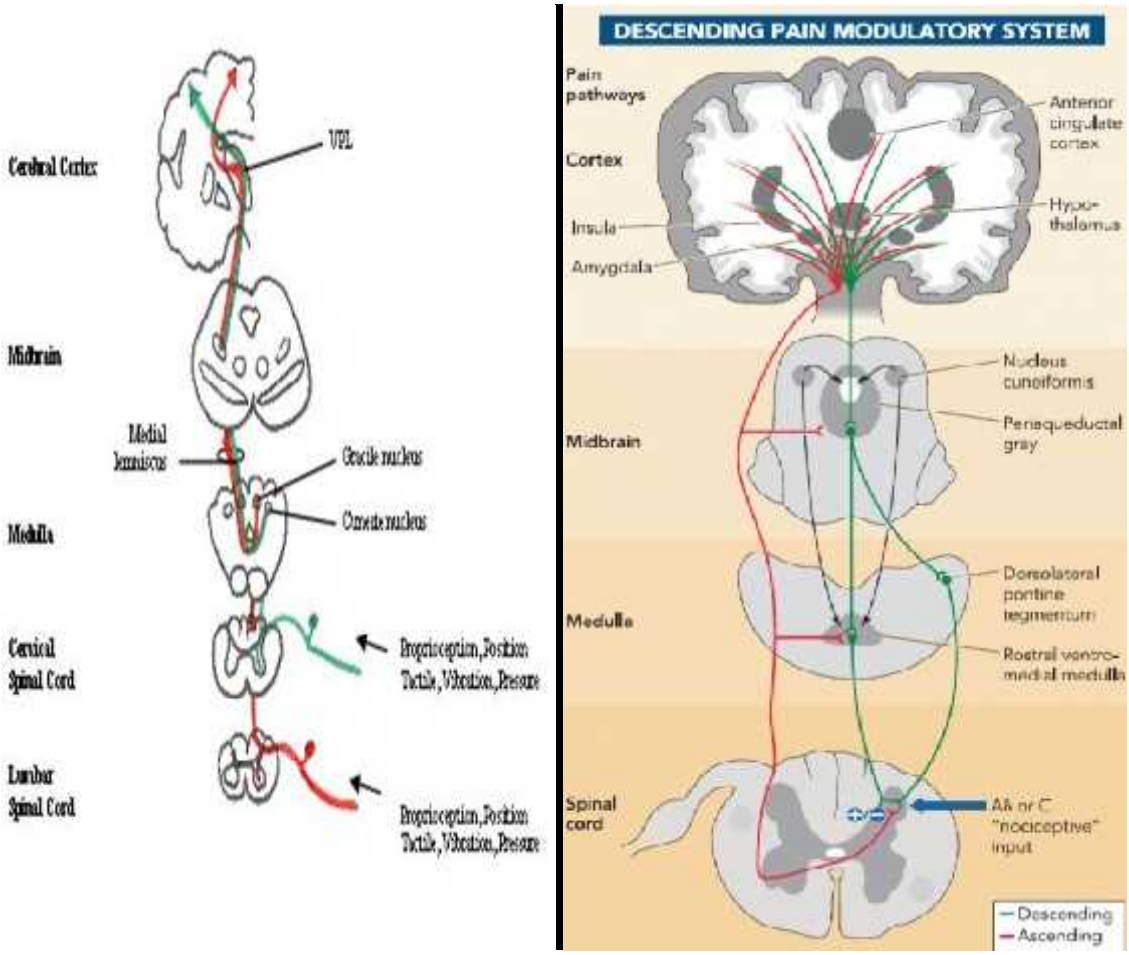
The pathways labour sensation travels after entry into the central nervous system includes both the ascending and the descending pathways.

Ascending pathways

The first synapse in the pathways occurs in the dorsal grey matter of spinal cord (Rexed's Laminae I to V). Most of the primary afferent neurons synapse initially in the more superficial laminae I and II (substantia gelatinosa); locally projecting interneuron's in turn synapse on the more deeply located wide dynamic range (WDR: lamina V) neurons. The WDR neurons receive synaptic excitatory input from both the large myelinated Aâ and Aä mechanoreceptor afferents and C polymodal nociceptive afferents. The fact that all of the lamina V cells which respond to visceral high threshold afferents also respond to low threshold cutaneous afferent from an area of skin supplied by the same spinal cord segments is important. Thus the lamina V cells provide the neural basis for the phenomenon of referred pain which occur during each uterine contraction. Projections from the dorsal grey matter cross to the contra lateral ventral white matter of the cord and then cephalad via the spinothalamic tract to the thalamus, brainstem, and cerebellum, (fig 4.a) where spatial and temporal analysis occurs, and to the hypothalamic and limbic systems, where emotional (affective) and autonomic responses originate.[25]

Descending pathways

These pathways originate in primary sensory cortex and project to peri aqueductal grey matter in the midbrain which further project to rostral ventral nuclei in thalamus. Projections from thalamus enter the spinal cord through dorsi-lateral funiculus and end in dorsal grey matter of the spinal cord fig 4(b).[25]



Figures 4 : Central pathway of Labour pain,[25]

(a) Ascending pathway (b) Descending pathway

METHODS OF LABOUR ANALGESIA

The experience of labour pain is different for each woman, and the different methods chosen to relieve pain depend upon the techniques available locally and the personal choice of the individual.[26,27]

Table 2 : Methods of Labour Analgesia[27]

Methods of labour analgesia		
Non pharmacological	**Pharmacological**	
	Systemic	**Regional**
• TENS • Relaxation/breathing techniques • Bio feedback and physical therapies • Temperature modulation; hot or cold packs, water immersion • Hypnosis • Massage • Acupuncture • Aromatherapy • Water block	1. Inhalational methods 2. Systemic analgesic Opioid analgesics (Meperidine, Morphine, Fentanyl, Sufentanil, Alfentanil, Remifentanil) Non opioid analgesics • Agonist-antagonist analgesics (Nalbuphine,Butarphanol, Tramadol) • Sedative tranquillizers (Barbiturates, Phenothiazine derivatives, Benzodiazepines) • Dissociative or amnesic drugs (Ketamine, Scopolamine)	1. Lumbar epidural analgesia 2. CSEA 3. CSA 4. Alternative regional anaesthetic techniques - Lumbar sympathectomy block - PNB - PCB

NON-REGIONAL TECHNIQUES FOR LABOUR ANALGESIA

Non-regional methods available for analgesia in labour may be divided into non-pharmacological and pharmacological methods.[26]

A. Non-pharmacological methods

The advantages of non-pharmacological techniques include their relative ease of administration, easy availability and minimal side-effects; however, there is little evidence to support the efficacy of many of these techniques, and some may be costly and time consuming. Some of the more commonly used non pharmacological methods are:

1.Transcutaneous electrical nerve stimulation(TENS)

Electrodes are placed about 2 cm over the T10–L1 dermatomes on either side of the spinous processes to provide analgesia for the first stage of labour. A second set of electrodes is placed over the S2–S4 dermatomes for second stage pain relief. Women can alter the amount of current supplied to the electrodes providing some degree of control throughout their labour. Blockade of pain transmission to the brain through stimulation of A-fibre transmission and local release of ß-endorphins are suggested theories for TENS analgesia; however, there is no evidence that TENS provide more analgesia than placebo.[27]

2. Acupuncture

The needles are inserted to a depth of 2.5-3 cm and manipulated manually or a low voltage 2–3 Hz current is passed through the needle to achieve analgesia. Acupuncture analgesia is thought to be mediated through release of endorphins or release of Serotonin and Metencephalin. However; this technique provides pain relief which is incomplete, unpredictable and inconsistent.[27]

B. Pharmacological methods

1.Inhalational methods

Entonox (50% nitrous oxide in oxygen) provides analgesia within 20-30 seconds of inhalation, with a maximum effect after about 45 seconds. Current clinical data suggest that it relieves labour pain to a significant degree in most women, however it does not provide complete and predictable analgesia and atmospheric pollution is a cause for concern. Several volatile anaesthetic agents have been inhaled intermittently for labour analgesia like Trichloroethylene, Methoxyflurane, Isoflurane, Enflurane, Sevoflurane and Desflurane. Their use is limited by technical difficulties in their safe administration, scavenging, requirement of specific vaporizers and issues of theatre pollution.

2.Systemic analgesics

Opioid analgesics :

Some of the commonly used parentral opioids for labor analgesia are Morphine, Pethidine, Fentanyl, Sufentanil, Alfentanil, and Remifentanil. If regional analgesia is unavailable or contraindicated, then Patient controlled intravenous analgesia (PCA) is a useful method for painless labour. Remifentanil, an ultra-short-acting Opioid, is rapidly hydrolysed by blood and tissue esterase's and does not accumulate, even after prolonged infusions. There are increasing reports of its use in PCA, although, like Fentanyl, the ideal regimen remains unclear. A bolus dose of 0.25-0.5g/kg with a 2 minute lockout has been used successfully.[28] However, close monitoring is essential and supplementary oxygen with ready access to Naloxene is mandatory.

Non-Opioid analgesics:

a. Agonist-Antagonist analgesics-

Nalbuphine (2-4 mg IV), Butorphanol (2 mg) Buprenorphine (0.3 mg) have all been used as systemic analgesics for providing relief from labour pain. Drowsiness, dizziness, and nausea, vomiting have limited the wide spread use of these analgesics in obstetrical pain relief.

Ketamine

Ketamine interacts with NDMA receptors, Opioid receptors, Monoaminergic receptors, Muscarinic receptors and voltage sensitive ca^{2+} channels and does not interact with GABA receptors like other general anaesthetic agents.

Ketamine has excellent analgesic property even in sub anaesthetic doses, low dose Ketamine provide excellent labour analgesia.[6,28]

B. Regional techniques for labour analgesia

Regional techniques represent the "Gold Standard" for labour analgesia.

1. Lumbar epidural analgesia-

Effective analgesia during the first stage of labour can be achieved by blocking the T10 to L1 dermatomes with low concentrations of Opioids or local anaesthetics. The block has to be extended up to S2-4 dermatomes in the second stage of labour to ameliorate the pain due to vaginal distension and pressure on the perineum of the descending fetal part. Recent evidence suggests that there is minimum to no alterations in duration and outcome of labour with regional analgesia, there is no increase in the need for labour augmentation with Oxytocics neither is there any difference in the rates of normal vaginal delivery but there was a significant increase in maternal satisfaction in parturient administered epidural analgesia. Concern about early initiation of epidural analgesia at <4cms cervical dilatation has been refused by several studies which claim

that it does not affect the overall progress of labour or incidence of surgical interventions. However, there is still a concern that early initiation of labour may result in higher incidence of operative delivery.

There are advantages and disadvantages to the different techniques available for delivery of epidural analgesia. Some of the popular methods are:[29]

a. Intermittent top-ups.

b. Continuous epidural infusion (CEI).

c. patient controlled epidural analgesia (PCEA).

2. Combined spinal epidural analgesia (CSEA)

The CSE technique has gained increasing popularity in recent years. It is one technique wherein, selected advantages of both spinal and epidural techniques are combined without an increase in complications. It provides rapid onset of analgesia with minimal local anaesthetic doses and has the flexibility and unlimited duration of an epidural technique. Because CSE allows for ambulation of the parturient it has been called the "Walking epidural" (also refers to any epidural or spinal technique which allows for ambulation). There are certain situations where CSE may be the preferred technique. These include the multiparous parturient who had an ineffective epidural on a previous occasion or the patient having a rapid painful labour. The technique and doses for CSE labour epidural analgesia.[30]

Table 3 : Suggested Drug doses and mixtures for CSE labour analgesia

Administration	Local anaesthesia	Opioid
Intrathecal inj	Bupivacaine 1-2.5mg	Fentanyl 20-25mg or Sufentanil 3-5 mg
Epidural top-ups	Bupivacaine(0.1%- 0.125%) 10-15mg for 1 & 2 stage of labour or assisted delivery	Fentanyl 20-25mg or Sufentanil 5-10mg

3.Continuous spinal analgesia

Spinal analgesia given as a single shot technique provides only 1 to 3 hrs of pain relief which may not be adequate to cover the whole duration of labour, though it may be a useful option in the absence of other methods of pain relief, in a mother in the very advanced first stage of labour and in need of an instrumental delivery. CSA with micro catheters (size 28G) offers some advantages over the single shot spinal or the continuous epidural techniques, however it increases the likelihood of complications, like cauda equina syndrome and may be inherently more dangerous than the other two techniques. CSA is typically provided by either intermittent bolus or continuous infusion techniques[31] and may be preferred in case of accidental dural puncture.

4. Alternative regional anaesthetic techniques

These include Lumbar sympathetic block (LSB),[32] Para cervical block(PCB)[32] and Pudendal nerve block (PNB). Para cervical block using low-dose Bupivacaine provides up to 2 hours of first stage analgesia, the drawback being the high incidence of fetal bradycardia. Pudendal nerve (S2,3,4) block is safe and effective for only the second stage, while Para vertebral lumbar sympathetic block provides only first-stage labour analgesia and though it requires expertise to perform this block, it may speed cervical dilatation in nulliparous women. These alternative techniques do not have the flexibility of epidural or CSE analgesia, they are technically difficult to perform and produce more frequent complications. However, they can be used in special circumstances such as:

i. Failed or inadequate neuraxial analgesia.
ii. Contraindications to neuraxial techniques (e.g.– spinal deformity, previous spine surgery, abnormal coagulation).
iii. Absence of qualified anaesthesia personnel.

Complications of regional analgesia in labour[33]

Some immediate serious complications of obstetric epidural analgesia include:

i. Massive misplaced injection: intravascular, intrathecal or subdural.
ii. High or total spinal block.
iii. Hypotension.
iv. Local anaesthetic induced convulsions.
v. Local anaesthetic induced cardiac arrest.
vi. Delayed complications.
vii. Post dural puncture headache.
viii. Transient backache.
ix. Urinary retention.
x. Epidural haematoma, abscess or meningitis.
xi. Permanent neurologic deficit.

Most obstetric neurologic injuries are not directly related to neuraxial analgesia but rather are intrinsic to labour and delivery. However, strict attention to technique may further limit the rare injury directly related to anesthesia.

KETAMINE

Ketamine is a phencyclidine derivative, It was synthesized in 1962 by stevens and first used in humans in 1965 by crossed and domino, and released for clinical use in 1970. It produces dissociative anesthesia , rather than generalized CNS depression , through antagonistic actions at the phencyclidine (pcp) site of NMDAR.[34,35] It is a racemic mixture of R(-) ketamine and S(+) ketamine, It does not depress the cardiovascular and respiratory systems , but it does have some of the adverse psychological effects found with other phencyclidines.

PHYSIOCHEMICAL PROPERTIES

Ketamine is partially water soluble and forms a white crystalline salt, It is only 12% protein bound and its bioavailability is 93% after parenteral administration.[36,37]

PHARMACOKINETICS

Ketamine is metabolized by hepatic microsomal enzymes. It involves N-demethylation to form norketamine (metaboliteI), which is then hydroxylated to hydroxynorkrtamine , which is further conjugated to water soluble gluccuronide derivatives and excreted in the urine.[38,39,40]

PHARMACODYNAMICS

a. Effects on central nervous system[41]

Ketamine produces dose related unconsciousness and analgesia. It acts on multiple receptors the NMDARs, Opioid receptors and Monoaminergic receptors. The most important action of ketamine is inhibition of NMDAR- mediated glutamergic input to GABA-ergic system that leads to changing excitatory activity in the cortex and limbic system that in the end results in unconsciousness. At the spinal cord level , ketamine has potent antinociceptive effects on the NMDAR and inhibit ACH release.[42] It induces DISSOCIATIVE ANAESTHESIA because patients who receive ketamine alone appear

to be in a cataleptic state, in contrast to other states of anesthesia that resembles normal sleep.

b. Effects on respiratory system

Ketamine has minimal effects on central respiratory drive. Ketamine is a bronchodilator(acts by bronchial smooth muscle relaxation). It can be given in patients with reactive air way disease , bronchospasm and in status asthmaticus unresponsive to conventional therapy.[43]

c. Effects on cardiovascular system

Ketamine increases arterial blood pressure, heart rate, and cardiac output in biphasic manner. It means in low doses it acts as a CVS stimulant, by release of Catecholamines, inhibition of the vagal nerve and inhibition of NE reuptake at peripheral nerves and non neuronal tissues such as myocardium and sympathetic ganglia. In high doses or after continuous infusion it acts as a depressant after stimulatory effects because of depletion of transmitters .

USES OF KETAMINE

a. Induction and maintenance of anaesthesia:

Ketamine is a suitable drug for induction in unstable cardiovascular patients because of its sympathomimetic actions on heart. Ketamine is one of drug in rapid action induction sequence in hypovolaemia & in shock patients.

b. pain management:

Post operative pain management is a major concern in many patients. Now it is increasingly using for pain management through multimodal pathway. ketamine in sub anaesthetic doses are required for this purpose. Its dramatically reduces the post operative dosage of opiate and other NSAID drugs. Its psychomimetic actions are balanced by adding a benzodiazepine. Now it is increasingly used for chronic pain conditions because

of its action on opiate tolerance and hyper analgesia, usually its been administered through epidural or caudal administration, but because of its favourable hemodynamic effects it can be administered through the intravenous or intranasal route.[44]

c. Sedation

Ketamine often combined with premedication with a barbiturate or benzodiazepine and a antisialagogue (glycopyrrolate), it is increasingly used for short, painful procedures in the emergency department. The dose will be between 0.1to0.6 mg/kg. It can be safely administered in critical care unit patients because of its combined sedative and analgesic and favourable effects on hemodynamic.

DOSES AND ROUTE OF ADMINSTRATION[34]

Ketamine can be administered by the IV, Intramuscular(IM), Transcutaeneous, oral, nasal, and rectus routes and as a preservative -free solution epidurally or intrathecally.

Intranasal administration has an onset closer to that of IV administration, an oral dose of 3 to 10 mg/kg generates a sedative effect in 20 to 45 minutes.

Table 4 : Ketamine uses and doses[34]

USES AND DOSES OF KETAMINE	
Induction of general anaesthesia	0.5 -2 mg/kg IV 4-6 mg/kg IM
Maintenance of general anaesthesia	0.5-1 mg/kg IV with N2O 50% in O2 15-45 µg/kg/min IV with N2O 50-70% in O2 30-90µg/kg/min IV without N2O.
Sedation and analgesia	0.2-0.8 mg/kg IV over 2-3 min 2-4 mg kg IM
Pre-emptive or preventive analgesia	0.15-0.25 mg/kg IV

SIDE EFFECTS AND CONTRAINDICATIONS

Its contraindicated in patients with increased ICP because it increases ICP and causes apnoea and in open eye injury or ophthalmologic disorders, in which ketamine induced increase in intraocular pressure.[45] ketamine has propensity to cause hypertension and tachycardia, with a commensurate increase in myocardial oxygen consumption, so contraindicated as sole anaesthetic in IHD, and also in vascular aneurysms. Finally, liver and renal toxicity occurs in the recreational abuse of ketamine.

KETAMINE IN LABOUR ANALGESIA

Ketamine inhibits the NMDAR and has analgesic, amnetic and hypnotic properties while having only minimal respiratory depression effects. At typical doses, ketamine causes central stimulation of sympathetic nervous system and inhibits the reuptake of norepinephrine. This helps in maintain arterial pressure, heart rate, and cardiac output. no neonatal depression observed with standard induction doses. Larger doses can increase uterine tone, reduce uterine perfusion, and lower maternal seizure threshold.

ASSESMENT OF VISUAL ANALOG SCALE AND RICHMOND AGITATION-SEDATION SCALE IN LABOUR ANALGESIA:

The VAS is a simple and often used method for evaluating variation in pain intensity. subjects are instructed to indicate the intensity of the pain by marking a 100mm line anchored with terms describing the extremes of pain intensity. Its usefulness has been validated in setting of chronic pain by several investigators. In this setting, vas is superior to fixed interval scales, relative pain scales, and verbal reports of pain.[46]

Patients who have undergone anesthesia degrades the relationship of the VAS with the subjective pain experience, which leads to a range of imprecision of each individual measurement. Understanding this imprecision will help to interpret studies using VAS (fig 5) as the outcome measure.[47]

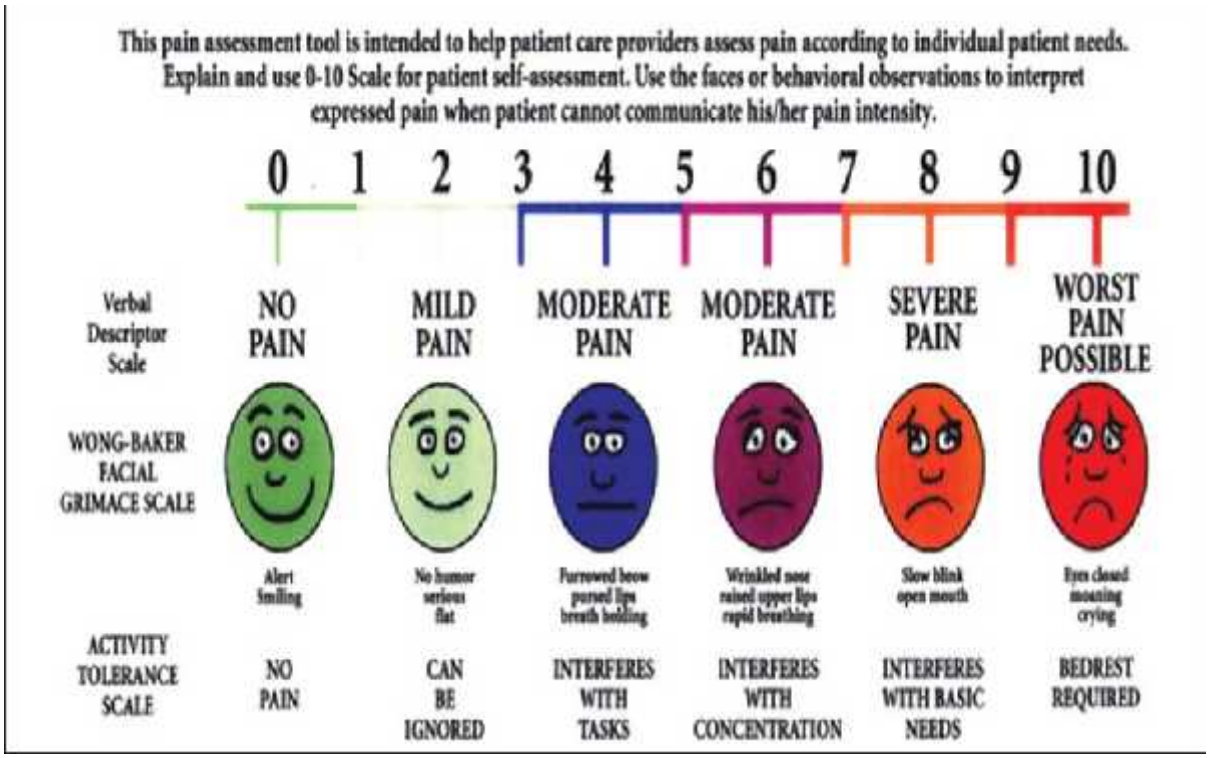


Figure 5 : Visual Analogue Scale[46]

Richmond agitation-sedation scale is a medical scale used to assess the agitation and sedation rate of the patient. The Richmond Agitation–Sedation Scale (RASS) was developed in a collaborative effort with practitioners representing critical care physicians, nurses, and pharmacists. RASS as is a 10-point scale, with four levels of anxiety or agitation (+1 to +4 [combative], one level to denote a calm and alert state (0), and 5 levels of sedation (1 to 5) culminating unarousable (-5). The values and definitions for each level of agitation and sedation are displayed.(pic 6)[48,49]

Score	Descriptor	Characteristics
+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact >10 seconds)
-2	Light sedation	Briefly awakens to voice (eye opening and contact <10 seconds)
-3		
-4	Moderate sedation	Movement or eye opening to voice (but no eye contact)
	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Figure 6 : Richmond Agitation - sedation scale.[48]

MATERIAL AND METHODS

SOURCE OF STUDY:

This study carried out in the department of Obstetrics and Gynaecology, at BLDE University's Shri. B. M. Patil Medical College, Hospital and Research Center, vijayapur from December 2014 to June 2016.

SAMPLING:

With 1% of level of significance (α) and power of test 90% (1-β)

Anticipated mean difference of pain between two groups is 33.4%.

Anticipated standard deviation is 45.3 in a study done by Krishna Jagatia[14]

The minimal sample size is 55 ≈ 60 per arm

Total sample size 60 + 60 =120

FORMULA FOR CALCULATION,

$$\eta = \frac{(Z\alpha + Z_\beta)^2 Z \cdot SD^2}{MD^2}$$

WHERE $Z_{\alpha} = 2.33$, $Z_\beta = 1.28$

STATISTICAL ANALYSIS :

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square (χ^2)/ Freeman-Halton Fisher exact test was employed to determine the significance of differences between groups for categorical data. If the p-value was < 0.05, then the results will be considered to be significant. Data were analyzed using SPSS software v.23.0.

PROCEDURE This clinical trial is conducted in all parturient who are in active phase, expected to have vaginal delivery with out any complications.

Inclusion criteria:

All parturient who are in active labour (>3cm) and expected to have normal vaginal delivery (includes singleton, term, vertex presentation).

No fetal or maternal complications.

Exclusion criteria:

Parturient with grand multies, mal presentations, multiple pregnancy, CPD, previous caesarean section.

Parturient with high risk obstetric problems like high blood pressure, gestational diabetics, epilepsy, cardiac disease and Parturient with PROM, IUGR.

The parturient after inclusion and exclusion criteria and obtained written informed consent are randomized in to two groups(study and control). Assigned to receive either ketamine or 0.9% normal saline.

STUDY GROUP (ketamine)- Loading dose of 0.2mg/kg Ketamine over 30mins followed by an infusion at 0.2 mg/kg/hr until the delivery of the baby.

CONTROL GROUP (placebo)- Infused with normal saline(0.9%) in similar volume.

PRIMARY OUTCOME

To study the low dose effectiveness of Ketamine as labour analgesic.

SECONDARY OUTCOME

To assess the maternal outcome in the form of duration of labour, mode of delivery, complications of third stage of labour.

Fetal outcome in the form of APGAR score at 1min and 5min, early initiation of breast feeding after(< 30min).

In all cases base line pulse rate, blood pressure, the pain score(VAS), the sedation score (RASS) and fetal heart rate was recorded and repeated at regular intervals. Anticipated side effects like headache, nausea, vomiting, occurrence of hallucinations, sleep disturbances, vivid dreams will be observed .The mothers and newborns will be observed for 48 hours after delivery.

RESULTS

P - value is calculated by chi-square test and P value <0.05 is considered to be statistically significant.

*P value<0.05, **P valve<0.01, ***P value<0.001.

TABLE 5 : DISTRIBUTION OF CASES BY AGE AMONG KETAMINE AND CONTROL GROUPS.

AGE(YRS)	KETAMINE		CONTROL		p value
	N	%	N	%	
≤20	23	38.3%	22	36.7%	0.135
21-25	35	58.3%	30	50.0%	
26-30	2	3.3%	8	13.3%	
Total	60	100.0%	60	100.0%	

In ketamine group, 38.3% belong to ≤20 yrs,58.3% belong to 21-25yrs,3.3% belong to 26-30, and mean age is 21.6.

In control group, 36.7% belong to ≤20 yrs, 50.0% belong to 21-25 yrs, 13.3% belong to 26-30 yrs, mean age is 23.3.

P valve is being p-0.135, which is insignificant.

GRAPH 1 :DISTRUBUTION OF AGE.

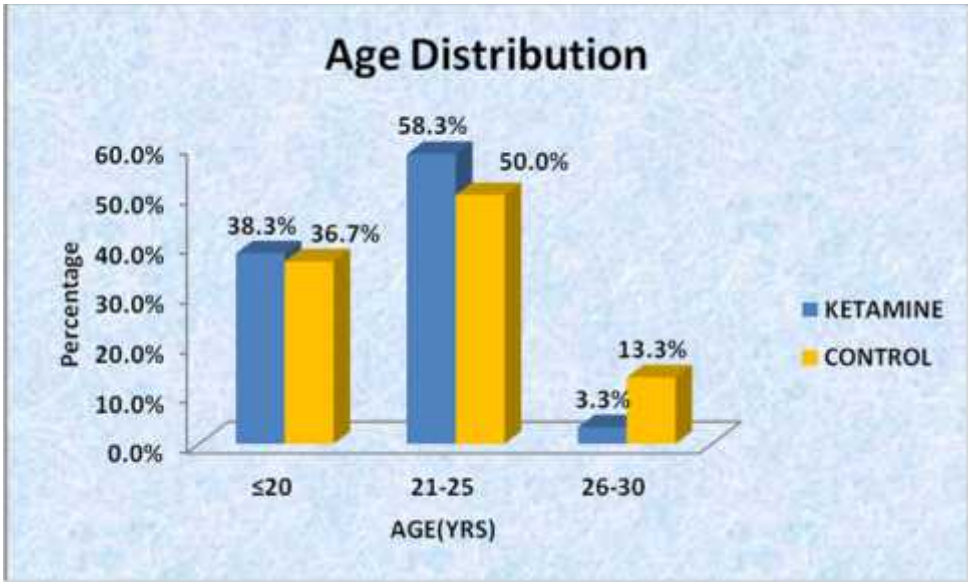


TABLE 6 : DISTRIBUTION OF CASES BY GESTATIONAL AGE BETWEEN KETAMINE AND CONTROL GROUPS.

GESTATIONAL AGE(WKS)	KETAMINE		CONTROL		p value
	N	%	N	%	
≤38	20	33.3%	24	40.0%	0.768
38-39	39	65.0%	35	58.3%	
>39	1	1.7%	1	1.7%	
Total	60	100.0%	60	100.0%	

Most of cases in both groups belong to 38-39 weeks of gestation is 65% and 58.3%. and P valve being is 0.768 and its insignificant.

GRAPH 2: DISTRUBUTION OF GESTATIONAL AGE

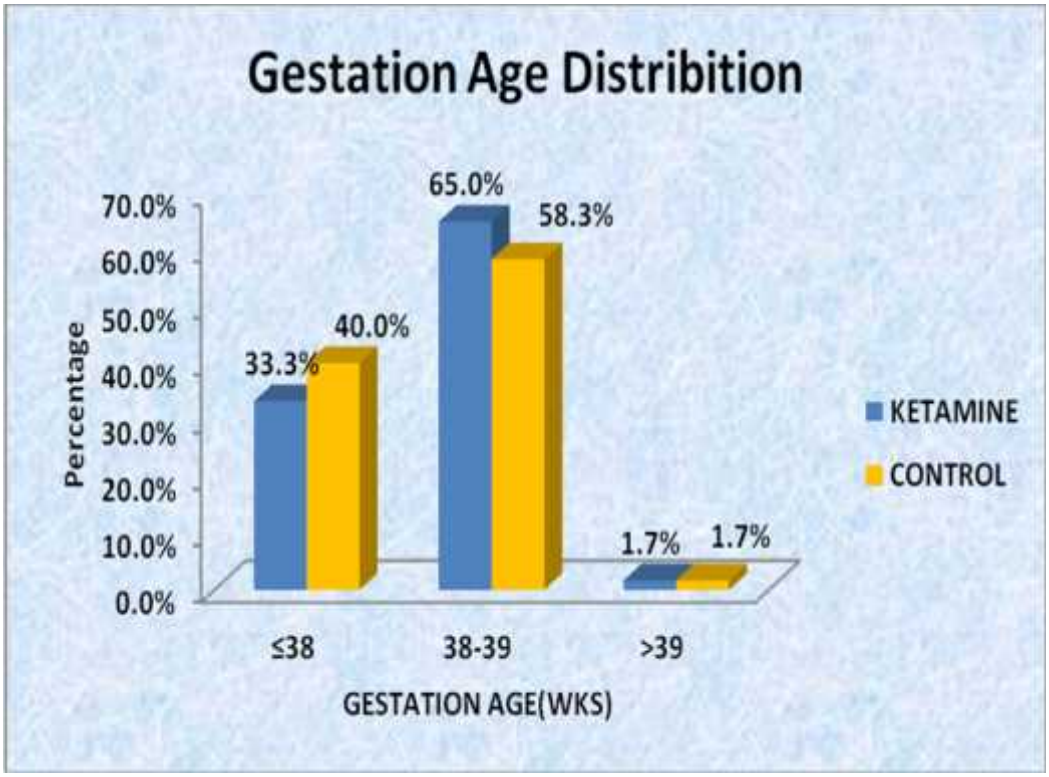


TABLE 7 : MEAN GESTATIONAL AGE BETWEEN KETAMINE AND CONTROL GROUPS.

GESTATIONAL AGE(WKS)	Mean	SD	p value
KETAMINE	38.6	4.5	0.413
CONTROL	38.9	3.4	

Mean gestational age in ketamine group is 38.6 and Mean gestational age in control group is 38.9 and SD are- 4.5 and 3.4. P valve is being 0.413 and its insignificant.

GRAPH 3: MEAN GESTATIONAL AGE

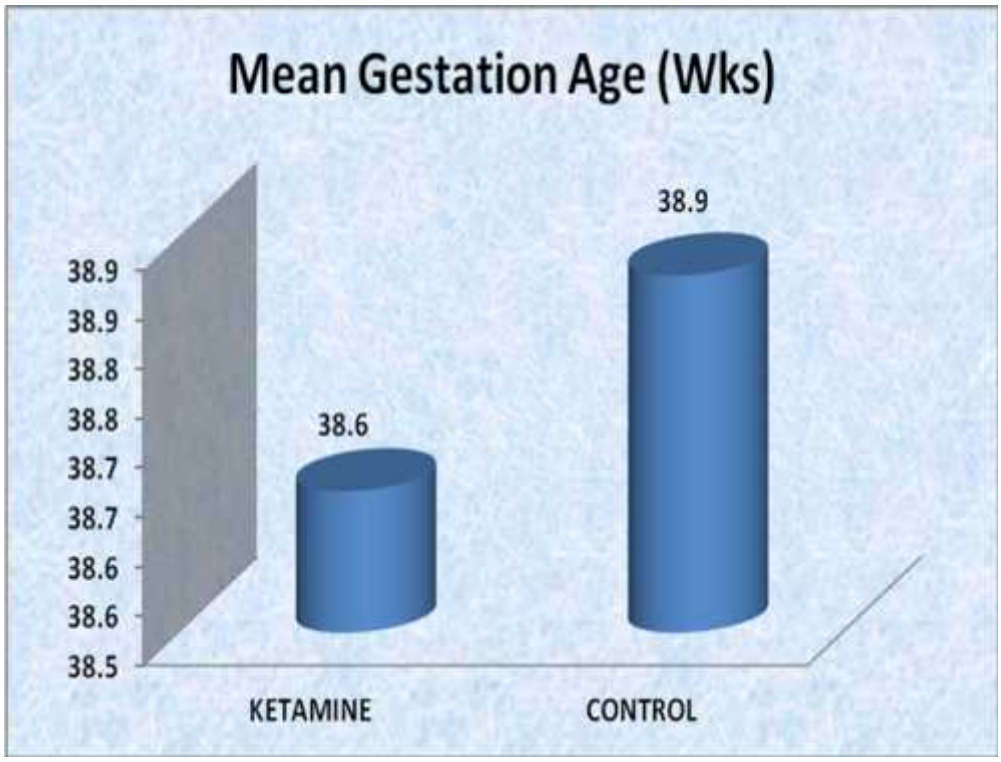


TABLE 8 : DISTRIBUTION OF CASES BY CERVICAL DILATATION AT INDUCTION OF DRUG IN KETAMINE AND CONTROL GROUPS.

DILATATION	KETAMINE		CONTROL		P value
	N	%	N	%	
3	23	38.3%	18	30.0%	0.442
4	37	61.7%	42	70.0%	
Total	60	100.0%	60	100.0%	

In Ketamine group, 23 cases (38.3%) at 3cms dilatation, 37 cases (61.7%) at 4cms dilatation.

In control group, 18 cases(30.0%) at 3cms dilation, 42 cases (70.0%) at 4cms dilatation.

P valve is being 0.442, which is insignificant.

GRAPH 4 : CERVICAL DILATATION OF CASES.

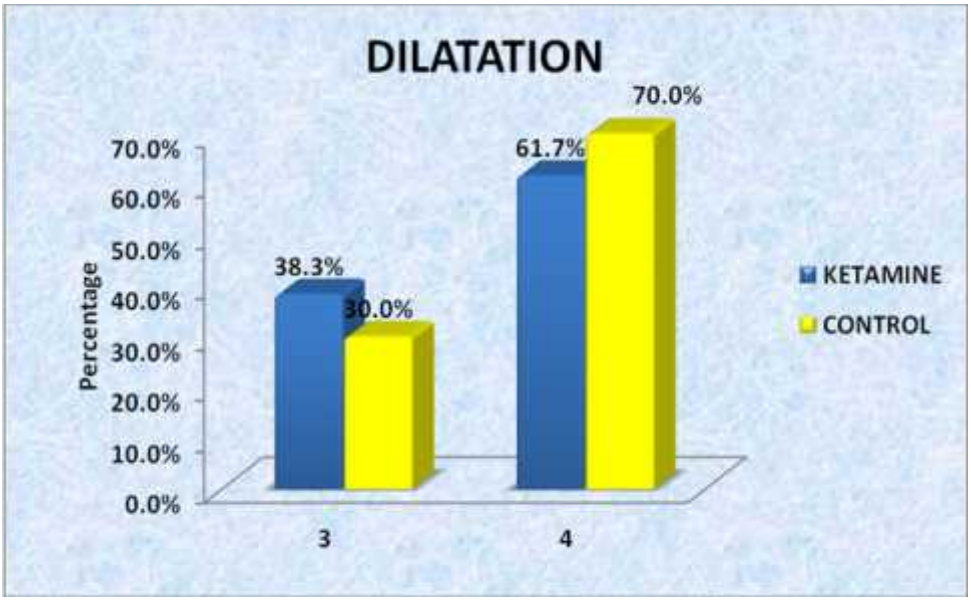


TABLE 9 : DISTRIBUTION OF CASES BY DURATION OF LABOUR AFTER INDUCTION OF DRUG BETWEEN KETAMINE AND CONTROL GROUPS.

DURATION (Hrs)	KETAMINE		CONTROL		p value
	N	%	N	%	
3-4	32	53.3%	12	20.0%	<0.001 (Sig)
4-5	25	41.7%	27	45.0%	
5-6	3	5.0%	19	31.7%	
>6	0	0.0%	2	3.3%	
Total	60	100.0%	60	100.0%	

The difference in duration of labour after induction of drug in both group is highly significant (p<0.001). 53.3% cases in ketamine group delivered in 3-4 hrs when compared to 20.0%, 41.7% cases in ketamine group delivered in 4-5 hrs when compared to 45%. 5% in ketamine group delivered after 5hrs when compared to 34%in control group. P valve being <0.001 which is highly significant.

GRAPH 5 : DURATION OF LABOUR.

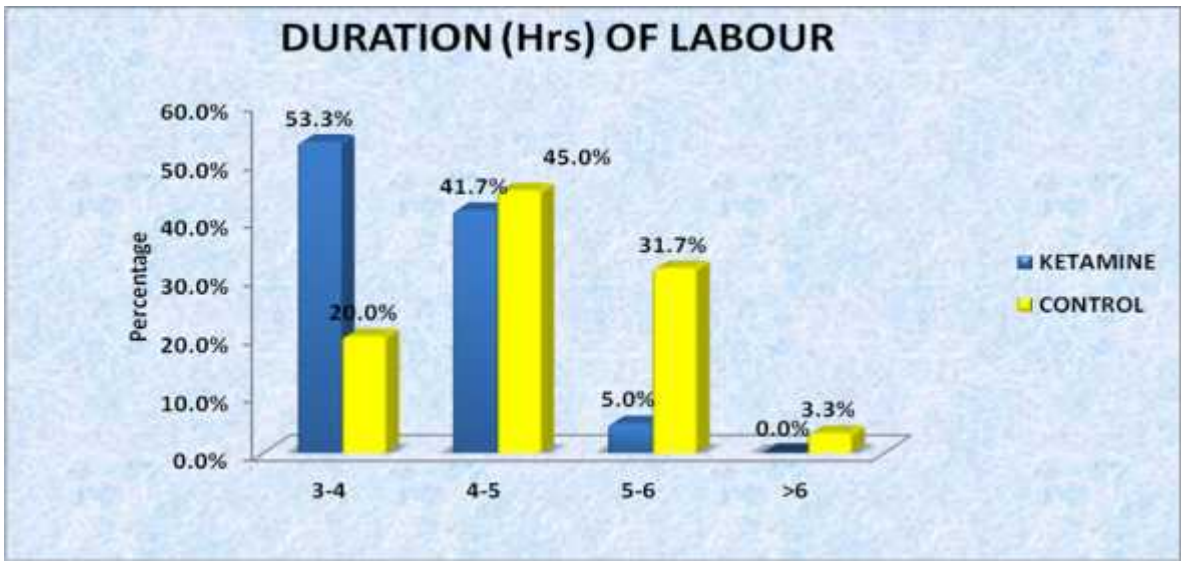


TABLE 10: DISTRIBUTION OF CASES BY MODE OF DELIVERY BETWEEN KETAMINE AND CONTROL GROUPS.

MOD	KETAMINE		CONTROL		p value
	N	%	N	%	
Normal Delivery	56	93.3%	56	93.3%	0.766
Instrumental Delivery	2	3.3%	1	1.7%	
Caesarean Section	2	3.3%	3	5%	
Total	60	100.0%	60	100.0%	

In a Ketamine group, 93.3% had normal delivery , 3.3% had instrumental delivery, 3.3% had caesarean section.

In control group, 93.3% had normal delivery, 1.7% had instrumental delivery, 5% had caesarean section.

The P valve is insignificant (0.766)

GRAPH 6: MODE OF DELIVERY

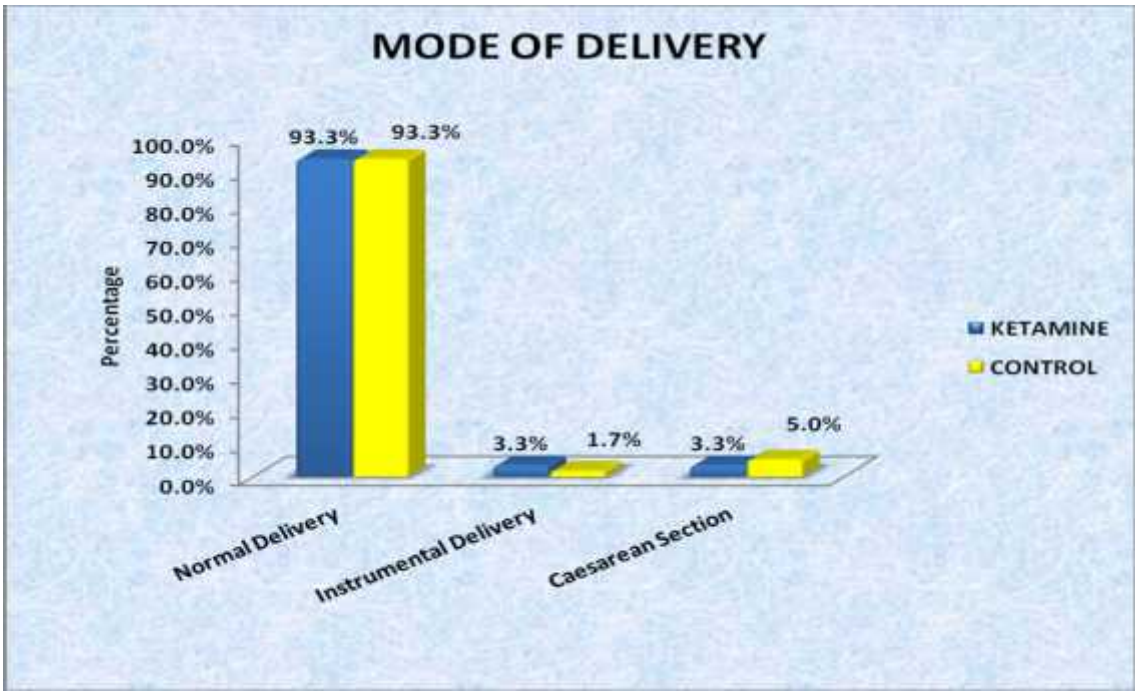


TABLE 11 : DISTRUTION OF CASES BY INDICATION OF C- SECTION IN KETAMINE AND CONTROL GROUPS.

INDICATION C-SECTION	KETAMINE		CONTROL		p value
	N	%	N	%	
Fetal Distress	2	3.3%	1	1.7%	0.491
MSL	0	0.0%	1	1.7%	
NPOL	0	0.0%	1	1.7%	

In our study(ketamine) group, 3.3% had fetal distress. In control group, 3 cases under went C-section, one (1.7%)case had fetal distress, one (1.7%) case had meconium stained liquor in active phase, one case had NPOL.

The P valve is not significant.

GRAPH 7 : INDICATION OF C-SECTION

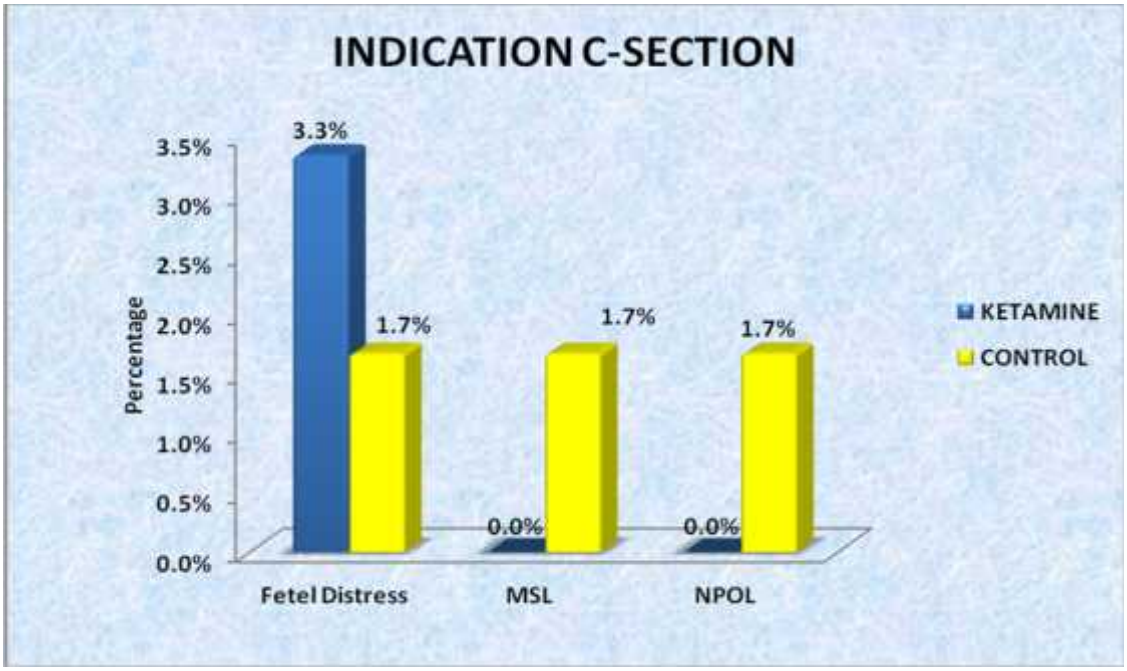


TABLE 12: DISTRIBUTION OF CASES BY VAS SCORE BETWEEN KETAMINE AND CONTROL GROUPS.

VAS SCORE	KETAMINE		CONTROL		p value
	N	%	N	%	
≤3	21	36.2%	1	1.8%	<0.001 (Sig)
4-5	33	56.9%	3	5.3%	
6-7	4	6.9%	32	56.1%	
≥8	0	0.0%	21	36.8%	
Total	58	100.0%	57	100.0%	

In the study group, 36.2% had mild pain,56.9% had mild pain to moderate pain, 6.9% had moderate to severe pain, None had severe pain.

In the control group, 1.8% had mild pain, 5.3% had mild to moderate pain, 56.1% moderate to severe pain, 36.8% had severe pain.

The P valve is highly significant <0.001

Mean vas score in Ketamine group is 4 and in control group is 6.8.

GRAPH 8 : VAS SCORE.

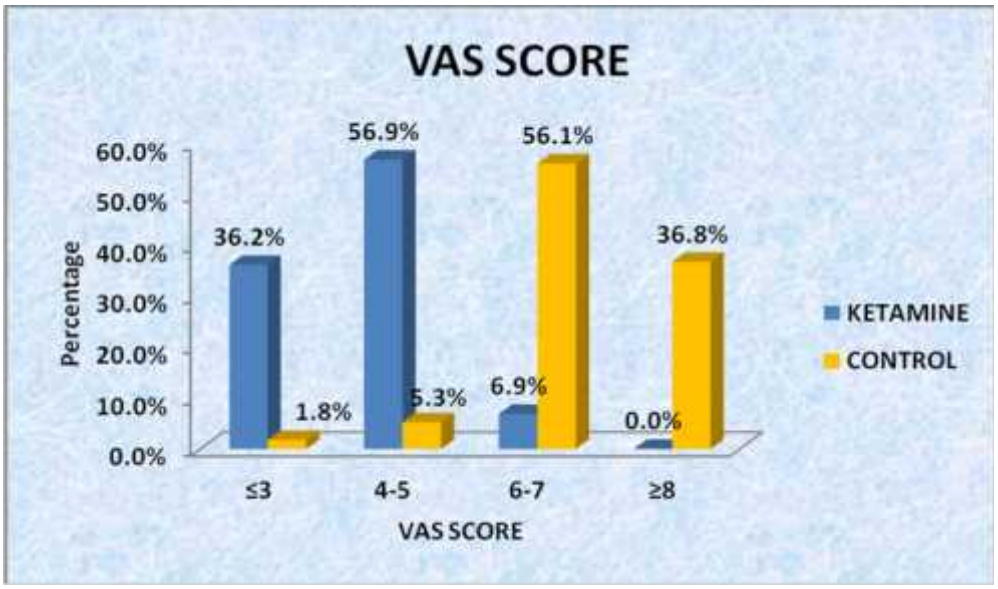


TABLE 13: DISTRIBUTION OF CASES BY RASS SCORE BETWEEN KETAMINE GROUP AND CONTROL GROUPS.

RASS SCORE	KETAMINE		CONTROL		P value
	N	%	N	%	
-1	4	6.9%	0	0.0%	0.071
0	52	89.7%	52	91.2%	
1	2	3.4%	5	8.8%	
Total	58	100.0%	57	100.0%	

89.7% are alert and clam, 6.9% are drowsy, 3.4% are restless in Ketamine group.

In control 91.2% are alert and clam, 8.8% are restless.

The p valve is not significant (0.073).

GRAPH 9: RASS SCORE.

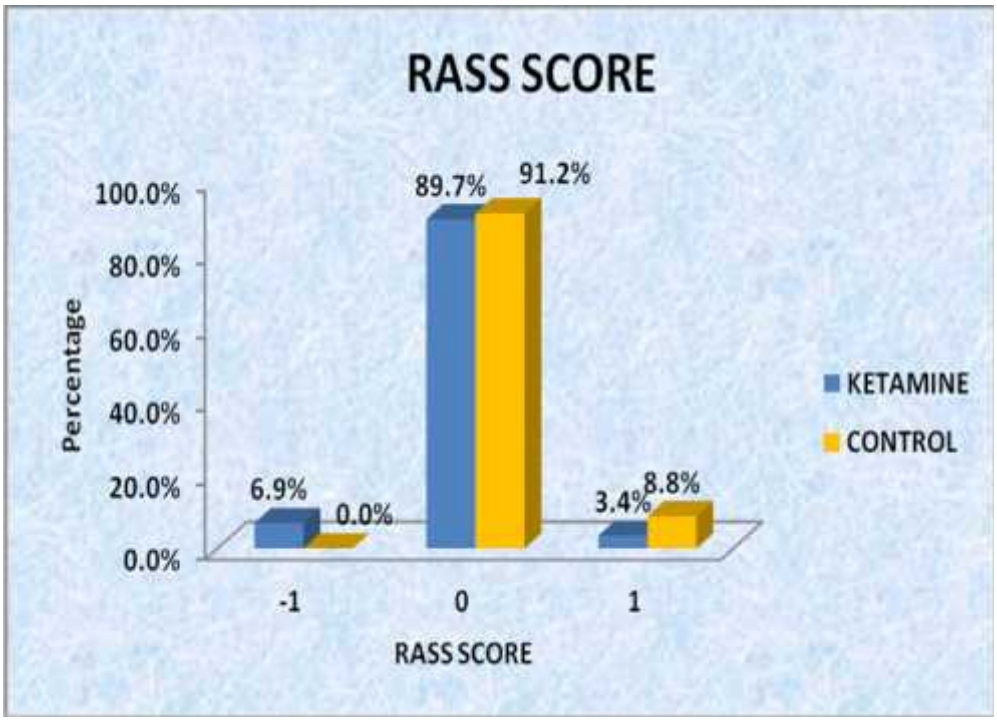


TABLE 14 : MATERNAL COMPLICATION AMONG KETAMINE GROUP.

MATERNAL COMPLICATION	KETAMINE	
	N	%
HEADACHE	8	13.3%
NAUSEA	5	8.3%
INCREASED BP	2	3.3%
INCREASED PR	5	8.3%
SLIGHT HEADEDNESS	1	1.7%
IRRELEVANT SPEECH	2	3.3%
NIL	46	76.7%

In Ketamine group, 13.3% had headache, 8.3% had nausea, 1.7% had slight headedness, 3.3% had irrelevant speech, 8.3% had rise in PR and 3.3% had rise in BP. 76.7% had no maternal side effects or complications.

GRAPH 10: MATERNAL COMPLICATION AMONG KETAMINE GROUP

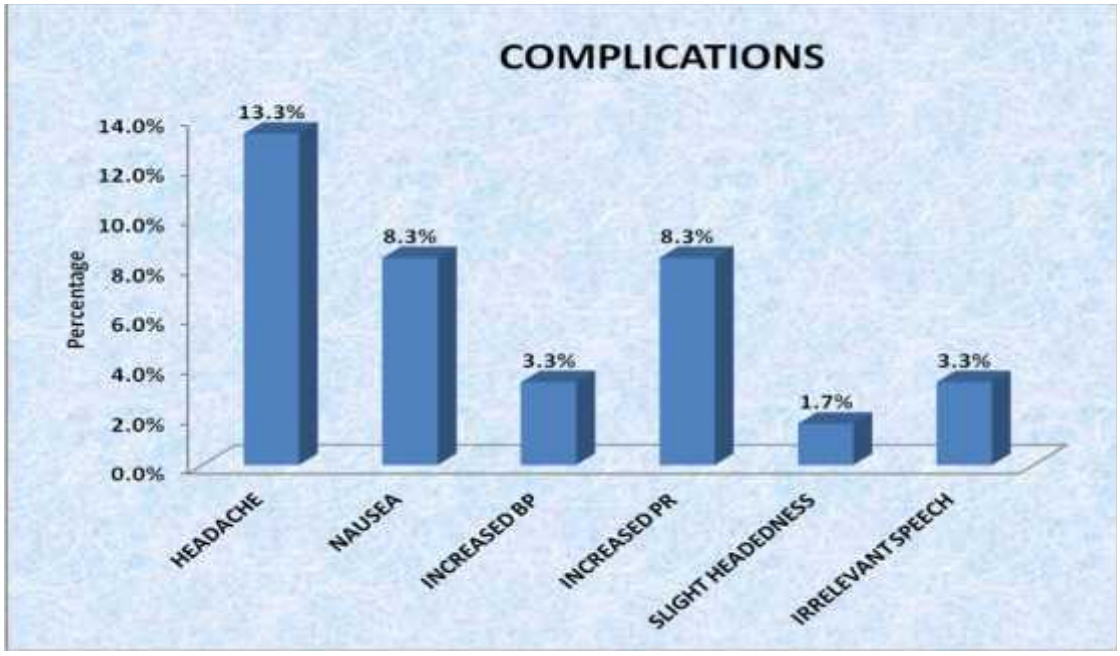


TABLE 15 : MATERNAL COMPLICATION AMONG CONTROL GROUP.

MATERNAL COMPLICATION	CONTROL	
	N	%
ATONIC PPH	1	1.7%
HEADACHE	2	3.3%
NAUSEA	1	1.7%
NIL	56	93.3%
Total	60	100.0%

In control group, 93.3% had no side effects, 3.3% had headache, 1.7% had nausea, 1.7% had atonic PPH.

GRAPH 11: MATERNAL COMPLICATION AMONG CONTROL GROUP

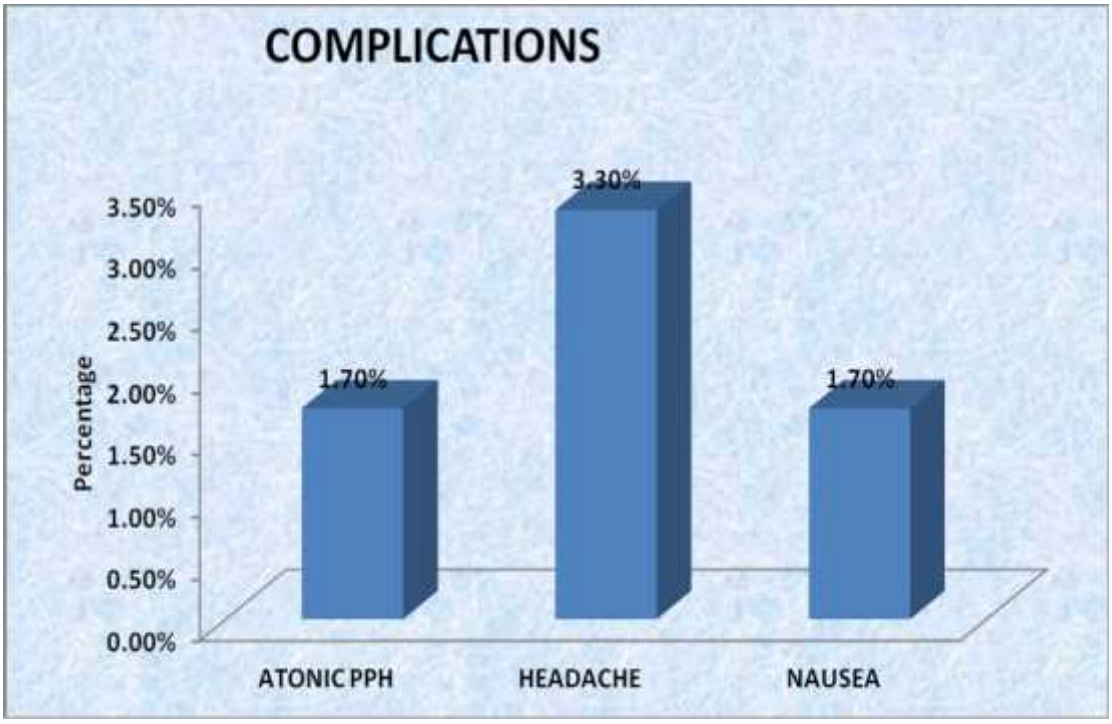


TABLE 16: DISTRIBUTION OF CASES BY APGAR SCORE AT 1 MIN BETWEEN KETAMINE AND CONTROL GROUPS.

APGAR SCORE AT 1 MIN	KETAMINE		CONTROL		p value
	N	%	N	%	
5	3	5.0%	4	6.7%	0.749
6-7	13	21.7%	10	16.7%	
8	44	73.3%	46	76.7%	
Total	60	100.0%	60	100.0%	

In study group, 73.3% has 8 APGAR, 21.7% has 6-7 APGAR, 5% has 5 APGAR at 1min.

In control group, 76.7% has 8 APGAR, 16.7% has 6-7 APGAR, 6.7% has 5 APGAR at 1min.

The p valve(0.749) is not significant

Mean APGAR score at 1 min in Ketamine group is7.60 and in control group is 7.58.

GRAPH 12 : APGAR SCORE AT 1 MIN.

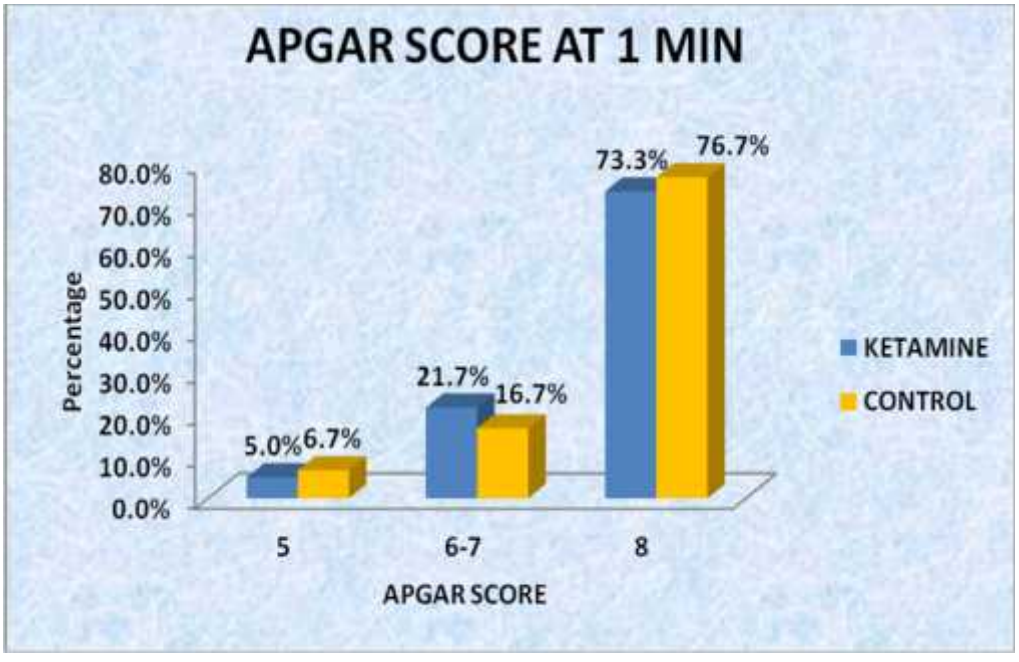


TABLE 17: DISTRIBUTION OF CASES BY APGAR SCORE AT 5 MINS BETWEEN KETAMINE AND CONTROL GROUPS.

APGAR SCORE AT 5 MIN	KETAMINE		CONTROL		p value
	N	%	N	%	
6-7	4	6.7%	3	5.0%	0.235
8	1	1.7%	5	8.3%	
9	55	91.7%	52	86.7%	
Total	60	100.0%	60	100.0%	

In Ketamine group, 93.4% (56 cases) has APGAR above 8 at 5mins, 6.7% has 6-7 APGAR at 5mins. In control group, 95 %(57 cases) has APGAR above 8 at 5mins and 5% has at 6-7 APGAR at 5mins. P valve being not significant(0.235).

Mean APGAR score at 5mins in Ketamine group is 8.9 and in control group is 8.8.

GRAPH 13:APGAR SCORE AT 5 MINS.

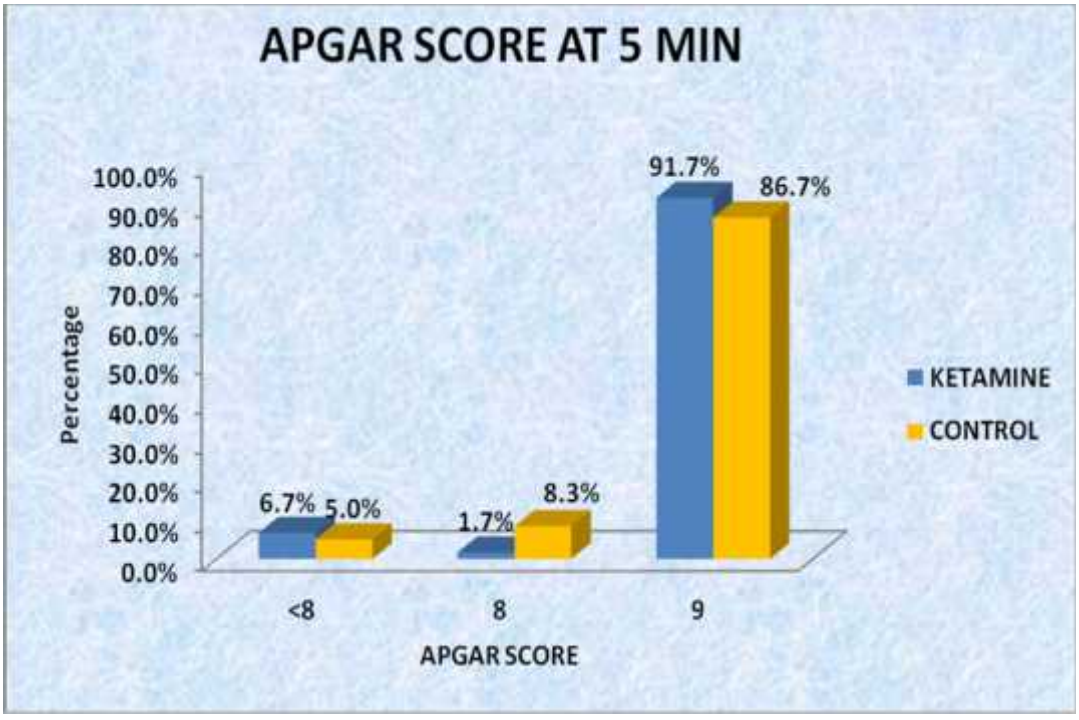


TABLE 18 : DISTRIBUTION OF CASES ADMITTED IN NICU BETWEEN KETAMINE AND CONTROL GROUPS.

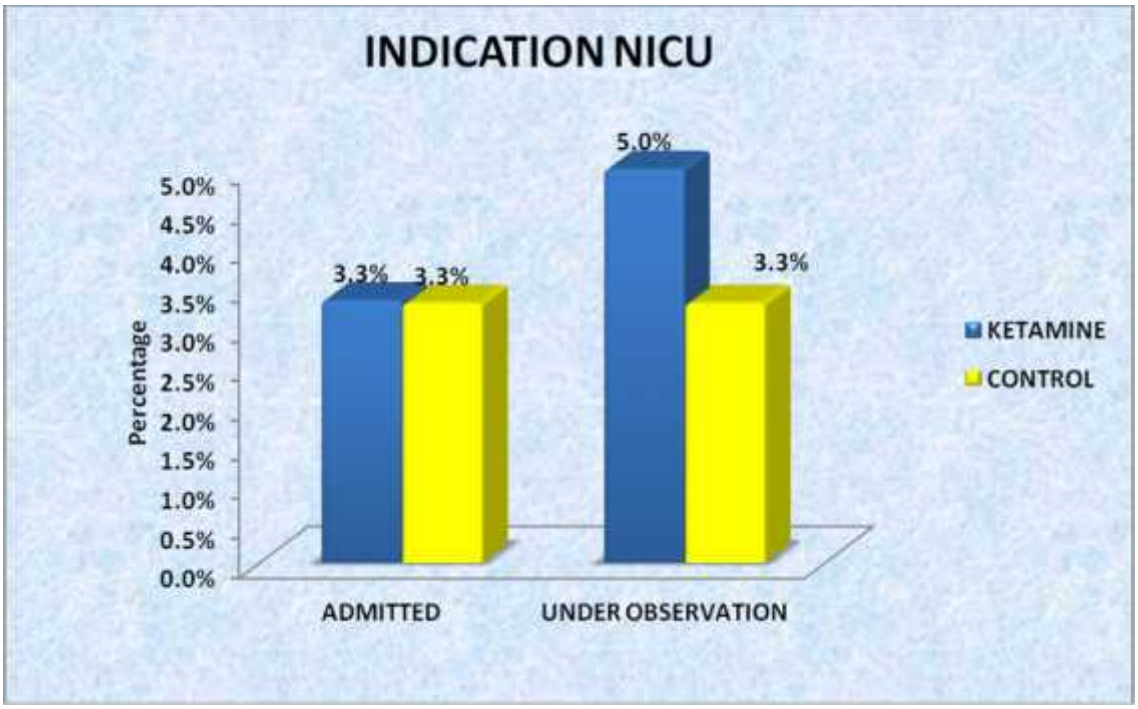
NICU CASES	KETAMINE		CONTROL		p value
	N	%	N	%	
ADMITTED	2	3.3%	2	3.3%	0.764
UNDER OBSERVATION	3	5.0%	2	3.3%	

In our study, in Ketamine group 2 cases (3.3%) and same number of cases in control group are admitted in NICU for <7days with no neurological deficit.

3 cases (5%) in Ketamine group and 2 cases (3.3%) in control group were under observation for 6-8 hrs and on O_2 inhalation.

The p valve being 0.764 which is not significant.

GRAPH 14 : NICU ADMISSION



DISCUSSION

The primary object of this study was to assess the efficacy, safety and feasibility of using low-dose IV Ketamine for labour analgesia.

This clinical trail was an effort to provide safe yet effective labour analgesia with no prolongation of labour and with no maternal and fetal complications. The result from the study were analysed and compared with cases in other studies, in which Ketamine and other analgesics were used.

INDUCTION DOSE OF KETAMINE-

In a study done by Sarkar and Sahu in1991, Initial dose of Ketamine at rate of 0.2-0.4mg/kg body weight followed by a continuous infusion of 0.5 to 1 mg/min.

In a study done by Krishna jagatia et al in 2013, Ketamine given at 0.4mg/kg/ IV over a period of 30-60secs and maintenance dose of 1mg/min on pump.

In Sam joel et al in 2009, and Maroof.M in 1998, Ketamine given in same doses as present study.

In a study by Desai and Daftary et al in 2000, loading dose Ketamine 0.25 - 0.5mg/kg given at 7-8cms dilation with other analgesics and no continuous infusion, top-up doses given at interval 30-40min (7.5mg - 15mg) if required and second dose after birth of baby.

In a study by Geethika duggal et al in 2014, both group had 0.2mg/kg bolus of Ketamine once at 3cms dilatation and maintenance of infusion of 50mg in 500ml in 5%D at 30 - 90 drops/ min. In group B additional dose of Tramadol 0.75mg/kg after loading dose of ketamine and repeated at fully dilatation (total 1.5mg/kg).

In present study, induction of ketamine started in active phase(3-4cms) with 0.2mg/kg over 30mins and maintenance dose of 0.2mg/kg/hr continuous intravenous infusion.

INDUCTION DELIVERY INTERVAL-

In study by Krishna jagatia, Mean duration of first stage was 140.6mins in study group and 205mins in control group. Mean second stage interval was 32mins in study and 35.8mins in control group.

In study by Sam joel, Mean induction delivery of study group was 213.29mins and in control group its 244.14 min.

In study by Sarkar and Sahu, After 3-4cms of dilatation 26 cases(52%) delivered in 2 hours and 23 cases (46%) delivered in 2.1- 5 hrs and one case delivered after 5hrs.

In study by Maroof. M mean induction delivery of study group was 235.23mins and 4 required supplementary analgesia so are withdrawn from study as failure.

In study by Geethika duggal, mean duration of first stage is 136.68 ±56.62 in group A and 142±52.14 in group B. Mean duration of second stage 27.41±12.03 in group A and 28.06±11.28 in group B.

In Desai and Daftary mean duration of induction delivery interval in study group is 3.2 hrs and in control group its 5.2 hours.

In present study, mean induction delivery interval in study group is 245.0mins and in control group is 286.2mins. 53.3% delivered in 4hrs and 41.7% women's delivered in 4- 5hrs, 5% delivered in 5-6hrs in study group when compared to control group only 65% delivered in 5 hrs, 31.7 delivered in 5-6hrs, 3.3% delivered after 6 hrs (P valve <0.001).

MODE OF DELIVERY-

In study by Krishna jagatia, 98% had normal delivery in study group and 100 % in control group 2% had instrumental delivery.

In study done by Geethika Duggal, 88% had normal delivery, 8% had instrumental delivery, 4% had LSCS in group A and in group B 92 % had normal delivery, 8% had instrumental delivery.

In study by Ganla 84% delivered normally, 6% had forceps delivery, 4% had vacuum assisted delivery, 6% had LSCS.

In study by Desai and Daftary, 24.5% had instrumental delivery in study group and 21% control group. 12% had LSCS in study group and 17% in control group.

In present study, 56 cases(93.3%) had normal delivery and 2 cases (3.3%) had instrumental delivery(prolonged 2nd labour) and 2 cases(3.3%) had LSCS (fetal distress) in study group where as in control group 56 cases(93.3 %) had normal vaginal delivery and 1case(1.7%) had instrumental delivery(prolonged second stage)and 3 cases(5%) had LSCS(MSL, NPOL, FD) and P valve is 0.766.

PAIN RELIEF-

In study by Krishna Jagatia, 90 % had excellent pain relief, 8% had satisfactory relief and 2%had no pain relief.

In study by Sarkar and Sahu, 35 womens had excellent analgesia, 13 women had fair analgesia, 2 was unsatisfactory.

In Ganla study, 36 cases had excellent pain relief, 8 cases had moderate pain, 6 had mild pain.

In Desai and Daftary study, 24% had excellent pain relief and 62% substantial pain relief 14% had in sufficient pain relief in study group. 32% had substantial pain relief and 56% had insufficient pain relief, 12% had no pain relief.

In study by Geethika Duggal, 28% had no pain, 36% had mild pain, 20% had moderate pain, 4% severe pain in group A. 48% had no pain, 36% had mild pain, 8% moderate pain and 8% had severe pain.

In study by Maroof. M, pain score is 2.3±1.6 in ketamine group and 8.1±0.8 in non ketamine group according to visual analogue scale.

In study of Sam Joel, 82.6% had mild pain (<5) and 17.5 had in sufficient pain relief in study group. 45.7 had insufficient pain relief. Overall pain relief in all cases was significantly higher in ketamine group when compared to placebo group(p- 0.028).

In present study, In study group, 36.2% had mild pain,56.9% had mild pain to moderate pain, 6.9% had moderate to severe pain, None had severe pain. In the control group, 1.8% had mild pain, 5.3% had mild to moderate pain, 56.1% moderate to severe pain, 36.8% had severe pain. Mean vas score in ketamine group is 4 and in control group is 6.8.

MATERNAL OUTCOME

In a study done by Krishna Jagatia, 30%had marginal rise in pulse, 16% had marginal rise in blood pressure, and 10% had nausea but no vomiting and none of them had dissociative sleep or hallucinations. Uterine contractions and cervical dilatation were not interfered by ketamine because of its Oxytocin property.

Chodoff and Stella study found out Oxytocin property of Ketamine. The 3rd stage of labour in this group was characterized by prompt uterine contractions with rapid expulsion of placenta. Following delivery of placenta uterus remind firmly contracted and Oxytocin needed in only 3 patients.

In Sarkar and Sahu study, No signifiacant maternal complications were noticed 5 cases had unpleasant dreams, 2 cases had hallucinations subsided by inj. Lorezepam and 5 cases had nausea and vomiting.

In study done by Sam joel, None of the patients complained of psychomimetic side effects such as hallucinations or vivid dreams. 17(48.5%) had light headedness after loading dose and subsided by time, Two of them had Nystagmus in ketamine group, 6(18 %) had nausea and vomiting.

In study done by Gregory f. Janeczko at al, the difference between high dose and low dose ketamine is highly significant ($p<0.001$) in term of maternal complications and in APGAR score.

In Ayangade.O study, 78% had total pleasant experience, while rest found it unpleasant and uncertain. 8% had unpleasant dreams and 5 % had hallucination and subsided by treatment.

In present study, None of the subject had major complication, 13.3% had headache, 8.3% had nausea none had vomiting, 3.3% had irrelevant speech gradually subsided in 6hrs after delivery, 8.3% had rise in PR, 3.3% marginal rise in BP in study group. In control group only 1(1.7%) subject had Atonic PPH, 3.3% had headache, 1.7% nausea, no marked change in vital parameters.

NEONATAL OUTCOME

In Chodoff and Stella study had significant number of depressed newborns requiring resuscitation IPPV and oxygen and concluded Ketamine could be effective in low dose.

In Gregory Janeczko study, APGAR scores with low doses ketamine for delivery were compared to normal dose resulted in lower APGAR score and is significant($P<0.001$).comparing the result of higher dose to other general anaesthetics were borderline significant($p<0.05$).

In study done by Sarkar and Sahu stated no significant outcome, Mean APGAR score at 1min is 8.26 and 5mins is 9.62.

In Krishna Jagatia study, Ketamine had no effect on APGAR score at 1min and 5mins, 98% had score of 7-8 at 1min and 100% >8 at 5mins. None had respiratory distress or delayed response.

In Sam Joel study, out of 70 neonates deliveries, 2 (from each group under went caesarean section) were depressed. one from ketamine group APGAR score <4 at 1st min and 9 at 5mins and on O_2 inhalatoin. Other from placebo group had Grade 3 meconium aspiration and needed NICU admission. The neurological examination was normal in the rest of neonates and were breast fed immediately.

In our present study, in Study group 5 cases admitted in NICU out of 5, 2 cases (underwent caesarean section) were depressed and admitted for 3-4 days and 3 cases were under observation for 6-8 hrs , in those 2 cases had prolonged 2nd stage (underwent forceps delivery) and one case had delayed cry. In control group, 4 cases admitted in NICU, out of 4, 2 cases underwent caesarean section were depressed and admitted for 3-4 days, 2 cases were under observation for 6-8hrs, in those one had prolonged 2nd stage(underwent forceps delivery) and one case had distress in 2nd stage(P valve 0.764).

CONCLUSION

Our study strongly suggest that low dose intravenous Ketamine in Labour analgesia with continuous infusion had marked effect on pain relief and duration of labour.

In developing countries like India where labour analgesia is still in its infancy and various techniques have been tried for pain relief during labour. Most popular method of pain relief during labour used worldwide is epidural analgesia. But because of poorly equipped labour room and economic constraints not being so popular, and prolongation of 2nd stage labour, increased instrumental delivery decreased the usage of it.

Low dose ketamine infusion in pre operative period has shown to produce analgesia and decrease the requirement of Opioid analgesics. In obstetrics, it is being used to provide analgesia during labour in continuous and intermittent infusion.

This clinical trail was an effort to study the efficacy, safety and feasibility of intravenous continuous low dose Ketamine to provide analgesia during labour and also to standardize a technique, with an intention to propose for labour analgesia in primary and secondary level hospital having a lower level of supervision.

- In our study, Low dose Ketamine infusion (0.2mg/kg in 30hrs followed by 0.2mg/kg/hr until delivery) provided effective analgesia but proper selection of parturient in active labour and expected to have normal labour were included.
- It is safety, with out significant maternal and fetal outcome
- It does not prolong the duration of labour and there no increased incidence of instrumental delivery or caesarean section.
- It is easy to administer and monitor with out help of an expertise.
- It is cost effective and economic.

SUMMARY

This is a single blinded randomized study conducted in Shri B.M patil medical college, vijayapur, from December 2014 to july 2016. 120 parturient were randomized into two groups, study(Ketamine) group and control(placebo) group, 60 cases in each study. parturient who are in active labour (3-4cm) and expected to have normal vaginal delivery **(**includes singleton, term, vertex presentation) with no maternal and fetal complications were included in the study.

A detailed history of age, parity, gestational age, ANC care, detailed h/o past labour events, previous medical and surgical history, a through detailed general and obstetrics examination was made. Routine investigations and screening were carried out in all cases. Parturient with grand multies, mal presentations, multiple pregnancy, CPD, previous caesarean section, high risk obstetric problems like high blood pressure, gestational diabetics, epilepsy, cardiac disease, premature rupture of membrane, IUGR, were exclude from study. Parturient were randomly assigned to receive either ketamine at loading dose of 0.2mg/kg in 30mins followed by continues infusion of 0.2mg/kg/hr until delivery and normal saline at similar volume, were compared for the safety and efficacy of drug, duration of labour, pain relief, sedation score and maternal and neonatal outcome.

Outcomes in both study(Ketamine) and control group-

- Mean age in study group 21.6 and control group is 23.3, p valve being is not significant(p-0.612).
- Mean gestational age in study group is 38.6 and control group is 38.9 , p valve being is not significant(0.413).
- Mean duration of labour in study group is 245, and in control group is 286.2 and P valve is being <0.001 which is highly significant.

- Mode of delivery- 93.3% delivered normally, 3.3% had instrumental delivery, 3.3% had caesarean section in study group when compared to control group, 93.3% had normal delivery, 1.7% instrumental delivery, 5% had caesarean section and p valve being insignificant 0.766.
- In study group, 36.2% had mild pain,56.9% had mild pain to moderate pain, 6.9% had moderate to severe pain, None had severe pain. In the control group, 1.8% had mild pain, 5.3% had mild to moderate pain, 56.1% moderate to severe pain, 36.8% had severe pain P<0.001 is highly insignificant. Mean vas score in Ketamine group is 4 and in control group is 6.8.
- No sedation in study group,89.7 were alert and clam, 6.9% were drowsy, 3.4% were restless. 91.2% were alert and clam, 8.8% were restless in control group.
- 76.7% had nil maternal side effects, 13.3% had headache, 8.3% had nausea, 3.3% had increased BP, 8.3% had increased PR, 1.7% had slight headedness, 3.3% had irrelevant speech in study group.
- 93.3% had nil maternal side effects, 1.7% nausea, 3.3% headache, 1.7% Atonic PPH in control study.
- Mean APGAR score at 1min in study group is 7.60 and In control group is 7.58, P valve being insignificant (P-0.912).
- Mean APGAR score at 5mins in study group is 8.9 and in control group is 8.8, P valve being insignificant (P-0.617).
- In study group, 2 cases (3.3%) had admitted in NICU and 3 cases (5%) were under observation for 6-8 hrs. In control group, 2 cases (3.3%)had admitted in NICU and 2 cases (3.3%) were under observation.

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ANNEXUE – I

ETHICAL CLERANCE CERTIFICATE

Institutional Ethical Committee BLDE's S.B.M. Patil Medical College, BIJAPUR-586 103. OUTWARD No. 54/14 Date 27/11/14

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 *at* 3-30pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title Safety and efficacy of low dose intravenous Ketamine in labour analgesia. A Single blinded randomized controlled trail.

Name of P.G. student Dr Chitta. Sree Lakshmi, Dept of OBG.

Name of Guide/Co-investigator Dr Vijayalakshmi. R. Gobbur Professor of OBG.

for
DR.TEJASWINI VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE- III

BLDE UNIVERSITY'S SRI BM PATIL MEDICAL COLLEGE VIJAYAPUR-586103

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH:

I the undersigned…… s/o.D/o.W/o.....……..... aged……years ordinarily resident of……. do here by state/ declare that Dr…….. of ……. Hospital has examined me thoroughly on…… at …….. and has explained to me in my own language……. that I am suffering from ……..disease (condition) and this disease/ condition mimic following diseases…….. Further Doctor…….informed me that he/ she is conducting dissertation/ research titled **"SAFETY AND EFFICACY OF LOW DOSE INTRAVENOUS KETAMINE IN LABOUR ANALGESIA. A SINGLE BLINDED RANDOMIZED CONTROLLED TRIAL"** under guidance of Dr…….requesting my participation in the study. I will be giving intravenous fluids, which relieves from pain during labour. The outcome and effectiveness will be noted.

Doctor has also informed me that, during conduct of this procedure few adverse effects like light headedness, nausea and vomiting may be encountered. The complications are very rare but are not anticipated. They are usually treatable but in rare circumstance may prove fatal in spite of anticipated diagnosis & best treatment made available. Further Doctor has informed me that my participation in this study help in

evaluation of results of the study which is a useful reference for treatment of other similar cases in near future, and also i may be benefited in getting relieved of pain that I am suffering and outcome may also be improved if the treatment is found to be useful.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not accessed by the person other than me or my legal hirer except for academic purposes. The Doctor did inform me that though my participation is purely voluntary based on information given to me, I can ask any clarification during the course of treatment/ study related to Diagnosis, Procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can with draw from my participation in this study at any time if I want or investigator can terminate me from study at any time from the study but not the procedure of treatment & follow up unless I request to discharge.

In view of anticipated/ unexpected complications during the course of study, that I will be treated free of cost, as explained by the investigator.

After understanding the nature of dissertation or research, Diagnosis made, mode of treatment I the under signed smt. …….under my full conscious state of mind I agree to participate in the said research/ Dissertation.

Signature of patient:

Signature of Doctor:

Witness 1.

2.

Date: Place:

ANNEXUE - II

CASE SHEET PROFORMA

SERIAL NO: IP NO. :

NAME : OCCUPATION :

AGE: SOCIOECONOMIC STATUS:

ADDRESS:

DATE OF ADMISSION:

DATE OF STUDY:

1. **CHIEF COMPLAINTS :**
2. **HISTORY OF PRESENTING COMPLAINTS :**
3. **OBSTETRIC HISTORY :**
    a. Married Life:
    b. Obstetrics score: Status of gravida, parity,miscarriage, MTP and living issues.
    c. Labour events and mode of previous delivery
4. **MENSTRUAL HISTORY:**

    LMP- A/C TO 1ST TRIMESTER SCAN

    EDD- EDD-

    POG- POG-
5. **PAST HISTORY :**

    TB / Bronchial asthma/ Diabetes mellitus / Hypertension/ RHD/Blood transfusion / Thyroid disorders/Any operations.
6. **FAMILY HISTORY :**

    TB / Bronchial Asthma / Diabetes mellitus / Hypertension / Any cancer / Bleeding disorders / Thyroid disorders

7. PERSONAL HISTORY :

Diet :

Appetite:

Bowel and bladder :

Micturation :

Sleep:

Addictions

8.GENERAL PHYSICAL EXAMINATION

Nutritional status and built

Vitals

Temperature :

Pulse rate:

blood pressure:

Pallor / Icterus / Cyanosis/ Clubbing/ Oedema/ Lymphadenopathy

Thyroid:

spine:

Breast:

10. SYSTEMIC EXAMINATION

CVS:

Respiratory system:

Per abdomen:

Per speculum examination: for leak

Per vaginal examination:

Dilation of cervix -

Effacement of cervix -

Membranes -

vertex station-

Pelvis assessment - spines, inter-spinous, side walls, outlet.

11. INVESTIGATIONS :

HB %, Platelet count

Urine routine

BT, CT

HIV, HB_SAg

USG Obstetrics

12. MATERNAL OUTCOME :

Duration of labour:

Mode of delivery:

VAS score:

RASS score:

Vital parameters:

Any complication:

13.NEONATAL OUTCOME :

1. APGAR score at 1min-

   5min-

   10min-

2. If NICU admission: Indication-

   Duration-

3. Breast feeding after birth (in minutes)-

ANNUXURE IV

KEY TO MASTER CHART

Obstetrics score-

Primi	-	Primigravida
G	-	Gravida

Mode of delivery-

ND	-	Normal delivery.
LSCS	-	Lower segment Caesarean section.
FAVD	-	Forceps assisted vaginal delivery.

Indications-

FD	-	Fetal distress.
MSL	-	Meconium stained liquor.
NPOL	-	Non progression of labour.

VAS SCORE - Visual analogue scale.

RASS SCORE- Richmond agitation and sedation score.

MATERNAL OUTCOME-

PR	-	Pulse rate.
BP	-	Blood pressure.
PPH	-	Post partum haemorrhage.

NEONATAL OUTCOME-

NICU	-	Neonatal intensive care unit.
MAS	-	Meconium Aspiration Syndrome.
RD	-	Respiratory distress.

MASTER CHART

STUDY (KETAMINE) GROUP

Sl No	NAME	AGE	WT	OBS SCORE	GEST AGE	DILATATION	DURATION	MOD	IND	VAS SCORE	RASS SCORE	MATERNAL COMP	A/G		NICU	IND
													1min	5min		
1	SAVITRI	20	50	G2P1L1	38+2	3	210	VD	-	4	0	NIL	8	9	-	-
2	JYOTHI	24	52	PRIMI	37+3	4	240	VD	-	3	0	NIL	7	9	-	-
3	GAYATHRI	23	48	G2P1L1	38	4	180	VD	-	3	0	NIL	8	9	-	-
4	PREMA	22	50	PRIMI	38	4	260	VD	-	4	0	NIL	8	9	-	-
5	RENUKA	20	51	PRIMI	38+5	4	280	VD	-	4	0	HEADACHE ^ PR	7	9	-	-
6	RESHMA	21	50	PRIMI	39	4	260	VD	-	5	0	NIL	8	9	-	-
7	SHARANAMMA	21	52	PRIMI	38	3	280	VD	-	5	0	NIL	7	9	-	-
8	DANAMMA	27	56	G2P1L1	38	4	210	VD	-	3	0	NIL	8	9	-	-
9	BHAGYA SHREE	24	56	G2P1L1	39	4	270	VD	-	5	0	NIL	8	9	-	-
10	REKHA	24	54	G2P1L1	39	3	210	VD	-	5	0	^PR, NAUSEA	8	9	-	-
11	LAXMI	24	54	G2P1L1	39	3	210	VD	-	5	0	NIL	8	9	-	-
12	REKHA	25	52	PRIMI	38+4	4	320	FAVD		6	+1	NIL	6	8	OBSERVATION FOR 4HRS	
13	RENUKA	20	50	G2P1L1	38	4	220	VD	-	3	0	NIL	8	9	-	-
14	SWATHI	19	52	PRIMI	38+2	4	270	VD	-	5	0	NIL	8	9	-	-
15	HEENA	24	50	PRIMI	38+4	4	330	FAVD		7	0	NIL	5	7	OBSERVATION FOR 6HRS	
16	VIJYALAXMI	22	52	PRIMI	39	4	270	VD	-	5	0	NIL	8	9	-	-
17	RENUKA	24	50	PRIMI	39	4	290	VD	-	5	0	^PR,SLIGHT HEADEDNESS	7	9	-	-
18	SUMITRA	21	52	G2A1	38+5	4	270	VD	-	5	0	NIL	8	9	-	-
19	GAYATRI	20	52	G2P1L1	39	3	230	VD	-	4	0	^PR ,NAUSEA	7	9	-	-
20	SOUMYA	20	52	PRIMI	38	4	300	VD	-	4	0	NIL	8	9	-	-
21	SUCHITRA	22	52	G2P1L1	38+4	4	220	VD	-	3	0	NIL	8	9	-	-
22	HASEENA	22	56	G2P1L1	39	3	200	VD	-	4	0	NIL	8	9	-	-
23	MAHANANDA	19	54	G2P1L1	38	3	210	VD	-	3	0	NIL	8	9	-	-
24	RAJESHRI	19	50	G2P1L1	39	3	200	VD	-	3	0	HEADACHE, NAUSEA	7	9		
25	ASHWINI	20	52	G2P1L1	38+5	4	300	LSCS	FD	-	-	NIL	5	7	ADMITTED FOR 4 DAYS	MAS
26	BHAGAMA	20	56	PRIMI	38+4	4	280	VD	-	3	0	NIL	8	9		
27	POOJA	20	52	G2P1L1	38+5	4	230	VD	-	5	0	NIL	8	9		
28	PAVITRA	21	54	G2P1L1	38+2	3	210	VD	-	5	0	^BP, HEADACHE	7	9		
29	DEEPA	22	52	G2P1L1	38+5	3	190	VD	-	3	0	NIL	8	9		
30	SREEDEVI	22	52	G2P1L1	38+4	3	240	VD	-	4	0	NIL	8	9		
31	VIJYALAXMI	22	48	PRIMI	39	4	280	VD	-	3	-1	NIL	8	9		
32	SHREEDEVI	21	50	G2P1L1	39	3	240	VD	-	4	0	NIL	8	9	-	-
33	LAXMIBAI	20	50	G2P1L1	38+2	4	200	VD	-	3	0	NIL	7	9		
34	SARASWATI	20	50	G2P1L1	38+4	3	240	VD	-	3	0	^BP, HEADACHE	8	9		

35	KAVITA	19	52	G2P1L1	39	4	180	VD	-	3	0	NIL	8	9		
36	NIDHI	20	50	PRIMI	38+6	4	200	VD	-	4	0	NIL	8	9		
37	SANGEETA	20	54	G2A1	39	4	210	VD	-	4	-1	NIL	8	9		
38	SAVITA	25	52	G2P1L1	39	4	200	VD	-	4	0	NIL	7	9		
39	POORNIMA	23	50	G2P1L1	38+3	4	190	VD	-	4	0	NIL	8	9		
40	SAVITRI	20	52	PRIMI	38+5	3	240	VD	-	4	+1	IRRELEVANT SPEECH	8	9		
41	ANUSUYA	22	52	G2P1L1	39	3	270	VD	-	5	0	NIL	6	7	OBSERVATION FOR 6HRS	
42	SUREKHA	25	54	G2P1L1	38+5	4	210	VD	-	3	0	NIL	8	9		
43	SAVITA	28	52	G2P1L1	38+1	4	200	VD	-	3	0	NIL	8	9		
44	LAXMI	23	52	G2P1L1	39	4	200	VD	-	3	0	HEADACHE	8	9		
45	MAHADEVI	21	54	PRIMI	38+4	4	270	VD	-	4	0	NIL	8	9		
46	NIRMALA	21	50	PRIMI	39	4	270	VD	-	4	0	NIL	8	9		
47	VANI	23	50	G2P1L1	39	4	210	VD	-	3	-1	IRRELEVANT SPEECH	7	9		
48	LAXMI	19	54	G2P1L1	38+3	4	180	VD	-	3	0	NIL	8	9		
49	NEELAMMA	24	54	PRIMI	39	3	290	VD	-	3	0	NIL	8	9		
50	REKHA	21	54	PRIMI	38+4	4	270	VD	-	4	-1	HEADACHE	8	9		
51	HEENA	21	50	PRIMI	39	4	290	VD	-	4	0	NIL	7	9		
52	SAVITRI	20	54	PRIMI	38	3	300	VD	-	5	0	HEADACHE, NAUSEA	8	9		
53	JYOTI	20	52	PRIMI	38+5	3	300	VD	-	6	0	NIL	8	9		
54	GEETA	20	48	PRIMI	39	3	300	VD	-	3	0	NAUSEA	8	9		
55	ASHWINI	20	51	G2P1L1	39	4	220	VD	-	3	0	NIL	8	9		
56	BAGAMMA	23	50	PRIMI	38	3	270	LSCS	FD	-	-	NIL	5	7	ADMISSION F0R 2 DAYS	RD
57	SREEDEVI	23	52	G2P1L1	39	3	220	VD	-	4	0	NIL	8	9		
58	YAMNAVVA	21	52	PRIMI	38+3	4	270	VD	-	4	0	NIL	8	9		
59	LAXMI	18	50	PRIMI	39	3	310	VD	-	7	0	NIL	8	9		
60	RENUKA	22	50	G2P1L1	39+2	3	280	VD	-	4	0	^PR, HEADACHE	8	9		

CONTROL (PLACEBO) GROUP

Sl No	NAME	AGE	WT	OBS SCORE	GEST AGE	DILATATION	DURATION	MOD	IND	VAS SCORE	RASS SCORE	MATERNAL COMP	A/G		NICU	IND
													1 min	5 min		
1	BASAMMA	23	50	G2P1L1	39	3	260	VD	-	6	0	NIL	8	9	-	-
2	YELLAWWA	24	53	PRIMI	38+4	4	270	VD	-	6	0	NIL	7	9	-	-
3	PRIYA	21	48	G2P1L1	38+2	4	220	VD	-	6	0	NIL	8	9	-	-
4	LAXMI	22	50	PRIMI	39	4	340	VD	-	8	+1	NIL	8	9	-	-
5	PRATHIMA	20	50	PRIMI	38+2	4	320	VD	-	8	0	NIL	8	9	-	-
6	GEETHA	22	54	PRIMI	39	4	270	VD	-	8	0	NIL	7	9	-	-
7	SAVITA	22	50	PRIMI	38+4	4	320	VD	-	8	0	NIL	5	7		-
8	LAXMI	24	56	G2P1L1	39+2	4	270	VD	-	6	0	NIL	8	9	-	-
9	VIJAYALAXMI	28	56	G2P1L1	39	3	200	VD	-	6	0	NIL	8	9	-	-
10	SUJATHA	22	54	PRIMI	39+2	4	250	VD	-	8	+1	NIL	8	9	-	-
11	JYOTHI	22	58	G2P1L1	38+3	3	380	VD	-	8	0	NIL	6	8	-	-
12	RAJWANA	24	56	G2P1L1	39+2	3	260	VD	-	6	0	NIL	8	9	-	-
13	BHARATHI	22	54	G2P1L1	38+4	3	250	VD	-	6	0	NIL	8	9	-	-
14	SREEJA	20	50	PRIMI	39+5	4	330	LSCS	MSL	-	-	NIL	6	8	ADMITTED FOR 4 DAYS	MAS
15	AMMABASAPPA	24	52	G2P1L1	38+4	3	300	VD	-	6	0	NIL	8	9	-	-
16	PRIYANKA	19	52	G2P1L1	38+5	3	220	VD	-	6	0	NIL	8	9	-	-
17	NELAMMA	26	52	G2P1L1	39+2	3	330	VD	-	7	0	NIL	7	9	-	-
18	BOURAMMA	26	54	PRIMI	39+1	4	230	VD	-	5	0	NIL	8	9	-	-
19	SANGEETA	20	55	PRIMI	38	4	300	VD	-	8	0	NIL	8	9	-	-
20	MAHANANDA	25	56	PRIMI	38+6	3	340	VD	-	8	0	NIL	8	9	-	-
21	PREMA	26	54	G2P1L1	39+2	4	300	VD	-	8	+1	NIL	8	9	-	-
22	KAVITHA	20	48	G2P1L1	39+3	3	200	VD	-	5	0	NIL	8	9	-	-
23	NEELAMMA	20	50	G2P1L1	39+4	4	360	LSCS	NPOL	-	-	NIL	7	9	-	-
24	VIDHYA	24	56	PRIMI	39+2	4	320	VD	-	8	0	NIL	8	9	-	-
25	SUREKHA	22	50	PRIMI	38+6	4	360	VD	-	8	0	NIL	8	9	-	-
26	MEHABOOBA	20	52	G2P1L1	39+3	4	270	VD	-	8	0	NIL	8	9	-	-
27	SUVARNA	21	54	PRIMI	38+2	4	320	VD	-	7	0	NIL	8	9	-	-
28	ASHWINI	20	53	G2P1L1	38+5	4	210	VD	-	3	0	NIL	8	9	-	
29	SAVITA	24	55	G2P1L1	38+6	4	300	VD	-	7	0	NIL	8	9	-	-
30	RENUKA	26	58	G2P1L1	38+1	4	240	VD	-	6	0	NIL	8	9	-	-
31	SUREKHA	20	54	PRIMI	38+5	4	270	VD	-	8	+1	NIL	8	9	-	-
32	KAVITA	24	56	G2P1L1	39+1	4	250	VD	-	6	0	NIL	8	9	-	-
33	PRIYANKA	25	58	G2P1L1	39+3	4	280	VD	-	6	0	NIL	8	9	-	-

34	LAXMI	24	55	PRIMI	38+3	3	280	VD	-	8	0	HEADACHE	8	9	-	-
35	SUNANDA	19	50	PRIMI	38+4	4	380	VD	-	8	0	NIL	8	9	-	-
36	LAXMI	23	54	PRIMI	38+5	3	310	LSCS	FD(MSL)	-	-	NIL	5	7	ADMITTED FOR 2 DAYS	RD
37	HASEENA	22	53	PRIMI	39+1	4	360	VD	-	8	0	NIL	8	9	-	-
38	ROOPA	22	58	G2P1L1	38+4	4	220	VD	-	6	0	NIL	8	9	-	-
39	POOJA	24	50	PRIMI	39	3	330	VD	-	6	0	NIL	8	9	-	-
40	VAISHALI	20	52	PRIMI	38+6	4	250	VD	-	7	0	NIL	7	9	-	-
41	HONAWWA	20	50	G2P1L1	38+4	4	270	VD	-	6	0	NIL	8	9	-	-
42	ASHWINI	20	52	G2P1L1	39+2	3	200	VD	-	6	0	NIL	6	8	-	-
43	KASTURI	20	54	PRIMI	39+4	4	340	VD	-	8	0	NIL	8	9	-	-
44	LALITHA	20	50	PRIMI	38+5	3	240	VD	-	8	0	HEADACHE	8	9	-	-
45	KAVITHA	19	56	PRIMI	39	3	280	VD	-	6	0	NIL	8	9	-	-
46	BHARATHI	24	52	G2P1L1	39+2	4	280	VD	-	6	0	NIL	8	9	-	-
47	RIYANA	20	52	PRIMI	38+4	4	340	VD	-	6	0	NIL	8	9	-	-
48	REVATHI	19	56	G2P1L1	38+5	4	300	FAVD	-	7	+1	NIL	5	8	OBSERVATION FOR 6 HRS	-
49	NIRMALA	24	56	PRIMI	39+5	4	270	VD	-	6	0	NIL	7	8	-	-
50	SUNITHA	26	54	PRIMI	39+2	4	330	VD	-	8	0	NIL	8	9	-	-
51	PARVATHI	24	53	G2P1L1	38+5	4	280	VD	-	6	0	NIL	8	9	-	-
52	LAXMI	25	55	G2P1L1	39+1	4	220	VD	-	6	0	NIL	8	9	-	-
53	HONAMMA	26	54	PRIMI	39+1	4	280	VD	-	8	0	NIL	8	9	-	-
54	RIJWNA	19	58	G2P1L1	38+5	4	280	VD	-	6	0	NIL	5	6	OBSERVATION FOR 6 HRS	-
55	SAVITRI	20	56	G2P1L1	39+2	4	330	VD	-	7	0	NAUSEA	8	9	-	-
56	POOJA	26	54	G2P1L1	38+6	4	300	VD	-	6	0	NIL	8	9	-	-
57	KAVITA	22	55	PRIMI	39	4	320	VD	-	6	0	NIL	8	9	-	-
58	VIJAYALAXMI	19	58	G2P1L1	38+3	3	220	VD	-	5	0	ATONIC PPH	8	9	-	-
59	SUNANDA	22	56	G2P1L1	39+3	3	280	VD	-	7	0	NIL	8	9	-	-
60	REKHA	20	52	PRIMI	39+4	4	340	VD	-	8	0	NIL	8	9	-	-

A RANDOMIZATION PLAN

From

http://WWW.randomization.com

GROUP 1- STUDY (KETAMINE) GROUP

GROUP 2- CONTROL(PLACEBO) GROUP

1. grp 2 _____

2. grp 2_____

3. grp 1_____

4. grp 1_____

5. grp 2_____

6. grp 1_____

7. grp 2_____

8. grp 2_____

9. grp 2_____

10. grp1 _____

11. grp1_____

12. grp 1_____

13. grp 2_____

14. grp 1_____

15. grp 2_____

16. grp 1_____

17. grp 2_____

18. grp 1_____

19. grp 2_____

20. grp 2_____

21. grp 2_____

22. grp 1_____

23. grp 1_____

24. grp 1_____

25. grp 2_____

26. grp 1_____

27. grp 2_____

28. grp 2_____

29. grp 1_____

30. grp 1_____

31. grp 2_____

32. grp 1_____

33. grp 2_____

34. grp 2_____

35. grp 1_____

36. grp 1_____

37. grp 2_____

38. grp 1_____

39. grp 2_____

40. grp 2_____

41. grp 1_____

42. grp 1_____

43. grp 2_____

44. grp 1_____

45. grp 1_____

46. grp 2_____

47. grp 1_____

48. grp 2_____

49. grp 2_____

50. grp 1_____

51. grp 1_____

52. grp 1_____

53. grp 2_____

54. grp 2_____

55. grp 2_____

56. grp 1_____

57. grp 1_____

58. grp 1_____

59. grp 2_____

60. grp 2_____

61.grp 2_____

62. grp1_____

63. grp 1_____

64. grp 1_____

65. grp 2_____

66. grp 2_____

67. grp 2_____

68. grp 1_____

69. grp 2_____

70. grp 1_____

71. grp 2_____

72. grp 1_____

73. grp 2_____

74. grp 1_____

75. grp 2_____

76. grp 1_____

77. grp 1_____

78. grp 2_____

79. grp 1_____

80. grp 2_____

81. grp 2_____

82. grp 1_____

83. grp 1_____

84. grp 2_____

85. grp 2_____

86. grp 1_____

87. grp 2_____

88. grp 1_____

89. grp 1_____

90. grp 2_____

91. grp 1_____

92. grp 2_____

93. grp 1_____

94. grp 2_____

95. grp 2_____

96. grp 1_____

97. grp 2_____

98. grp 1_____

99. grp 2_____

100.grp 2_____

101.grp 1_____

102.grp 1_____

103.grp 1_____

104.grp 1_____

105.grp 2_____

106.grp 2_____

107.grp 1_____

108.grp 2_____

109.grp 2_____

110.grp 1_____

111.grp 1_____

112.grp 2_____

113.grp 1_____

114.grp 2_____

115.grp 1_____

116.grp 2_____

117.grp 2_____

118.grp 1_____

119.grp 1_____

120.grp 2_____

Randomization of 120 subjects with Block sizes**:** 6.