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Comparative efficacy of Drotaverine Hydrochloride And Valethamate Bromide on cervical dilatation in active labour

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ABSTRACT: Introduction: The aim of active management of labour is a reduction in the total duration of labour without causing any adverse effects on the mother or fetus and spasmolytic drugs have been used and tried in the past

Aims & Objectives: To compare the efficacy of Drotaverine Hydrochloride and Valethamate Bromide on cervical dilatation in active labour and their adverse effects on maternal and fetal outcome.

Materials &Methods: The randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, Burdwan Medical College over 1 year. Total 150 primigravida or multigravida mothers satisfying the criteria of having singleton term pregnancy with cephalic presentation with spontaneous onset of labour were included and allocated randomly into 3 groups- Drotaverine group (Group A), Valethamate group (Group B), Control group (Group C).

.**Results:** The duration of active phase was less in Drotaverine group as compared to Valethamate group, both in case of primigravida and multigravida, which is statistically significant ($p < 0.0001$). Both the drugs had no effect on the uterine contractions. The mean first injection to delivery interval was significantly reduced in Drotaverine group as compared to Valethamate ($p< 0.0001$). There was no significant shortening of second stage of labour. Majority (90.27%) of the patients had spontaneous vaginal delivery. There was no increase in incidence of instrumental delivery or abdominal delivery or other complications in either of the two groups. Incidence of maternal side effects with Drotaverine (5.5%) is significantly less compared to Valethamate (10.83%). There was no significant increase in incidence of meconium stained liquor or other fetal complications in either of the drug groups.

Conclusion: Drotaverine hydrochloride is a superior cervical dilatation agent than Valethamate bromide in significantly reducing the duration of labour with fewer side effects on the mother or the fetus.

KEYWORDS: Drotaverine hydrochloride, Valethamate bromide, duration of labour, cervical dilatation

I.INTRODUCTION:

Labour is a process of uterine contraction with the goal of producing progressive cervical effacement and dilatation in order to expel the fetus from the intrauterine to the extra-uterine environment.[1] Labour mostly sets in spontaneously but for various obstetrical and medical indications it needs to be induced when the benefits to either the mother or the foetus outweigh those of continuing the pregnancy.[2] Unduly prolonged labour is likely to give rise to 3 types of distress maternal, fetal or obstetrician and the last may be most dangerous. Prolonged and painful labour is not only a cause of mental anguish but also maternal and foetal morbidity and mortality due to increased risks of maternal exhaustion, postpartum haemorrhage and sepsis, fetal distress and asphyxia and requires early detection and appropriate clinical response.[3] The risks for complications of prolonged labour are much greater in poor resource settings.[4] Augmentation of labour is used to treat delayed

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labour when poor uterine contractions are the underlying cause. The traditional methods of labour augmentation is the use of oxytocin infusion and artificial rupture of the membranes (amniotomy).[5]

Spasmolytics and spasmoanalgesics mixtures are administered to facilitate dilatation of the cervix during delivery and to shorten first stage of labour.[6] An ideal antispasmodic for accelerations of cervical dilations should have a prompt and long lasting action, no adverse effects on uterine contractility and be free from risk of uterine inertia. It should also have minimal side effects in the mother and foetus.[5] Application of antispasmodics in obstetrics to relieve cervical spasm was first introduced by Von Kries and his pupils in 1923.

Drotaverine is an isoquinoline derivative which binds to the surface of smooth muscles and changes their membrane potential and permeability. It inhibits phosphodiesterase IV enzyme which breaks cAMP and cGMP which play an important role in regulation of smooth muscle tone.[8] It acts specifically on spastic sites and corrects the cAMP and calcium imbalance relieving mooth muscle spasm.[8] Valethamate bromide or epidosin is from the group of 'Efosin' described by Steinmann (1954) for use in hastening labour.[9] It is an ester with quaternary N atom, which by virtue of its anticholinergic, parasympatholytics and musculotropic action relieves spasm of smooth muscle of cervix. These two drugs are used for cervical dilatation in modern obstetrics without deleterious effects on mother/fetus.

Prolonged labour has been a dreaded problem for obstetricians. The most common cause of prolonged first stage of labour is cervical spasm leading to cervical dystocia.

The aim of active management of labour is a reduction in the total duration of labour without causing any adverse effects on the mother or fetus. Many spasmolytic drugs have been used and tried in the past, Drotaverine is a newer Spasmolytic drug acts by inhibiting phosphodiesterase enzyme IV, which is claimed to reduce the duration of labour by accelerating cervical dilatation without causing side effects.

II. MATERIALS AND METHODS

Study design: prospective open-label randomized trial.

Study time: 1year- February 2019 to January 2020.

Study setting: Labour room of Department of obstetrics and gynaecology, Burdwan medical college.

Study subjects: Antenatal mothers admitted in department of obstetrics and gynaecology, Burdwan medical college for delivery. The study population was divided into 3 groups

1. Drotaverine Hydrochloride group. (group A)
2. Valethamate Bromide group.(group B)
3. Control group.(group C)

Inclusion criteria

- Live singleton pregnancy at term
- Both primigravida and multigravida
- Cephalic presentation
- Spontaneous onset of labour
- Prior caesarean delivery
- Grand mulipara
- Cephalopelvic disproportion
- Previous h/o cervical surgery
- Preterm
- Hypertensive disorder

Exclusion criteria

Ruptured membranes
Cervical dilatation >4 cm at admission
Multiple gestation
Non-cephalic presentation

Sample size:

Duration of Active phase of labour in is taken as the primary outcome. Mean duration of active phase of labour in one group was 121.4±22.18 minutes and in another group was 127.3±21.4 minutes. Considering effect size as 0.8, α error as 0.05, and power (1-ß error) as 0.8, the sample size was calculated as 46 in each group. A dropout of 10% is expected. Therefore, a total of 50 cases in both study groups and 50 in control group will be taken in this study.

So, total of 150 women were randomized to 3 groups- Drotaverine group (A), Valethamate group (B) and Control group(C), 50 in each group.

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$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\delta_0} \right)^2 \times p \times (1-p)$$

Sampling Technique
Random Allocation

Randomization was performed by computer generated random code, created in blocks of ten. The code was used by employee of our college who were not part of the research team as a basis for sealing cards in consecutively numbered envelopes; the cards read either "A" (Drotaverine hydrochloride), "B" (Valethamate bromide) or "C" (Control). When a new participant was enrolled in the study, site staff opened the next envelope in the numbered series and the woman received the treatment specified there in.

Group A
Injection Drotaverine (40mg) was administered intravenously during labour at an interval of 2 hours upto a maximum of 3 injections.

Group B
Injection Valethamate (8mg) was administered intravenously at an interval of 30 minuites upto a maximum of 6 injections.

Group C
In this group subjects were administered distilled water intravenously as placebo.

Outcome

The patients were monitored for pulse rate, blood pressure, uterine contractions, progress and descent of presenting part, cervical dilatation and fetal heart sound. Maternal side effects like tachycardia, fever, dryness of mouth, nausea, vomiting would be recorded.

Mode of delivery, duration of 1, 2, 3 stage of labour and fetal outcomes were recorded and compared to know the efficacy of Drotaverine and Valethamate on cervical dilatation and in shortening the duration of first stage of labour. Pantograph was be maintained during labour.

Study variables
Independent variables
Age, Religion, Socio-economic status, Residence, Gravida
Dependent variables

- Duration of 1st stage of labour
- Injection to delivery interval
- Rate of cervical dilatation
- Number of injection required
- Rate of caesarean delivery
- Instrumental vaginal birth
- Dryness of mouth and vomiting
- Transient tachycardia
- Vomiting
- Retention of urine
- PPH
- Postpartum fever
- Birth asphyxia
- Meconium aspiration syndrome
- APGAR Score at 1min. and 5min
- Neonatal sepsis

III. STATISTICAL ANALYSIS:

Data was checked for completeness and consistency and entered in the excel sheet. This was then imported into SPSS version 21 (IBM, SPSS Inc, Chicago, IL, USA) for analysis.

The normality of the used variables will be first tested. Differences between the continuous variables will be done using t-test (parametric test for normally distributed data) and Mann–Whitney U-test (nonparametric test for non normally distributed data).

Differences between percentages will be compared with the Fisher's exact test. P value less than 0.05 will be considered as statistically significant.

IV. RESULTS

Mean duration of active phase of labour in Drotaverine group was 169.43 ±24.51 minutes and 145.22±11.58 minutes respectively in primigravida and multigravida. Mean duration of active phase of labour in Valethamate group was 210.94±17.9 minutes and 178.93± 12.14 minutes in primigravida and multigravida respectively. The duration of active phase was less in Drotaverine group as compared to Valethamate group, both in case of primigravida and multigravida, which is statistically significant ($p < 0.0001$). The mean rate of Cervical dilatation in the Drotaverine group was 3.04 ± 0.5 cm/hr and 3.56 ± 0.3 cm/hr in primigravida and multigravida respectively. The mean rate of cervical dilatation in the Valethamate group was 2.56 ± 0.33 cm/hr and 3.04 ± 0.33 cm/hr in primigravida and multigravida respectively. The

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mean rate of cervical dilatation in Drotaverine group was faster as compared to Valethamate group in both primigravida and multigravida. The difference of the rates in both the groups is statistically significant (p <0.0001).Both Drotaverine Hydrochloride and Valethamate had no effect on the uterine contractions.

The mean first injections to delivery interval in Drotaverine group were 188.06 ± 23.85 minutes and 139.27±6.30 minutes in primigravida and multigravida respectively. The mean first injections to delivery interval in Valethamate group were 255.48 ± 14.54 minutes and 254.45 ± 14.83 minutes in primigravida and multigravida respectively. The mean first injections to delivery interval was significantly reduced in

Drotaverine group, as compared to Valethamate (p < 0.0001). There was no significant shortening of II stage of labour. Majority (90.27%) of the patients underwent spontaneous vaginal delivery. There was no increase in incidence of instrumental delivery or abdominal delivery in either Drotaverine or Valethamate groups.The incidence of complications in third stage of labour was almost equal in both the groups.

Incidence of PPH was 6.1% (12 in Drotaverine group and 10 in Valethamate group). Cervical tear and par urethral tear accounted 1.39% in both drug groups. The results were statistically insignificant. Incidence of maternal side effects with Drotaverine (5.5%) was significantly less compared to Valethamate (10.83%). Both the groups had equal incidence of vomiting, but the incidence of dryness of mouth ,

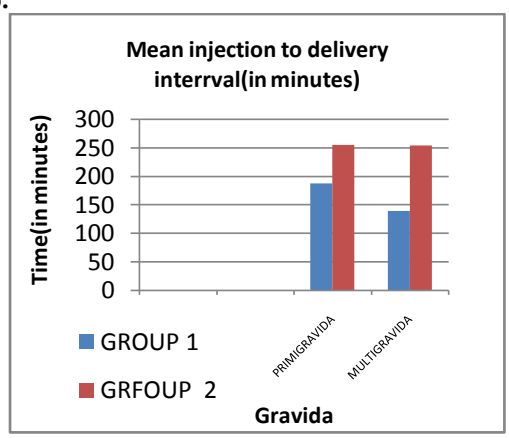
transient tachycardia and fever was slightly higher in Valethamate group as compared to Drotaverine group. There was no significant increase in incidence of meconium stained liquor in both the drug groups. Fetal complications in both of the groups were almost equal and statistically insignificant. 82.78% and 88.29% of newborns in Drotaverine group had Apgar score > 7 at 1 minute and 5minuite respectively. 77.78% and 86.11% of newborns in Valethamate group had Apgar score > 7 at 1 minute and 5 minuite respectively.

There was no intrapartum or early neonatal deaths in both the study groups.

MEAN INJECTION TO DELIVERY INTERVAL

MEAN INJECTION TO DELIVERY INTERVAL	GROUP 1 (N=180)	GRFOUP 2 (N=180)	P VALUE
PRIMIGRAVIDA	188.06 ± 23.85	255.48 ± 14.54	<0.0001
MULTIGRAVIDA	139.27 ± 6.30	254.45 ± 14.83	<0.0001

Group 1 is Drotaverine group
Group 2 is Valethamate group.



P value < 0.0001 (STATISTICALLY SIGNIFICANT).

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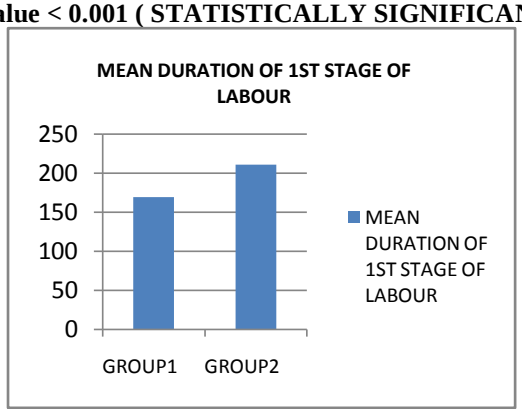
MEAN DURATION OF 1ST STAGE OF LABOUR IN PRIMIGRAVIDA

PRIMIGRAVIDA	GROUP1	GROUP2
MEAN DURATION OF 1ST STAGE OF LABOUR	169.43±24.51	210.94±17.9

P value < 0.001 (STATISTICALLY SIGNIFICANT).



MEAN DURATION OF 1ST STAGE OF LABOUR IN MULTIGRAVIDA

MULTIGRAVIDA	GROUP1	GROUP2
MEAN DURATION OF 1ST STAGE OF LABOUR	145.22±11.58	178.93±12.14

V. DISCUSSION:

In the present study, the mean duration of active phase of labour in Drotaverine group was 169.[24] (±24.51) and 145.22(±11.58) min in primigravida and multigravida respectively whereas in Valethamate group results were 210.94(±17.90)and 178.93(±12.14) min. There was a statistically significant reduction in the duration of active phase of labor in both primigravida and multigravida given drotaverine when compared with Valethamate bromide. Drotaverine was significantly more effective than Valethamate ($p<0.0001$). The results of another study done by Malaysarkar et al are similar showing the duration of active phase to be 174.7 min in primigravida and 148.2 min in multigravidae given drotaverine compared to 196 min in primigravida and 176.1 min in multigravida given valethamate bromide.[19] Mishra et al also found duration of active phase of labor to be less in women given Drotaverine (205 min in primigravida and 105 min in mutigravida) compared to Valethamate bromide (275 min in primigravida and 210 min in mutigravida).[20]No Significant shortening of duration was noticed in second and third stage of labour in previous studies (on Epidosin) of Beck (1956), Walter (1957), and Schmidt (1957)[27]. In study of S.N. Daftary (1991)[25,26] Second and third stage of labour was unaffected by I/V Epidosin.Present study results were very similar with results of another study done by Jayashree et al.[21] In study of Sharma JB mean injection to delivery interval was 220.07±86.12 min and 194±57.04 min respectively.[23] Total 22(6.12%) patients had atonic PPH. Out of them 10 was in Valethamate, 12in Drotaverine. In study by J.B Sharma, there was 18% incidence of PPH in Drotaverine group.[23]In another study had shown that total 14(4.7%) patients had atonic PPH. Out of them 5 were in Valethamate, 5 in Drotaverine.[22]

VI.CONCLUSION

Drotaverine hydrochloride is a superior cervical dilatation agent, significantly reducing the duration of labour without any ill effects on the mother or the fetus. It is significantly better than Valethamate bromide with less side effects due to selective action. Hence it is recommended that Drotaverine Hydrochloride may be given to low risk women in active labour. Drotaverine hydrochloride has definitely proven to shorten the duration of labour and provide early relief from distress for the labouring woman. The cost

effectiveness and patient compliance was increased with Drotaverine. The drugs do not reduce the tone of uterine contractions, and rather cause normalizing of irregular uterine contractions. Duration of second and third stage of labour was not affected by either drug. Neonatal complication was more or less equal.

Drotaverine is a safer and convenient approach towards acceleration of labour. Maternal complications were also fewer in patients treated with Drotaverine as compared to Valethamate. Thus it can be concluded that Drotaverine is a new aid in the management of a convenient, shorter, physiological and uncomplicated delivery.

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