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Original Research Paper

# Effect of Drotaverine on cervical dilatation – A comparative study with Valethamate bromide.

Gynaecology

**KEYWORDS:** : Drotaverine hydrochloride, Duration of 1st stage of labor, Maternal and fetal outcome, Valethamate bromide

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## ABSTRACT

**Objectives** To compare the efficacy and safety of Drotaverine hydrochloride and Valethamate bromide in shortening of 1st stage of labour. **Study design** The prospective study was conducted at ALLURI SITARAMA RAJU ACADEMY OF MEDICAL SCIENCES, ELURU between August 2013 to October 2015. 300 patients in labor ( spontaneous or induced ) were selected. They were equally divided into three groups. In group 1, an injection of Valethamate bromide 8 mg intramuscularly every half an hour for three doses. Group 2 consisted of 100 women who were administered one injection of Drotaverine hydrochloride 40 mg intramuscularly and repeated 2 hourly for maximum of three injections. Group 3 (n=100) acted as Control and were not given any drug. Comparative analysis was carried out regards to duration of early active phase of labour, rate of cervical dilatation, injection to delivery interval, mode of delivery, maternal outcome. t - test and chi - square test was used as statistical test of significance. **Result** 1. The average injection to delivery interval in Drotaverine is 192.26±75.155 minutes and in Valethamate is 262.72±134.5 minutes. The injection to end of first stage is 168.89±69.57 minutes in Drotaverine and 241.46±130.27 minutes in Valethamate. 2 The rate of cervical dilatation in Primigravida was 1.974 ±1.95 cm/hr in Valethamate , 2.188±0.63 cm/hr in Drotaverine and 1.163±0.45 cm/hr in Control group. In Multigravidae the values were 1.739±0.96 cm/hr in Valethamate, 2.496±1.23 cm/hr in Drotaverine and 1.482±0.58 cm/hr in Control group. **Conclusion :** In conclusion, as per the present study, it is found that the Drotaverine is superior to Valethamate as it reduces the duration of labor more effectively with very less adverse effects on mother and fetus compared to Valethamate and contol groups. When compared to Valethamate, Drotaverine is cost effective. Hence, Drotaverine can be recommended for shortening the duration of labor by hastening the cervical dilatation.

## INTRODUCTION

The aim of active management is a reduction in the total duration of labour without causing any adverse effects on the mother and fetus[1]. Application of antispasmodics in obstetrics to relieve cervical spasm was first introduced by Von Kries and his pupils in 1923. Today, with the advent of various forms of pharmacological interventions which have helped in shortening the duration of labour by augmenting uterine contractions or by accelerating the rate of cervical dilatation, the night mare of prolonged labour and its consequences is rare[2].

An ideal antispasmodic for acceleration of cervical dilatation should have prompt and long lasting action, no adverse effect on uterine contractility, and be free from risk of cervical inertia.

Valethamate bromide or epidosin is from the group of 'Efosin' described by Steinmann (1954) for use in hastening labour[3]. It is an ester with quaternary N atom, which by virtue of its anticholinergic, parasympatholytic and musculotropic action relieves spasm of smooth muscle of cervix.

Recently a new drug, Drotaverine hydrochloride, an isoquinoline used primarily to relieve gastrointestinal and rena colics has been tried and found to be effective in reducing the duration of dilatation stage of labour with excellent results. These two drugs are used for cervical dilatation in modern obstetrics without deleterious effects on mother or fetus.

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[4]. It acts specifically on spastic sites and corrects the cAMP and cGMP and calcium imbalance relieving smooth muscle spasm[5].

Drotaverine hydrochloride and Valethamate bromide, exert their main effect on the cervix, facilitating its dilatation and can only be used for augmentation of labour in women with established labour preferably with 4cm dilatation of cervix and good uterine contractions.We chose these two drugs to ascertain their role in augmentation of labour as to whether they can be recommended in routine use.

Shortening the duration of painful first stage of labour without having any effect on mother and fetus is very crucial. However, there is no adequate controlled studies in this subject. This study will be conducted to find out the efficacy and safety of Drotaverine and Valethamate with control in our setup.

## AIMS AND OBJECTIVES

1. To analyze and compare the efficacy of Drotaverine on cervical dilatation and to compare its efficiency and safety with Valethamate bromide.

2. To observe the effect of Drotaverine and Valethamate on improving cervical dilatation, and promoting progress of labour
3. Reduction in first stage of labor.
4. Its effect on uterine contractions.
5. Effect on second and third stages of labor.
6. To observe the effect of these two drugs on maternal morbidity.
7. To observe the effect of these two drugs on neonatal morbidity.

## MATERIALS AND METHODS:

In this study 300 demographically similar women, both primigravida and multigravida, with full term pregnancy in early active stage of labour having 2-3 contractions per 10 minutes lasting for 30 seconds and both induced and spontaneous labour are included. Comparative analysis is carried out as regards to duration of first stage, rate of cervical dilatation, mode of delivery, maternal side effect and fetal outcome.

**Study design:**
Randomized Prospective Study.

**Study location**
Department of Obstetrics and Gynaecology, Alluri Sita Rama Raju Academy of Medical Sciences, ELURU, Andhra Pradesh.

**Duration of study**
24 months (August2013 - October2015)

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**SampleSize**
200 cases and 100 controls

**Sampling procedure**
Informed Consent was taken from women satisfying the selection criteria. Women were randomly assigned to group 1, group 2 and group 3 by computer generated randomization. Group **1** consisted of 100 women who were administered an injection of Valethamate bromide 8mg intramuscularly every half an hour for three doses.Group 2 consisted of 100 women who were administered one injection of Drotaverine hydrochloride 40mg intramuscularly and repeated 2 hourly for maximum of three injections. Group3(n=100) acted as Control and were not given any drug.The three groups were matched for age, parity and cervical findings and duration of first stage

**INCLUSION CRITERIA:**
1.Age group between 20 and 35 years
2. No obstetric complications
3. Sinleton pregnancy.
4. Both primigravidae and multigravidae.
5. 37-41 weeks gestation.
6. Vertex presentation
7. More than 80 % effaced cervix
8. Regular established uterine contractions at the rate of 3/10 minutes each lasting for 30-40 seconds either spontaneously or with oxytocin.
9. Cervical dilation 3-4 cm

**EXCLUSION CRITERIA:**
1. Previous uterine scar
2. Malpresentation
3. Multiple pregnancies
4. Antepartum Haemorrhage
5. Cephalopelvic disproportion
6. Preclampsia and other pregnancy complications
7. Patient with glaucoma and heart disease
8. Drug hypersensitivity.

**OBSERVATIONANDRESULTS**
**Analysisofdata:**
The data collected was entered in to excel software and mean, percentages was calculated by analyzing on SPSS software. **The** appropriate statistical tool and technique was used to identify the significant of the variables depending upon the nature of data collected. An ova test and chisquare test was used and"p"value was calculated.

The mean age in Valethamate, Drotaverine and Controlwas23.53, 23.09 and 23.38 respectively. Maternal age was not siginificant statistically in this study..Out of 300 paitents 60 were primigravida and 40 were multigravida in Valethamate group,56were primigravida and 44 were mulitgravida in Drotaverine group, 65 were primigravida and 35 were multigravida in control group.Parity had no statistical significance.

**TABLE: 1 ,DURATION OFEARLYACTIVE PHASEOFLABOUR**

| **Druggroup** | **Meanduration (mins.)** | **Standard deviation** | **F-value** | **Pvalue** |
|---|---|---|---|---|
| **Valethamate** | 263.73 | ±93.396 | 69.028<br>69.028 | <0.05 |
| **Drotaverine** | 189.19 | ±73.531 | | <0.05 |
| **Control** | 354.81 | ±123.300 | | <0.05 |

Table 1, shows the mean duration of early active phase of labour in three groups.The mean duration in Drotaverine is comparable to Valethamate and Control with p-value<0.05.

**TABLE 2 , COMPARISON OF DURATION BETWEEN THREE GROUPS**

| Group | Meandifference | P-value |
|---|---|---|
| 2vs1 | 74.51 | <0.001 |
| 1vs3 | 91.08 | <0.001 |
| 2vs3 | 165.62 | <0.001 |

Table 2,shows the comparison of mean difference in duration of early active phase of labour. Drotaverine reduces the duration by 74.51 minutes when compared with Valethamate and reduces the duration by 165.62 minutes when compared with Control.Valethamate also reduces the duration by 91.08 minutes with Control. It is seen that this difference is comparable and is statistically significant.

**TABLE:3 ,COMPARISON OF INJECTION TO DELIVERY INTERVAL IN TWO DRUG GROUP**

| Drug | Meanduration(min.) | SD | F-value | P-value |
|---|---|---|---|---|
| Valethamate | 262.72 | ±134.510 | 20.911 | <0.001 |
| Drotaverine | 192.26 | ±75.155 | | <0.001 |

As shown in table 3, the mean duration from injection to delivery in Valethamate is 262.72 min and Drotaverine is 192.26 min with p-value less than 0.001 which is significant statistically.F value is 20.911.

**TABLE 4,COMPARISON OF INJECTION TO END OF 1ST STAGE IN TWO DRUG GROUP**

| Drug | Meanduration(min.) | SD | F-value | P-value |
|---|---|---|---|---|
| Valethamate | 241.46 | ±130.274 | 20.91 | <0.001 |
| Drotaverine | 168.89 | ±69.57 | 24.144 | <0.001 |

Table 4, shows the mean duration of injection to end of 1st stage in Valethamate is 241.46±130.274 minutes and in Drotaverine group is 168.89±69.57 minutes.The values between two drugs are comparable and significant statistically with p-value<0.001.

**TABLE:5 , RATE OF CERVICAL DILATATION**

| Group | Primigravida | Multigravida ~ |
|---|---|---|
| Valethamate | 1.9742±2.953cm/hr | 1.7395±0.967 |
| Drotaverine | 2.1884±0.6382cm/hr | 2.4968±1.23 |
| Control | 1.1637±0.456cm/hr | 1.4825±0.58860 |

Table 5, shows rate of cervical dilatation in cm/hr from early active phase to end of 1ststage. Cervical dilatation is comparable among three study groups as well as between primigravida and multigravida.

**TABLE:6 , MATERNAL SIDE EFFECTS**

| Sideeffects | Valethamate | Drotaverine | Control |
|---|---|---|---|
| Tachycardia | 21 | 4 | 5 |
| Fever | 5 | 0 | 2 |
| Flushing | 5 | 1 | 3 |
| Dryness | 8 | 0 | 3 |
| Nausea | 4 | 4 | 7 |
| Vomiting | 5 | 2 | 2 |
| Headache | 6 | 3 | 8 |
| Giddiness | 4 | 2 | 0 |
| Urineretention | 1 | 0 | 0 |
| Needtocatheterize | 1 | 0 | 0 |

Table 6 ,shows maternal side effects seen in three groups. Of these 21% patients in Valethamate, 4% in Drotaverine and 5% in Control had tachycardia.5% in Valethamate and 2% in Control had fever.8% in Valethamate and 3 in Control complained dryness of mouth. 6% in Valethamate,8% in Control and 3% in Drotaverine complained of headache.One patient in Valethamate group had urinary retention and was catheterized but the catheter was removed after 24hours.In Drotaverine group,4% complained nausea,3% headache,2%

giddiness, 2% vomiting, 1% complained flushing. These values were comparable among Valethamate and Control. More side effects of drug was seen in Valethamate group but not the serious one.Side effects like Hypotension,impaired alertness,allergic reaction was not seen in any groups.

**TABLE:7 , MODE OF DELIVERY IN THREE GROUPS**

| Mode of delivery | Valethamate | Drotaverine | Control | Percent |
|---|---|---|---|---|
| SVD | 96 | 100 | 95 | 97 |
| Forceps | 2 | 0 | 0 | 0.7 |
| Emergency LSCS | 2 | 0 | 1 | 1 |
| Vacuum | 0 | 0 | 4 | 1.3 |

Table 7, ,shows mode of delivery in three groups. 97% had SVD, 1.3% had vacuum, 1% had LSCS and 0.7% had forceps application

**DISCUSSION**

Despite good uterine contractions, inhibitory impulses in the form of spasm often impair cervical dilatation and prolong the duration of labour.Any method which aids in reducing the tone of cervical musculature will certainly favour early dilatation of cervix and hasten labour The mean age in group 1 (Valethamate), group 2(Drotaverine), and group 3 (control) was23.53, 23.09 and 23.38 respectively which had no statistical significance. Similar study was conducted by Anju Huria et al which showed that the mean ages of women were 24.24, 23.03 and 23.64years.In our study 66%, 56% and 65% of women were primigravidae. In their study 68%, 66%and65%were primigravidae respectively. Parity had no statistical significance.

In our study out of 300 women, 32 women were induced with different inducing agent and the value had no statistical significance when three groups were compared.

In our study the mean period of gestation in weeks in three groups were 39.231, 39.434 and 39.451 respectively. There was no significant difference in the effacemen of cervix, station of presenting part or position of cervix in three groups. In similar study conducted by J.Bsharma et al,the mean period of gestation in weeks was38.9±1.19,38.8±1.13and38.6±1.06 respectively.In study by Anju Huria et al,the mean period of gestation39, 38.92 and 39.08 respectively.

Out of total patients, 141 had cervical dilatation of 3cm at the time of start of study and remaining 159 had 4cm. When compared to see whether drug given at dilatation of 4cm was more effective in shortening the duration of first stage of labour, it was found that there was no difference whether drug was given at 3or4cm dilatation.

In our study,the mean duration of early active phase of labour in primigravida in three groups was 263.73 ±96.396, 189.95 ±60.04 and 380.74 ±121.74 respectively whereas in multigravida it was267.05 ±99.72, 188.23±88.5 and 306.66 ±112.66 respectively. The results were compared with similar studies done by AnjuHuriaetal,DasKKetal,S.LMishra etal.

In our study both Valethamate and Drotaverine cause significant reduction in the duration of early active phase of labour irrespective of parity. Drotaverine was significantly more effective than Valethamate($p<0.001$).

In our study the rate of cervical dilatation in Valethamate was 1.97±1.9 cm/hr in primigravida and 1.73±0.9cm/hr in multigravida. In Drotaverine it was 2.18± 0.63 and 2.49±1.23 and in control it was 1.16±0.4 and 1.482±0.58 cm/hr in primigravida and multigravida respectively.In similar study conducted by J. Bsharmaetal, it was1.87±0.67, 2.04±0.68 and 1.01±0.40 respectively.In study by Javhari Getal,it was 1.76, 2.06 and 1.02 respectively.

When injection to end of first stage were compared between two drug group,it was found that the mean duration in Valethamate was 241.46±130.27 and in Drotaverine was 168.89±69.57. Injection to delivery interval was 262.72±134.51and 192.26±75.15 in Valethamate and Drotaverine group. In study of J.Bsharma mean injection to delivery interval was 220.7±86.12and194±57.04 respectively. There was significant difference when two study groups were compared.

In our study it was seen that there was no difference in duration of early active phase of labour when drug was given at different Bishop's score in two groups.

In our study, it was found that total 30(10%) patients had tachycardia,out of them 21(7%) were in Valethamate, 4 in Drotaverine and 5 in control group.7 (2.3%) patients had fever,out of them 5 were in Valethamate and 2 in control group. 9(3%) patients complained of flushing. 17(5.7%)complained of giddiness and 15(5%)complained of nausea. Only one patient had urinary retention and was catheterized and she was of Valethamate group.

Total 14(4.7%) patients had atonic PPH.Out of them 5 were in Valethamate,5 in Drotaverine and 4 in control.In our study ,one patient from Valethamate group had cervical tear and one patient from Control had lateral vaginal wall tear.The complication was managed appropriately and there was no untoward incident.In study by J.Bsharma,there was 18% incidence of PPH in Drotaverine group.We had no such experience.

Out of 300 patients, 9 patients(3%) had other modes of delivery than vaginal. 2 patients in Valethamate had forceps delivery for foetal distress and 2 patients had emergency LSCS.4 patients in control group had vacuum delivery and one patient had emergency LSCS. Surprisingly none of the patient in Drotaverine group had instrumental delivery or caesarean section.Total 8 babies were admitted for neonata lsepsis, meconium aspiration syndrome and birth asphyxia,but they were discharged in good condition. Out of these 4 were in Valethamate, 2 in Drotaverine and 2 in control group. One baby in Drotaverine group died after birth due to tracheal stenosis but not pertaining to drug administration.

| No | Authors | Drotaverine Dose | Rate of Cervical Dilatation Cm/hr | Duration of first stage (minutes) | IDI In minutes | Side Effects | Valethamate Bromide Doses | Rate of cervical dilatation Cm/hr | Duration of first stage (minutes) | IDI in Minutes | Side Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Malay (2000) | 40mg I.V Infusion | 2.71 | P - 174.7 M -148.72 | - | 1% | 16 mg IV infusion | 2.39 | -196 ±16 M-176.96 | - | DM28% P 04% M 03% |
| 2 | Sharma (2001) | 40mg IM 2 hourly maximum 3 inj | 2.04 | | 194 | N-4% T-4% | 8mg IM 1hourly for 3 doses | 1.87 | | 220.7 | DM* 10% P 20% M 41% |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | Mishra (2002) | 40 mg IM | P*-2.05 M*-3.68 | P*-205 M*-105 | | 2 % | 8mg IM 1/2 hourly maximum 6 inj | P*-1.53 M*-2.00 | | - | |
| 4 | Ranka (2002) | 40 mg IM | | 190 | | N-2% T-2% | | | | - | |
| 5 | Kaur (2003) | 40 mg IM | 3.99±2.21 | 116.34 | 149.82 | H-3.2% T-4% | 8 mg IM Ihourly for 3 doses | 2.74 | 158.78 | 191.32 | H-2% DM-10% T-28% F-6% |
| 6 | Pai (2003) | 40mg IM | | P*-194.3 M*-165.8 | | None | | | | | |
| 7 | Khosla (2003) | 40mg IM | | 175.92 | | None | 8mg IM 1/2 hourly for 3 doses | | | | Minimum SE |
| 8 | Singh (2004) | 40mg IM 4 hourly maximum 3 inj 2 | 2.35 | 265.44 | | | | | | | |
| 9 | Nagaria (2009) | 40mg IM 2 hourly maximum 2 inj | Total-3.38 P-2.89 M-4.55 | 113.51 | 135.87 | N-3% V-1% T-3% | 16 mg IV infusion | | | | N-5% V-2% T-9% DM22% F-2% |
| 10 | Jayashree S et.al (2013)1 | 40mg IM 2 hourly maximum 2 inj | P-3.31 M-3.71 | P-123.12 M113.94 | | | 8mg IM 1/2 hourly maximum 3 inj | P-2.58 M-2.61 | P-180.40 M-147.12 | | |
| 11 | Jogi SR (2015) | 40mg IM 2 hourly maximum 3 inj | Avg-2.81 P*-2.50 M*-3.33 | 149.78 | Avg 176.78 P-197.22 M 156.35 | T-4% N-1% | 8mg IM 1hourly for 3 doses | Avg-1.42 P-1.30 M-1.57 | Avg 294.62 P-321.71 M-267.54 | Avg 319.62 P-346.71 | T-31% D-19% F-08% |
| 12 | Present study | 40 mg IM 2 hourly maximum of 3 inj | P- 2.18 M- 2.48 | 168.89 | 192.26±75.155 | T- 4% N-4%H-3% | | P- 1.97 M- 1.73 | 241.46 | 262.72± 134.510 | T-21% H-6% D-8% |

**CONCLUSION**

1. Drotaverine is a musculotropic antispasmodic drug which is used with very satisfactory result to shorten the duration of labor both in primi gravidae and multi gravidae by hastening the active phase of cervical dilatation.

2. The mean duration of early active phase of labour was reduced by 74.51 minutes between Drotaverine and Valethamate,91.08minutes between Valethamate and Control and 165.62 minutes between Drotaverine and Control. These differences are statistically significant.

3. The injection to delivery interval in Drotaverine is 192.26±75.155 minutes and in Valethamate is 262.72±134.5 minutes. The injection to end of first stage is 168.89±69.57 minutes in Drotaverine and 241.46±130.27 minutes in Valethamate.

4. The rate of cervical dilatation in Primigravida was 1.974 ±1.95 cm/hr in Valethamate , 2.188±0.63 cm/hr in Drotaverine and 1.163±0.45 cm/hr in Control group. In Multigravidae the values were 1. 739±0.96 cm/hr in Valethamate, 2.496±1.23 cm/hr in Drotaverine and 1.482±0.58 cm/hr in Control group.

5. Drotaverine did not interfere with uterine contractions and moreover helps by increasing the co-ordination in the weak regular uterine action.

6. There was no increased incidence of post partum complications. No cervical tears were detected in study groups where as two cervical tears were found in control group.

7. Incidence of after pains was less in patients who received either Drotaverine or Valethamate.

8. Though the Drotaverine is an isoquinoline denvative it has got no morphine like effects. So it is not an addictive drug.

9. Drotaverine does not involve the autonomic nervous system, hence it is free from anticholinergic side effects. No serious untoward side effects either on the mother or on the fetus were observed. So it can be used safely during labor.

10. Drotaverine is cost -effective and compared to Valethamate. As only one ampoule of Drotaverine injection is required for all the cases in the present study. Where as Valethamate injection of two ampoules in most cases and even three ampoules in few cases are required.

In conclusion, as per the present study, it is found that the Drotaverine is superior to Valethamate as it reduces the duration of

labor more effectively. Drotaverine coordinated the uterine activity by hastening the cervical dilatation. The side effects on mother are much less when compared to Valethamate, except for mild-headache and nausea. A total of 8 babies were admitted to ward. Of them 4 were from Valethamate, 2 each from Drotaverine and Control group. The intra-partum and post-partum complications are also insignificant with Drotaverine. When compared to Valethamate, Drotaverine is cost effective. Hence, Drotaverine can be recommended for shortening the duration of labor by hastening the cervical dilatation.

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