THE COMPARATIVE STUDY OF DROTAVERINE HYDROCHLORIDE VS VALETHAMATE BROMIDE IN LABOR

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ABSTRACT: Child birth is one of the most important events in the life of a woman. Though it is a physiological event it is painful. The pain experienced is beyond description and is basically due to process of cervical dilatation. The duration of the first stage is longest of the 3 stages of labour and it is due to painful progressive cervical dilatation. It is ideal for any obstetrician to achieve reduction of pain and suffering during labour by accelerating the rate of cervical dilatation.

INTRODUCTION: The cervix is a cylindrical fibro-muscular component of the lower end of the uterus measuring 3cm in length and 2cm in thickness.¹ The cervical canal is 3cm in length extending from the internal os to the external os. The surrounding tissue components of cervical canal are fibrous, ground substance and cellular elements. The distribution of muscular component is 29% in upper 1/3rd, 18% in the middle 1/3rd, 6% in lower 1/3rd i.e., maximum at the level of internal os offering maximum contractile response to the advancing foetal head following uterine contractions.²

The fibrous component predominantly contains fibrils and collagen fibres arranged in the form of bundles and the elastin fibres which are in the form of sheets interspersed with in the collagen. The elastin fibres are capable of stretching and returning to its original size. The ground substance contains glycosaminoglycans like dermatan sulphate and hyaluronic acid, the proteoglycans like decorin and biglycan. The decorin-collagen interaction is responsible for orderly arrangement of the bundles of collagen.^{3,4}



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The cervical canal is kept tightly closed from above downwards by the natural tone of smooth muscle cells and the orderly arrangement of collagen bundles throughout the pregnancy. This allows the conceptus to grow in utero till term. It is already mentioned that the concentration of cervical smooth muscle is maximum around the internal os. Several physiological changes occur in the cellular elements and ground substance throughout pregnancy and favours cervical softening. These changes reach their peak activity just before and during the first stage of labour.⁵ The initial change is softening which is essential for subsequent effacement and dilatation. Hyaluronic acid contributes 8-20% of the ground substance that attracts more water and collagen decorin interaction is decreased that causes disorganisation of collagen bundles. Both these changes soften the cervix initially and yields passively during subsequent effacement and dilatation. The integrity of smooth muscle cells is unaffected by these changes.

During labour two important changes occur in cervix i.e., effacement and dilatation. Among these the rate of cervical dilatation is most useful parameter in assessing the progress of labour in first stage. The dilatation of cervix is initiated by the onset of regular uterine contractions. The cervical dilatation occurs in two phases, latent phase and active phase. Active phase is again divided into acceleration phase, phase of maximum slope and deceleration phase.⁶ The duration of latent phase has little effect on the subsequent course of labour whereas the duration of active phase predicts the outcome of that particular labour. The rate of cervical dilatation depends upon the cervical smooth muscle contractile response or its variation to the hydrostatic pressure exerted by the bag of membranes and the foetal head successively. As the presenting part advances during labour with uterine contractions the fibrous connective tissue yields passively whereas the cervical smooth muscle contractile response resists dilatation.⁷ That means only the contractile response has significant role at this stage. Many pharmacological agents are in clinical usage to facilitate the rate of cervical dilatation and to shorten the duration of labour.

The drugs available are drotaverine hydrochloride, valethamate bromide, hyoscine N-butyl bromide, hyalase. Among these drugs we selected two drugs drotaverine hydrochloride and valethamate bromide to compare their efficacy in accelerating the rate of cervical dilatation. The reasons behind the selection of these two drugs are superiority over other smooth muscle relaxants routinely used in clinical practice, easy availability even in rural setup, cheap and have no proven adverse effects on mother, foetus and new born.

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Schematic representation of mechanism of smooth muscle contraction and relaxation process.⁸

Drotaverine Hydrochloride: Drotaverine is first launched in 1963 in Hungary. It is an isoquinoline derivative and its chemical name is 3, 4, 6, 7 tetraethoxy-1 benzyl 1, 2, 3, 4 tetrahydro isoquinoline hydrochloride.⁹



Molecular weight is 397.5: It is a unique smooth muscle relaxant. It acts by inhibiting phosphodiesterase-IV enzyme that results in increased cAMP10. An increased cAMP dampens the contractile response of smooth muscle cell by decreasing intracellular calcium. It can be given by oral or parenteral route. After intravenous (IV) administration the drug is rapidly absorbed by small intestine. Half-life is 12 minutes, reaches maximum concentration in 45 minutes.

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The primary elimination half-life is 2.4 hours. The drug rapidly enters into the organs after intravenous (IV) administration. It doesn't cross placental barrier. It is metabolised by O-demethylation and O-deethylation. It is excreted through urine and faeces as unchanged drug. The adverse effects are nausea, headache, vertigo, hypotension seen only in 3% of cases. In the post marketing study conducted for 37 years no serious side effects are attributed to drotaverine. It is free from anti-cholinergic side effects. Drotaverine is available in the market as DOT, NO-SPA, DROTIN, PASM, SPASMOTER, CYCLOFAS. In the present study we used DROTIN.

Valethamate Bromide: Valethamate bromide is an anticholinergic smooth muscle relaxant. It is an ester with chemical name Ethanaminium N, N–diethyl N-methyl 2(3 methyl-1-oxo-2 phenyl pentyl) 13 bromide.



H-bond donars-0 H-bond acceptors-2

It acts by competitively inhibiting the muscarinic receptors of smooth muscle cells followed by inhibition of phospholipase C and decreases intracellular calcium. It can be administered by intramuscular/intravenous route. After intramuscular (IM) administration action starts with in 20 to 30 minutes with plasma half-life of 4 hours. After intravenous (IV) dose action starts with in 5-10 minutes it crosses the placental barrier and is also secreted in breast milk, but has no proven deleterious effects on foetus and baby. It is completely metabolized by liver and excreted in urine as both unchanged drug and metabolites.

Dosage: 4-8mg IM/IV 3-4 times a day up to a maximum of 6 doses.

The common side effects are dryness of mouth, increased thirst, flushing, dry ness of skin, palpitations, mydriasis, cycloplegia and hypersensitivity. Toxic dose i.e. 60mg. may cause circulatory and respiratory failure leading to death very rarely.

Valethamate bromide available in the market as EPIDOSIN, EPIDOSAN, ELIST, VALAMATE, METHOCIN, FOETOCIN. In this present study we used EPIDOSIN.

AIMS AND OBJECTIVES: The present study aims to monitor the effect of drotaverine hydrochloride and valethamate bromide in labour.

The objective is to compare and evaluate the efficacy of drotaverine hydrochloride and valethamate bromide for effective cervical dilatation in labour.

The study also analyzes and evaluates their effect on maternal and fetal outcome.

MATERIAL AND METHODS: The study was conducted in Santhiram General Hospital, Nandyal over a period of 1¹/₂ years from November 2009 to April 2011.

- This is a prospective comparative study involving three groups of patients.
- 150 patients with 38-41 weeks of gestational age were selected.
- They were divided into three groups randomly.

Group-C: This group includes cases who were not received either drotaverine or valethamate.Group-D: This group includes cases who were given intravenous (IV) drotaverine.Group-V: This group includes cases who were given intravenous (IV) valethamate bromide.

Inclusion Criteria:

- Consent.
- Age group between 20-30 years.
- No obstetric complications.
- Cervical dilatation of 3-4cms.
- More than 80% effaced cervix.
- Intact membranes.

Regular established uterine contractions at the rate of 3/10 minutes each lasting for 30-40 seconds either spontaneously or with oxytocin.

Exclusion Criteria:

- Pregnancy Induced Hypertension.
- Post term pregnancy.
- Induced labour.
- Multiple pregnancy.
- Malpresentations.
- Drug hypersensitivity.

Parameters Collected:

- Age.
- Parity.
- Gestational age.
- Injection dilatation interval.
- Rate of cervical dilatation.
- Duration of active phase of labour.
- Duration of second stage of labour.
- Duration of third stage of labour.
- Obstetric complications.
- Side effects to drugs.
- Neonatal outcome.
- Patient satisfaction regarding the experience of pain.

Study Protocol: After considering inclusion criteria, 150 patients were selected. The cases were divided into three groups randomly.

Group-C: These cases doesn't receive either drotaverine or valethamate.

Group-D: These cases received 2ml of injection containing 40mg drotaverine hydrochloride intravenously, dose repeated after 2 hours if necessary up to a maximum of 3 doses.

Group-V: These cases received 2ml. of injection containing 8mg of valethamate bromide intravenously every half an hour up to a maximum of 6 doses.

These cases were monitored for pulse rate, blood pressure, uterine contractions, foetal heart rate, rate of cervical dialatation, second and third stage of labour. The results were plotted in partogram. Any adverse effects to the drug, third stage complications and neonatal outcome were noted.

Finally the patient's satisfaction regarding the experience of pain relief was taken.

DISCUSSION: The concept of active management of labour gained strength in clinical practice with the availability of cervical smooth muscle dilators. Drotaverine and valethamate are more frequently used by many institutes of obstetrics and foetal medicine.

In our study we evaluated and compared the effect of drotaverine hydrochloride and valethamate bromide on cervical dilatation, duration of second and third stages of labour, third stage complications and neonatal outcome.

The first stage of labour is longest and more painful especially in primigravidae. The smooth muscle content of cervix is 6-25% that offers contractile response to the advancing foetal head. This provides the physiological basis to use smooth muscle relaxants. The administration of smooth muscle relaxants at an appropriate time and dilatation phase can reduce the duration of labour successfully while providing pain reduction.

Ever since Farkas et al (1967) concluded that drotaverine effectively relieves the cervical smooth muscle spasm, many obstetricians used drotaverine for accelerating labour and proved it as an effective cervical dilator. Our study also proved the same.

In the study done by Sharma et al (2001) with drotaverine and valethamate in acceleration of labour, he concluded that both are effective but drotaverine accelerated labour more rapidly with less side effects. The injection dilatation interval was significantly reduced with drotaverine 193.96 minutes (3 hours 13 minutes) in contrast to valethamate bromide group 220.68 minutes (3 hours 40 minutes).

In the study conducted by S.L Mishra et-al (2002) it was proved that drotaverine is highly effective cervical dilating agent compared to valethamate and control groups.

The average duration of 3cm to full cervical dilatation was 3 hours 25 minutes (205 minutes) in primigravidae and 1 hour 45min (105 minutes) in multigravidae with drotin and 4 hours 35 minutes (275 minutes) in primigravidae and 3 hours 30min (210 minutes) in multigravidae with epidosin. They concluded that both the drugs were effective but epidosin was better in multigravidae.

In the study conducted by Monika Soni et al (2008) and C Madhu et al (2009)33 proved that both the drugs were effective in cervical dilatation but drotaverine hydrochloride is superior to valethamate bromide with less side effects.

In the present study the mean duration of active phase was 355.4 minutes (5 hours 55 minutes) in control group, 189 minutes (3 hours 9 minutes) with drotaverine and 254.2 minutes (4 hours 14

minutes) with valethamate in primigravidae and 276.5 minutes (4 hours 36 minutes) in control group, 140.76 minutes (2 hours 20 minutes) with drotaverine and 172.82 minutes (2 hours 52 minutes) with valethamate in multigravidae. The rate of cervical dilatation is 1.01cm/hour and 1.26cm/hour in control group, in primigravidae and multigravidae respectively, whereas it is 1.92cm/hour and 2.58cm/hour with drotaverine and 1.44cm/hour and 2.19cm/hour in primigravidae and multigravidae respectively. Both drotaverine and valethamate are effective in cervical dilatation compared to control group but drotaverine was superior to valethamate. The data from the studies of J.B Sharma et alS.L Mishra et al, and C. Madhu et al, also support this findings.

In the present study there is no significant difference in the duration of second and third stages with both the drugs and no incidents of obstetrical complications. This is supported by the studies done by Sharma et al, Anju et al, and C. Madhu et al. Some obstetricians have reserved opinions that the cervical spasmolytic action of drotaverine could weaken the uterine contractions thus delaying the progress of labour. However no scientific studies are available in defence of such opinions. But our study and previous studies proved that drotaverine hydrochloride has no such effect.

In our study of cases in valethamate group experienced 2% of vomiting, 4% of tachycardia and 6% of dryness of mouth. In drotaverine and control groups patients had no such complaints. Our findings are consistent with the findings of Anju et al, S.L. Misra et al, and Monika et al.

The APGAR scores were not adversely effected in valethemate and drotaverine groups and they were well compared with control groups where in the scores were absolutely normal. This observation is supported by previous studies.

The pain experienced in drotaverine and valethamate groups is less compared to control group. Multigravidae expressed definite satisfaction with pain experience compared to their previous labour pains. This is more with drotaverine than valethamate. This comparison is not obtained in primigravidae as they have no such experiences of labour pains previously.

The sum effect of reduction in total duration of labour reduced the maternal morbidity and did not adversely affect the of et al outcome. The process of labour as such becomes less anxious and less painful experience fulfilling the aim of the obstetrician and desire of the patient.

Both the drugs are easily available even in rural set up, less expensive, easy to administer, no need of anaesthetist and easy to monitor with less side effects.

Our study found an increasing role of drotaverine hydrochloride in reducing the total duration of labour, hastening cervical dilatation, ensuring smooth progress of labour with good maternal and foetal outcome.

We also proved the efficacy of drotaverine and its superiority over valethamate bromide.

SUMMARY: The present study is designed to evaluate the effect of drotaverine on cervical dilatation and compare its efficacy with that of valethamate bromide.

Santhiram Medical College and General Hospital is the venue for our study conducted over a period of 1½ year from November 2009 – April 2011. We studied 150 patients in labour with 50 patients each in drotaverine, valethamate and control groups including both primigravidae and multigravidae.

The age distribution in three groups is comparable i.e. between 20 to 30 years. Control group is studied without giving either drotaverine or valethamate bromide.

Drotaverine hydrochloride is given intravenously 40mg every 2 hours for a maximum of 3 doses.

Valethamate is given intravenously 8mg for a maximum of 6 doses half an hour apart.

The details of labour are plotted in partogram. Results obtained were tabulated and analyzed. The results were subjected to Chi-square test to test the significance.

In primigravidae the average duration of active phase is shortened by 2 hours 45 minutes with 1.90cm/hour cervical dilatation in drotaverine group and 1 hour 40 minutes with 1.44cm/ hour in valethamate group compared to control group.

In second gravidae the average duration of active phase is shortened by 2 hours 25 minutes with 2.46cm/ hour cervical dilatation in drotaverine group and 1 hour 40 minutes with 1.86cm/ hour in valethamate group compared to control group.

In drotaverine group the active phase is shortened by 2 hours 20 minutes with 2.76cm/hour cervical dilatation and in valethamate group it is 2 hours 10 minutes with 2.52cm/ hour cervical dilatation in third gravidae compared to control group.

There is no significant difference in the duration of second and third stages in three groups. No obstetrical complications like cervical tears, post-partum haemorrhage (PPH) are noted in both groups as well as in control group.

No major side effects were observed in either groups. However one case of maternal vomiting, two cases of maternal tachycardia and three cases of dryness of mouth were noted in valethamate group.

Both drugs have no effect on fetal outcome.

Drotaverine hydrochloride and valethamate bromide are better labour accelerators. But drotaverine accelerates labour better than valethemate.

The reduction of pain during labour is better with drotaverine than valethamate.

CONCLUSION: The drugs drotaverine and valethamate are in the practice of clinical obstetrics. Both the drugs effectively relieve the maternal pain by reducing the cervical contractile response and shorten the duration of labour.

Drotaverine is found to be better than valethamate in shortening the duration of labour and gives better pain relief with less side effects.

Both the drugs have no major side effects.

Both the drugs have good feto maternal outcome.

Drotaverine is useful for labour analgesia in rural setup where there is no facility for epidural anaesthesia.

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