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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.innovativepublication.com

Original Research Article

Role of ketamine combined with diazepam and pentazocine as labour analgesia and study of obstetrical outome

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ARTICLE INFO

Article history:
Received 08-02-2020
Accepted 29-03-2020
Available online 15-06-2020

Keywords:
Labour Analgesia
Ketamine
Diazepam
Pentazocine

ABSTRACT

Ketamine combined with diazepam and pentazocine as a labour analgesia and obstetrical outcome.

1. Introduction

Labour is a painful process. Pain relief during labour is generally inadequate and associated with myths and controversies. The concept of obstetrical analgesia came into existence by the pioneer work of James Young Simpson when he administered ether during parturition of a lady having deformed pelvis. It was the year 1953 when chloroform was administered by John Snow to Britain's queen Victoria who was delivering her eight's child.[1] In 1881 Stanslav Klikoviteh described the use of nitrous oxide in labour. It was in 1902 when Morphine and Hyoscine were first used in labour to reduce pain followed by Pethidine in 1940. In the year 1931, a Romanian obstetrician Evgen Bogdan Abmel described continuous caudal and lumboaortic plexus blocks in labour. Dr Cleland in 1949 described continuous lumbar epidural block in labour. In 1958 Ferdinand Lamaze described that pain was a conditioned reflex triggered by uterine contractions and that psychoprophylaxis could reduce pain.

Labour is a physiological event which is associated with severe pain. The agony and stress of labour-pain which a woman suffers is beyond description. Normal labour is the optimal integration of three Ps which are Power, Passenger and Passage. The "Powers" or the driving force is provided by the uterine contractions. Passenger is the fetus of optimal size and in favorable position and presentation. Passage is the birth canal made up of soft tissues and the bony pelvis which should be adequate in capacity. The concept of providing effective pain relief during parturition has been tardy in acceptance, however worldwise health care providers had experienced that labour analgesia methods not only markedly reduces the stress of mother but also decreases the duration of labour particularly of late first and early second stage of labour. One of the method which is being used world wise is epidural analgesia which not only reduces pain significantly but also improves obstetrical outcome. However in our country which is resource poor as maximum deliveries are being conducted at PHCs level, epidural analgesia is a distant dream. Constant efforts are being made to find out a alternative methods which can be utilized at PHC level by the nursing staff. The method should provide sufficient

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https://doi.org/10.18231/j.ijogr.2020.047

pain relief during labour and should be safe for the baby. Labour analgesia ensures relief from pain, controls alterations of placental circulation thereby safeguarding the fetus against hypoxia and depression at birth.[2,3] Pain relief prevents maternal hyperventilation and undue muscular efforts. It also favors cervical dilatation, resulting in shorter labour duration, less traumatic and require lesser obstetric intervention.[4] The methods of labour analgesia includes non pharmacological techniques, parenteral opiates, epidural analgesia, paracervical block and nitrous oxide. In the first stage of labour, pains are caused by uterine contraction and cervical dilatation and is transmitted through visceral afferent sympathetic nerve fibres entering the spinal cord from T10 through L1. In the second stage of labour, there is a sharper and continuous somatic pain in the perineum. Pressure or nerve entrapment caused by the fetal head can cause severe back or leg pain. Severity of pain is more in early stage in case of Nulliparous women[5,6] while rapid descent of fetal head in late first stage and second stage is experienced as severe pain in case of multiparous women.[5,7]

2. Material and Methods

The index study 'To study the role of ketamine combined with Diazepam and Pentazocine (Fortwin) in labour analgesia and its obstetrical outcome 'was carried out at a tertiary care centre. It is a prospective cohort study. The subject groups were primigravida at term gestation with cephalic presentation in active phase of labour. Ethical clearance was taken from the Hospital ethical committee.

In this study a total of 200 primigravida without any risk factor were enrolled after taking informed consent. Patients were randomly allocated to two groups of hundred patients each. The case group was given Inj Pentazocine, Inj Diazepam and Inj Ketamine as per protocol and the control group was given anti spasmodic. The starting point of active phase of labour was identified on the basis of following parameters:

1. Uterine contraction of frequency of 3 or more in 10 minutes lasting for 35-45 seconds.
2. Head is engaged.
3. Cervical dilatation of 3 cm or more and effacement of more than 50%.
4. No clinical suspicion of CPD.

2.1. Protocol for use of analgesic medication

As per the protocol Inj Diazepam, Pentazocine and Ketamine were used to provide effective pain relief which also helped in cervical softening. This protocol provided the benefits of drug synergism and also restricting the dose of drug to minimal amount to safeguard the mother and her fetus against any major adverse effects. An intravenous line was started with 5% ringer lactate @ 20 drops/min. it was ensured that pains are optimal i.e. 3-4 contractions in 10 minutes. If necessary than 5 U of Inj Oxytocin was started by infusion pump at appropriate rate to ensure optimal pain. An ampoule of 30 mg of Inj Pentazocine was diluted in 10 ml of normal saline and simultaneously an ampoule of 10 mg Inj Diazepam was diluted in 10 ml of saline. One fifth of each drug i.e. 6 mg of Inj Pentazocine and 2 mg of Inj Diazepam was administered slowly as IV bolus. To the control group Inj Tramadol was administered in the dose of 1mg/Kg intramuscularly along with Inj Drotavarine 40 mg which is a antispasmodics. Progress of labour was assessed on the basis of cervical dilatation and descent of head which is documented periodically in the partogram. When the patient was in advanced labour Inj ketamine was administered in the dose of 0.25-0.5 mg/kg body weight. The drug was diluted in 10 ml of saline and administered through IV access over few minutes. For a patient weighing 60 mg the initial dose of Inj Ketamine works out at 15-30 mg. The subsequent top up dose of ketamine was given at 20-30 minute intervals. These top up doses were half of the initial dose i.e. 7.5-15 mg in the patient weighing 60 Kg. The last top up dose was given after the birth of the baby. This would relax the patient and allow satisfactory inspection of the vulva, vagina and the cervix to exclude traumatic injuries and facilitate in episiotomy repair.

2.2. Management of third stage of labour

To shorten the duration of the third stage, minimize the blood loss, ensure sustained uterine contraction, and obviate entrapment of the placenta following options was adopted in the management of the third stage of labour:

1. Tab Misoprostol 400 microgram S/L given immediately after the birth of the baby.
2. Inj Oxytocin 20 units in 500 ml of normal saline i.v. @ 10-20 dp/min.
3. Inj Oxytocin 10 units i. m. stat.
4. Inj Methergin 0.2 mg i. v. after delivery of the placenta if bleeding is excessive
5. Inj Prostodin 125 mg i. m. if required in case there is excessive bleeding due to atonic uterus.

The following parameters were noted and appropriate statistical analysis was done using student t test and Pearson chi-square test.

1. Duration of first, second and third stage of labour.
2. Degree of pain relief. This was assessed by asking the patient to score the pain relief using a visual analogue scale.
3. Maternal and neonatal complications encountered.
4. Neonatal outcome and APGAR score.

2.3. Visual analogue scale

The patient was told to point at the position between the lines to indicate the amount the pain they had experienced.

The left far indicates no pain and far right indicates worst pain.

Fig. 1:

The control group was monitored during labour as per standard protocol and was given antispasmodics like Inj Tramadol and Drotavarine for pain relief.

2.4. *Inj Ketamine*[8,9]

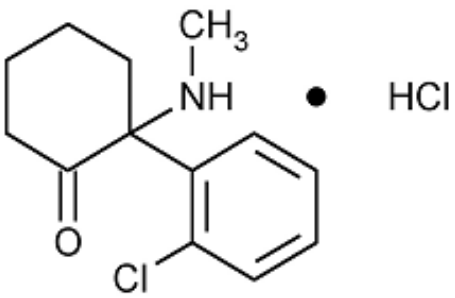

Fig. 2:

Ketamine is pharmacologically related to the hallucinogen phencyclidine, which induces a so called 'dissociative anaesthesia', immobility, amnesia with light sleep and feeling of dissociation from ones own body and the surroundings.

2.5. *Mechanism of action*

Although the exact mechanism of action is not known, ketamine appears to be an agonist at CNS muscarinic acetylcholine-receptors and opiate-receptors. The primary site of action is in the cortexand subcortical. Ketamine has no effects on pharyngeal or laryngeal reflexes.

2.6. *Pharmacokinetics*

Ketamine is administered parenterally and it is rapidly absorbed. It increases the heart rate, cardiac output and blood pressure due to sympathetic stimulation. Respiration is not depressed, reflexes are not abolished and muscle tone is increased. It crosses the placenta and enters the fetal circulation and rapidly distributed into the brain and other highly perfused tissues of the fetus. A dose of 1-3 mg/kg iv or 6.5-13 mg/kg in produces the above effects within a minute and recovery starts after 10-15 minutes, but patient remains amnesic for 1-2 hours. The half life of the drug is 3-4 hours and metabolites are excreted mainly through kidneys ren (90%) and fecally (5%). Approximately 4% of an administered dose excreted unchanged in urine.

2.7. *Uses*

Ketamine has been recommended for short operations. It is good for hypovolemic patients.

2.8. *Inj pentazocine (Fortwin)*[10–12]

Pentazocine is the first opioid agonist-antagonist which was used as an analgesic around 1970. It has weak antagonistic and more marked agonistic actions.

2.9. *Pharmacodynamics*

Analgesia caused by Pentazocine is through k receptors. Two subtypes of k receptors k1 and k3 are functionally important. Analgesia caused by Pentazocine has a different character than caused by morphine. It is mostly spinal. Parenterally 30 mg pentazocineis equal to 10 mg morphine but efficacy is lower. Sedation and respiratory depression is $1/3 - \frac{1}{2}$ of morphine at lower doses, but has a lower ceiling, does not increase much beyond 60 mg dose. It causes tachycardia and rise in BP due to sympathetic stimulation. Biliary spasm and constipation are less severe. Vomiting is less frequent. Subjective effects are pleasarableat lower doses. However, as dose is increased these become unpleasant.

2.10. *Pharmacokinetics*

Pentazocine is effective orally, though considerable first pass metabolism occurs. The oral: parenteral ratio is 1:3. It is oxidized and glucuronide conjugated in liver and excreted in urine. Plasma half life is 3-4 hours and duration of action of single dose is 4-6 hours.

2.11. *Therapeutic use in obstetrics*

Pentazocine appears to be an effective analgesic during labour. There is some evidence that uterine activity may be increased and the duration of second stage of labour may be shortened. Respiratory depression in the neonate is a concern and the apgar score is after delivery.

2.12. *Contraindications*

The drug is to be avoided in coronary ischaemia and myocardial infarction because of sympathetic stimulation. There are chances of abuse liability. If injected in morphine dependent subjects, it precipitates withdrawal.

2.13. Adverse reactions

It may cause respiratory depression at higher doses. Repeated use can cause agranulocytosis, pruritis at injection site. Epileptic fits are also reported in few cases. Symptomatic side effects are often dose-related, mild and self-limiting but can be severe at times.

2.14. Inj diazepam[13–15]

Diazepam is a benzodiazepine (BTZ) derivative. It was first introduced around 1960 as antianxiety drugs. Since than the BTZ class of drugs has gained popularity over other barbiturates as hypnotin and sedatives.

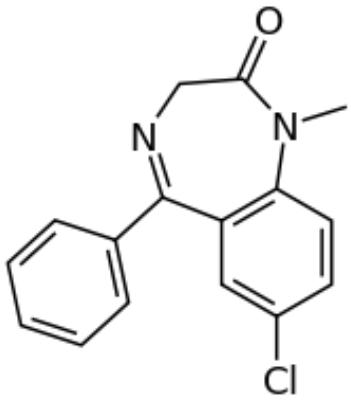

Fig. 3:

2.15. Mechanism of action

Diazepam and other benzodiazepine act preferentially on midbrain and on limbic system. They act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor which is an integral part of the GABA receptor-CL channel complex. The binding site of GABA is located on its beta subunit. The modulatory BZD receptors increases the frequency of CL channel opening induced by submaximal concentrations of GABA.

2.16. Pharmacokinetics

Absorption: After oral administration $>$ 90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 - 1.5 hours with a range of 0.25 to 2.5 hours.

Distribution: Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (days 3 to 9 post-partum). In young healthy males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg. After IV administration peak plasma concentration is achieved within minutes which also crosses the placental barrier.

2.17. Indications

Diazepam is indicated for the management of anxiety disorder. Diazepam is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; and stiff-man syndrome.

2.18. Side effects

The most common side effects are drowsiness, fatigue and ataxia. It also causes confusion, constipation, depression. There is also increased salivation, skin rash, slurring of speech and occassionally urinary retention.

2.19. Pregnancy

An increased risk of congenital malformations and other developmental abnormalities associated with the use of benzodiazepine drugs during pregnancy has been suggested in early trimester.

2.20. Contraindications:

Diazepam is contraindicated in patients with a known hypersensitivity to diazepam. Patients suffering from myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency are another group in which this drug should not be used. It may be used in patients with open-angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow-angle glaucoma.

3. Observation and Result

The mean duration of first stage of labour was 5.4 hrs and 6.13 hrs in case and control group respectively and this difference was statistically significant. Mean duration of second stage of labor was 57.58 min in case and 68.45 min in control groups which was significant ($P<0.001$). The time taken for onset of pain was 7.84 min in case and 31.11 min in control group which was significant ($P<0.001$). The mean value of approx blood loss also showed significant difference of 306.75 ml in case and 375.5 ml in control groups. In our study the duration of first stage and third stage of labor was found to be approximately same for both case and control. No significant difference was seen in the mode of delivery in both case and control group.

The status of pain relief in both the groups are shown in Figure 4. Significant pain relief was seen in case group which received protocol drugs with majority of the patients scoring 7/10 and 8/10 as per pain rating scale as compared to control group which received routine antispasmodics with

Table 1: Mean value of different parameter in study group

The data was summarized and analysis was done by SPPS version 17.						Software
	Group		**Mean**	**Std. Deviation**	**Std. Error Mean**	**P-value**
Duration of active first stage of labor (hrs)	Case	100	5.4650	.90525	.09052	<0.001
	Control	100	6.1300	1.00910	.10091	
Duration of second stage of labor (min)	Case	95	57.58	12.692	1.302	<0.001
	Control	92	68.45	11.737	1.224	
Duration of third stage of labor (min)	Case	93	5.88	1.020	.106	0.732
	Control	92	5.93	1.087	.113	
Time taken for onset of Pain (min)	Case	99	7.84	2.049	.206	<0.001
	Control	97	31.11	5.750	.584	
Approx blood loss (ml)	Case	100	306.7500	132.85211	13.28521	<0.001
	Control	100	375.5000	126.92856	12.69286	

majority patients scoring 3/10 and 4/10.

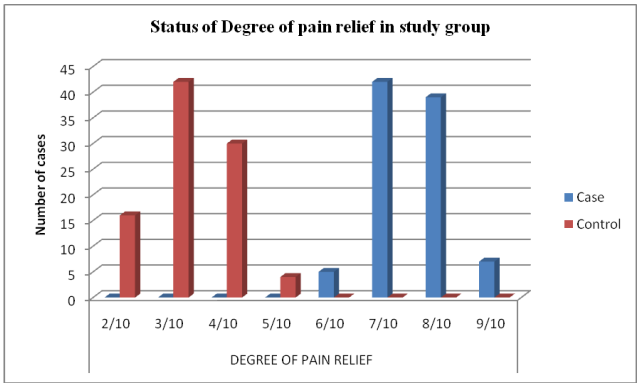

Fig. 4: Status of pain relief in study group

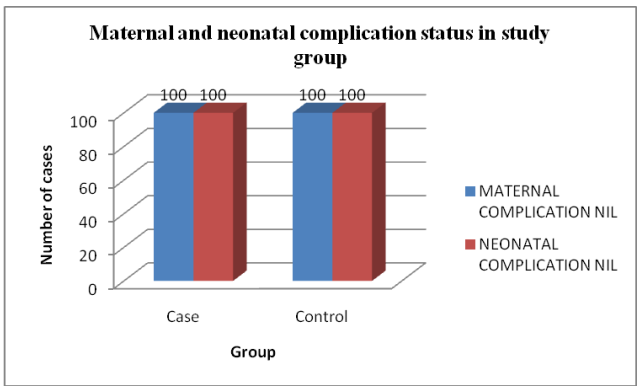

Fig. 5: Maternal and neonatal complications in study group
No maternal and neonatal complications were seen in either the case or control group. APGAR calculated at 1 and 5 min is shown in Figure 5. There is no significant difference in neonatal complication in case and control group.

4. Discussion

Labour is a physiological process which is characterized by progressive increase in frequency, intensity and duration

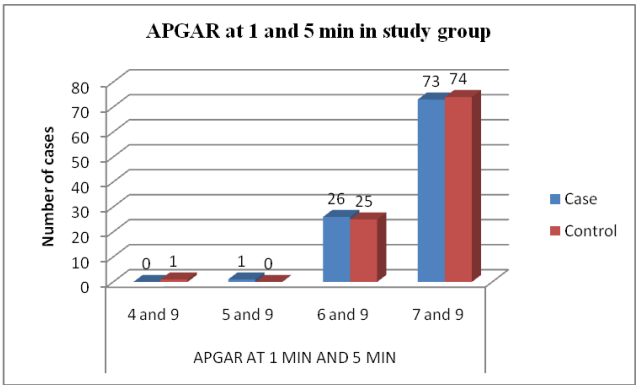

Fig. 6: Neonatal Apgar in study group

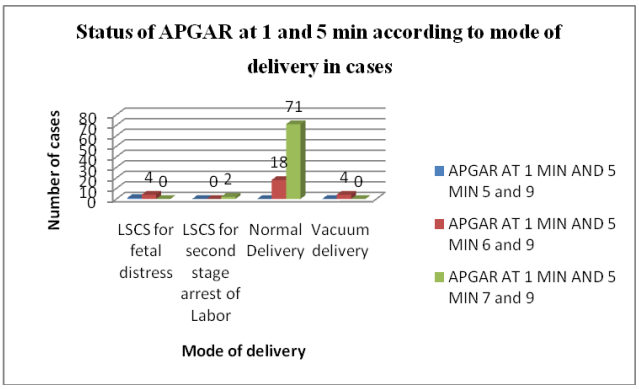

Fig. 7: Status of Apgar at 1 and 5 min according to mode of delivery in cases
Apgar status was better in patients who underwent normal delivery in case group as compared to vacuum delivery or LSCS delivery.

of uterine contractions, effacement and dilatation of cervix with descent of head through the birth canal. Labour and childbirth are natural events, but it is a harrowing experience for the mother due to pain. Stress of pain disturbs the maternal autonomic functions and release catecholamine's which predispose to dysfunctional labour and compromises fetal oxygenation (Chauhan and Gupta,

2003).[16] Programmed labour protocol (Daftary 2003),[17] provides relatively pain free, shorter and safe deliveries. Small dose ketamine has been proven to be a useful and safe additive to opioid analgesia (Subramanian et al. 2004).[18] Several studies have shown that continuous IV small dose ketamine infusion had improved the efficacy of perioperative opioid analgesia (Kararmaz et al., 2003).[19] Ketamine had been used in pregnant patients and found to be safe in low doses. A higher dose (greater than 2mg/kg) produce psycho mimetic effects and increased uterine tone. It may also cause low APGAR score and abnormalities in neonatal muscle tone (Birnbach and Browne, 2010).[20] Diazepam is proven to be a useful drug in the management of labour.[21,22] Maternal safety is a concern with any opioid based analgesia technique during labour including Pentazocine. Sedation score did increase over the time in the study, however this increase in sedation was usually from awake to drowsy and all women remained responsive throughout. Excellent pain relief was observed in 83% of case group as compare to 10% control group which was significant. This programming of labour is simple, easy and effective method for painless and safe delivery. The analgesia produced is quite effective and overall duration of labour is significantly reduced. As a result labour is cherished with pleasure and childbirth becomes a joyous event for the mother.

5. Summary and Conclusion

Labour analgesia protocol having combination of Pentazocine, Diazepam and Ketamine has good outcome in terms of pain relief. The overall grading of degree of pain relief was 7/10 and beyond on visual analogue of pain score. Apart from providing effective labour analgesia it reduced the duration of all three stages of labour. The blood loss was also lesser as compared to control group and this difference was statistically significant. No adverse maternal or fetal outcome was noted in either of the group. Presence of neonatologist and anesthetist is not necessary although patients were on continuous electro-fetal and pulse oximetry monitoring. This combination can be a effective modality in low resource countries like India where majority of deliveries are being conducted in PHCs where epidural analgesia is a distant dream.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Vishal AK, Babu B. Role of ketamine combined with diazepam and pentazocine as labour analgesia and study of obstetrical outome. *Indian J Obstet Gynecol Res* 2020;7(2):226-231.