

COMPARATIVE STUDY OF DROTAVERINE HYDROCHLORIDE AND VALETHAMATE BROMIDE IN MANAGEMENT OF LABOUR

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Abstract

Background: To Compare Effectiveness of Drotaverine hydrochloride and Valethamate bromide in management of Labour. **Materials and Methods:** Prospective Randomised study done on a total of 240 primigravida females with term pregnancy. Patient was divided into 2 groups, 120 in each group. Group A give drotaverine and group B given valethamate bromide. Strict adherence to inclusion and exclusion criteria was done. **Result:** Delivery is a complex physiological process, characterized by uterine contractions along with sequence of events such as cervical ripening, dilatation and effacement of cervix, so as to promote expulsion of fetus and placenta. Labour is characterized by 4 stages with varying duration of each stage. **Conclusion:** Valethamate bromide and Drotaverine hydrochloride both are effective antispasmodic agent and have effect on duration of labour. However, Drotaverine hydrochloride is more effective in improving the rate of cervical dilatation and reducing the duration of labour, with minimum side effects. As the requirement of injections are lower in Drotaverine group, it is cost effective method for reducing the duration of labour.

INTRODUCTION

Labour and delivery are complicated physiological processes that are defined by severe pain due to uterine contractions along with cervical ripening followed by dilatation and effacement of the cervix, leading to the expulsion of the fetus and placenta.^[1] The duration of labour is an important determinant of maternal and perinatal morbidity.^[2] Classically, labour is characterized by four stages, and the duration of labour is 12 to 14 hours in nulliparous females and is shorter in multiparous females. Cervical dilatation of more than 4 cm along with uterine contractions is termed "active labour," and once this threshold of 4 cm dilatation is reached, normal delivery can be expected in the proposed duration of 4 to 6 hours depending upon the parity status.^[3] If the fetus is not delivered within 24 hours after the beginning of labour, the labour is considered prolonged.^[4] Usually, the upper segment of the uterus contracts to maintain the polarity of the uterus. These contractions are important in promoting fetal expulsion because they promote cervical softening and cervix dilatation while decreasing passive tissue resistance. Cervical dilatation is known to be one of the key determinant of duration of labour. The duration of labour is affected by multiple factors

interfering with spontaneous progression of labour. Sometimes, when there are strong uterine contractions present and the cervix does not fully dilate or dilates just partially, this condition is known as dystocia. One of the most common cause of prolonged first stage of labour is increased activity of cervical musculature particularly circular muscle fibers, leading to cervical spasm, which can be further aggravated by fear tension pain syndrome or fibrosis of cervix.^[5] Other causes include cephalopelvic disproportion, inefficient uterine action etc.^[6] Scopolamine and buscopan are antispasmodic pharmacological agents which have been used to decrease the length of labour and relieve discomfort ; apart from this, morphine and diazepam have been tried for pain relief but has been associated with adverse foeto-maternal outcome.^[7-9] An ideal antispasmodic for management of dystocia and shortening duration of labour must have immediate, long lasting action, no effect on uterine contractility, and minimal side effects on fetus and mother.^[9] A benzyl isoquinoline derivative drotaverine hydrochloride was introduced in 1960, which causes myometrial smooth muscle relaxation by selectively inhibiting phosphodiesterase IV enzyme at cervical musculature near term, facilitating the dilation of cervix during the labour.^[9] This drug is associated

with minor maternal adverse effects in small minority of females such as nausea, vertigo, hypotension and palpitations, however, the drug is not known to cause neonatal side effects.^[10]

EPIDOSIN i.e. Valethamate bromide is a synthetic anticholinergic ester with spasmolytic activity having quaternary N-atom. This agent has an anticholinergic and musculotropic action, which act as competitively blocking the muscarinic receptors of smooth muscle cells and acting as an antispasmodic at visceral musculature, relieving spasms in the cervical smooth muscles, facilitating cervix dilatation, and hastening the rate of cervical dilatation.^[10,11] Use of epidosis have been associated with certain mild adverse effects in the form of self-limiting maternal tachycardia however, no major life-threatening adverse reactions have been documented with its use.^[11]

Various studies have been conducted in India and elsewhere suggesting the role of antispasmodics in acceleration of labour by promoting cervical softening and dilatation. In the present study, the efficacy of valethamate bromide and drotaverine hydrochloride in managing labour was compared. The rationale behind selecting these drugs was their easy availability, wide use in clinical practice, low cost, no proven adverse effect on mother and fetus. It has been observed that both of these drugs can be used independently or in combination with the active management of labour to reduce the need for oxytocin.

Aim

To Compare Effectiveness of Drotaverine hydrochloride and Valethamate bromide in management of Labour.

Primary Objective

To compare the injection delivery time of Drotaverine hydrochloride and Valethamate bromide in primigravida patient.

Secondary objectives:

To compare adverse effects seen with using drotaverine hydrochloride and Valethamate bromide in participants.

MATERIALS AND METHODS

The present study entitled “Comparative study of Drotaverine hydrochloride and Valethamate bromide in management of labour” was conducted as a Prospective Randomized study at Department of Obstetrics and Gynaecology during the study

period of one and a half year i.e. January 2021 to June 2022 on a total of 240 primigravida females with term pregnancy.

Study Population: Primigravida with term pregnancy

Study Period: January 2021- June 2022 (One and Half Year)

Study Design: Hospital based Interventional study

Study Type: Prospective Randomised study

Inclusion Criteria

1. Singleton pregnancy in primigravida with no antenatal complications.
2. With informed Consent
3. Cephalic presentation
4. Spontaneous onset of labour
5. Women in active phase of labour with uterine contractions of at least 3 in every 10 minutes, with each contraction lasting for at least 30 second.
6. Cervical dilatation of 3-4 cm.
7. Cervical effacement of 70 – 80 %
8. Intact Amniotic membranes
9. Gestational period of 37 to 42 weeks
10. Age group 20 to 30 yrs.

Exclusion Criteria

1. Any medical, surgical or obstetrical complications such as antepartum haemorrhage, pre-eclampsia, Gestational diabetes mellitus etc
2. History of cervical surgery in the past
3. Known hypersensitivity or contraindications to the use of Drotaverine and /or Valethamate
4. Use of any other agent augmenting labour and / or affecting cervical dilatation
5. Induced labour
6. Previous uterine scar.

RESULTS

The present study entitled “Comparative study of drotaverine hydrochloride and valethamate bromide in management of labour” was conducted on a total of 240 pregnant who presented in labour. All 120 females were randomly assigned to one of two groups: Group A got Inj. Drotaverine 40 mg intramuscularly every 2 hours for a maximum of three doses, whereas Group B received Inj. Valethamate Bromide (Epidosis) 8 mg intravenously every half hour for a maximum of three doses. The findings of present study are tabulated as under-

Table 1: Comparison of age between two treatment groups

Age (years)	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)	
	Frequency	Percentage	Frequency	Percentage
21-25	73	60.8	81	67.5
26-30	47	39.2	39	32.5
Mean±SD	25.04±1.85		24.65±1.99	
χ ²	1.16			
P value	0.28			

Mean age of cases belonging to Drotaverine hydrochloride group was 25.04±1.85 years whereas mean age of women of Valethamate bromide was 24.65±1.99 years. Majority of cases in both the groups belonged to age range of 21 to 25 years (>60%).

Table 2: Comparison of gestational age between the groups

Gestational age	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)	
	Frequency	Percentage	Frequency	Percentage
37-38 weeks	35	29.2	21	17.5
38-39 weeks	40	33.3	42	35.0
39-40 weeks	27	22.5	43	35.8
40-41 weeks	13	10.8	10	8.3
>41 weeks	5	4.2	4	3.3
χ^2	7.71			
P value	0.10			

All the cases with term pregnancy (37 completed weeks) were enrolled in our study. Majority of the cases of Drotaverine hydrochloride group presented with gestational of 38 to 39 weeks (33.3%), whereas majority of cases in Valethamate bromide group presented in 39 to 40 weeks of gestation. However, the observed difference in gestational age between two groups was statistically insignificant ($p>0.05$).

Table 3: Comparison of socioeconomic status between two groups

Socioeconomic status	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)	
	Frequency	Percentage	Frequency	Percentage
High	11	9.2	10	8.3
Medium	19	15.8	15	12.5
Low	90	75.0	95	79.2
χ^2	0.653			
P value	0.72			

In present study, more than one third of cases belonged to low socioeconomic status in both the treatment arms, and the two groups were comparable with respect to socioeconomic status ($p>0.05$).

Table 4: Comparison of number of injections between two groups

Number of injections	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)	
	Frequency	Percentage	Frequency	Percentage
1	60	50	12	10
2	40	33.3	32	26.7
3	20	16.7	76	63.3
Mean±SD	1.67±0.75		2.53±0.67	
χ^2	65.57			
P value	0.001			

Mean Valethamate bromide injection given to females was 2.53±0.67 whereas mean injections of Drotaverine hydrochloride was 1.67±0.75. Majority of cases in Drotaverine hydrochloride group received 1 injection (50%), whereas 63.3% cases in Valethamate bromide group received 3 injections. The number of injections required was significantly higher in cases with Valethamate bromide group as compared to Drotaverine hydrochloride group ($p<0.05$).

Table 5: Comparison of duration of labor between the groups

Duration of labour (minutes)	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)		T value	P value
	Mean	SD	Mean	SD		
1 st stage	244.96	96.21	277.58	100.96	92.56	0.011
2 nd stage	50.72	16.69	54.77	15.81	1.93	0.055
3 rd stage	5.31	0.88	5.56	0.99	2.07	0.04
Active stage	205.08	88.19	241.22	95.71	3.04	0.003
Total duration	300.78	104.62	336.09	112.51	2.52	0.012

In our study, mean duration of first stage of labor was found to be significantly higher in Valethamate Bromide group (277.58±100.96 minutes) as compared to Drotaverine hydrochloride group (244.96±96.21 minutes) ($p<0.05$). Similarly, mean duration of third stage of labour, active stage of labour and total duration of labour was found to be significantly higher in Valethamate Bromide group as compared to Drotaverine hydrochloride group ($p<0.05$). However, we found no significant difference in duration of second stage of labour between two groups ($p>0.05$). Thus, Drotaverine hydrochloride was helpful in significantly reducing the duration of labour.

Table 6: Comparison of rate of cervical dilatation between the groups

Rate of cervical dilatation	Drotaverine hydrochloride (n=120)	Valethamate bromide (n=120)
Mean	2.05	1.79
SD	0.63	0.51
T value	3.47	
P value	0.001	

In the present study, the mean rate of cervical dilatation was observed to be considerably greater in Drotaverine hydrochloride group (2.05±0.63) as compared to Valethamate bromide group (1.79±0.51) (p<0.05).

Table 7: Comparison of APGAR score at 1 minute and 5 minute between the groups

APGAR score		Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)		χ ²	P value
		n	%	n	%		
1 minute	6	3	2.5	7	5.8	3.89	0.27
	7	43	35.8	34	28.3		
	8	73	60.8	79	65.8		
	9	1	0.8	0	0		
	Mean±SD	7.60±0.56		7.60±0.60			
5 minute	7	2	1.7	4	3.3	0.74	0.69
	8	25	20.8	26	21.7		
	9	93	77.5	90	75		
	Mean±SD	8.76±0.47		8.72±0.52			

Mean APGAR score at 1 minute was 7.60±0.56 and 7.60±0.60 in Drotaverine hydrochloride and Valethamate bromide group respectively. Similarly, mean AOGAR score at 5 minute in Drotaverine hydrochloride was 8.76±0.47 and that in Valethamate bromide group was 8.72±0.52. Majority of cases in both the groups had APGAR score of 8 at 1 minute and 9 at 5 minute, with no significant difference in APGAR score between the groups at both the observations (p>0.05).

Table 8: Comparison of side-effects of drug between the groups

Side effects	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)	
	Frequency	Percentage	Frequency	Percentage
None	112	93.3	109	90.8
TMT	3	2.5	11	9.2
Vomiting	5	4.2	0	0
χ ²	9.61			
P value	0.008			

In present study, side-effects were noted in 6.7% cases in Drotaverine hydrochloride group and 9.2% cases of Valethamate bromide group. The observed difference in side effects between the groups was statistically significant (p<0.05).

Table 9: Comparison of complications between the groups

Complications	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)	
	Frequency	Percentage	Frequency	Percentage
None	89	74.2	89	74.2
Fetal distress	8	6.7	12	10
PPH	11	9.2	13	10.8
Tear	12	10	6	5.0
χ ²	2.97			
P value	0.39			

Complications in the form of fetal distress, PPH and tear were reported in 25.8% cases in both the groups. We found no significant difference in complications between two treatment arms (p>0.05).

Table 10: Comparison of mode of delivery between the groups

Mode of delivery	Drotaverine hydrochloride (n=120)		Valethamate bromide (n=120)	
	n	%	n	%
Spontaneous	99	82.5	97	80.8
Forceps	5	4.2	6	5
LSCS	8	6.7	12	10
Precipitate labour (Spontaneous)	8	6.7	5	4.2
χ ²	1.60			
P value	0.66			

More than 80% cases in both the treatment group delivered via spontaneous vaginal delivery.

However, LSCS was the mode of delivery in 6.7% cases in Drotaverine hydrochloride group and 10%

cases in Valethamate bromide group. However, in small proportions of cases, forceps and spontaneous precipitate labour was the mode of delivery. We found no significant difference in mode of delivery between two groups ($p>0.05$).

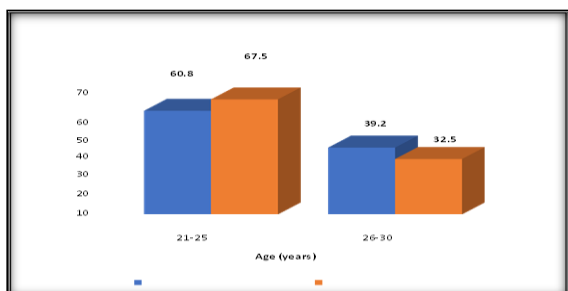


Figure 1: Comparison of age between two treatment groups

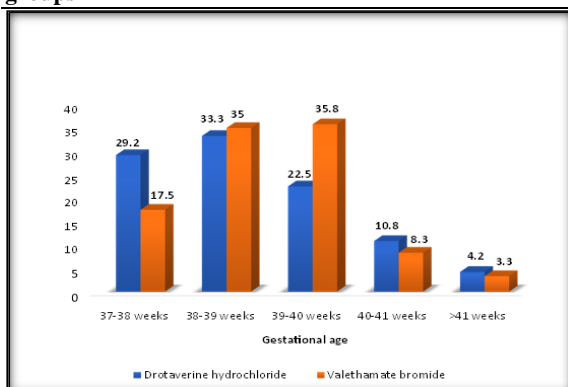


Figure 2: Comparison of gestational age between the groups

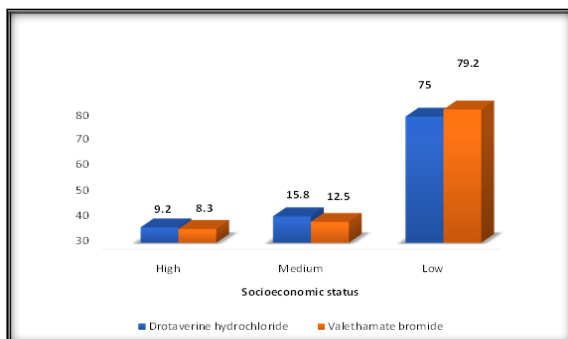


Figure 3: Comparison of socioeconomic status between two groups

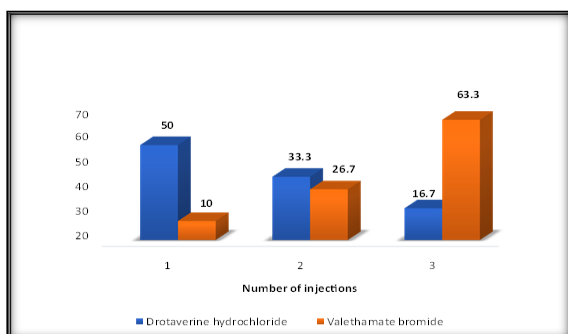


Figure 4: Comparison of number of injections between two groups

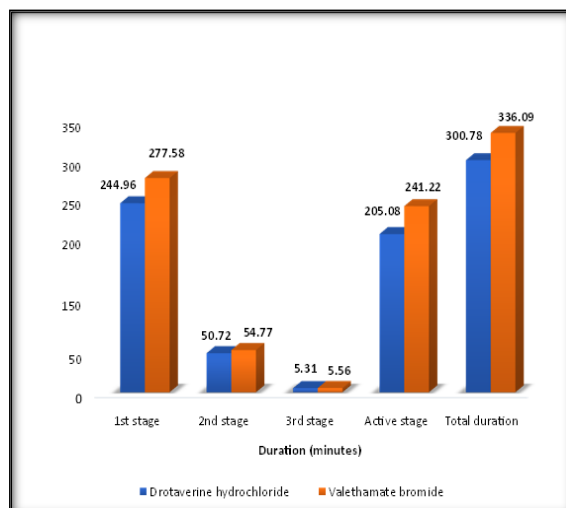


Figure 5: Comparison of duration of labor between the groups

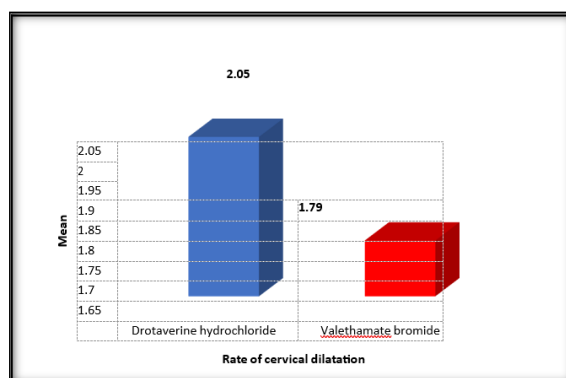


Figure 6: Comparison of rate of cervical dilatation between the groups

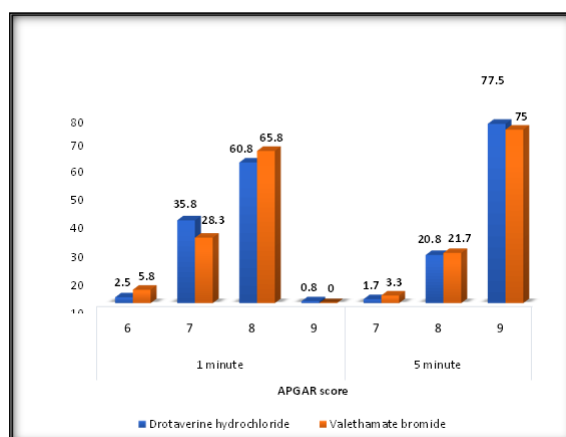


Figure 7: Comparison of APGAR score at 1 minute and 5 minute between the groups

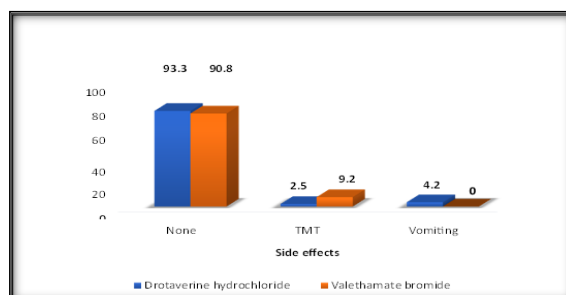


Figure 8: Comparison of side-effects of drug between the groups

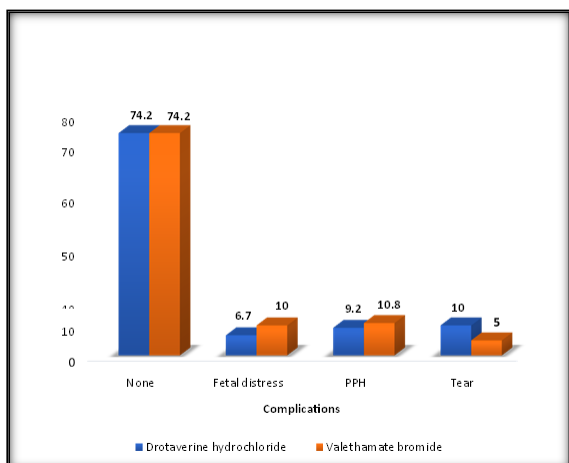


Figure 9: Comparison of complications between the groups

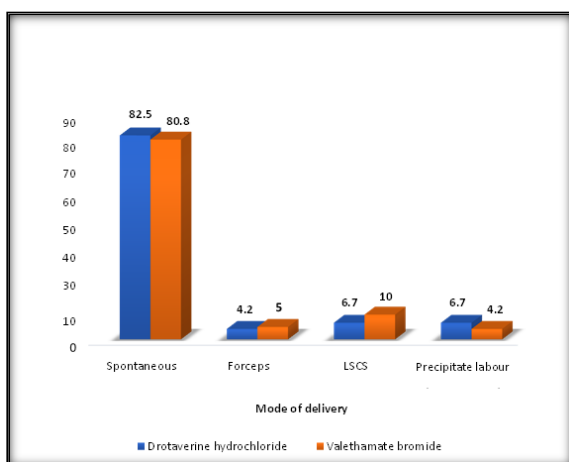


Figure 10: Comparison of mode of delivery between the groups

DISCUSSION

Delivery is a complex physiological process, characterized by uterine contractions along with sequence of events such as cervical ripening, dilatation and effacement of cervix, so as to promote expulsion of fetus and placenta.^[1] Labour is characterized by 4 stages with varying duration of each stage.^[2] Multiple factors affect the duration of labour, and cervical dilatation of labour is one of the key determinant of duration of labour. Other causes include dystocia, cervical spasms, cephalopelvic disproportion, inefficient uterine action etc.^[5,6] Labour if prolonged is associated with fetal as well as maternal complications and thus it is essential to detect the abnormal progress of labour as soon as possible.^[5] To shorten the duration of labour and augment the labour, various methods are available, which including mechanical methods and pharmacological methods.^[1,9]

The antispasmodic agents have been used for not only management of pain but for shortening the duration of labour. An ideal antispasmodic agent for shortening the duration of labour and management of dystocia must be long lasting with immediate

action and does not have effect on uterine contractility, and must have no or minimal side effects on mother and fetus.^[9] Drotaverine hydrochloride and Valethamate bromide are easily available low-cost drugs, widely used in clinical practice for active management of labour with no proven adverse effect on mother and fetus. Drotaverine hydrochloride act by selectively inhibiting phosphodiesterase 4 (PDE4) enzyme, which is involved in the degradation of cyclic adenosine monophosphate (cAMP). Drotaverine by inhibiting PDE4 cause relaxation of smooth muscles by elevation of cAMP levels. Valethamate bromide on the other hand has anticholinergic activity and act by competitively inhibiting the muscarinic receptors of smooth muscle cells, thereby acting as smooth muscle relaxant by anticholinergic

Number of Injections

In patients of Drotaverine group, Inj. Drotaverine 40mg was administered intramuscularly every 2 hourly for a maximum of 3 doses whereas in cases of Valethamate bromide group, Inj. Epidosin 8mg was administered intravenously in every 30 minutes for a maximum of 3 doses. Mean number of injections were higher in Valethamate bromide group (2.53 ± 0.67) as compared to Drotaverine hydrochloride group (1.67 ± 0.75). In our study, significantly higher proportions of cases of Drotaverine hydrochloride group received 1 injection (50%) whereas significantly higher proportions of cases in Valethamate bromide group received 3 injections (63.3%) ($p < 0.05$).

Rate of Cervical Dilatation

Normally, the rate of cervical dilatation in nulliparous females is at the rate of 1.2 cm/hr whereas that in multiparous females is 1.5 cm/hr.^[5] Rate of cervical dilatation was assessed in each case and we found that Drotaverine hydrochloride significantly increased the rate of cervical dilatation as compared to Valethamate bromide (2.05 ± 0.63 vs. 1.79 ± 0.51 ; $p < 0.05$).

Duration of Labour

Labour is categorized in 4 stages. Mean duration of first, second, third, active stage and total course of labour in Drotaverine hydrochloride group was 244.96 ± 96.21 , 50.72 ± 16.69 , 5.31 ± 0.88 , 205.08 ± 88.19 and 300.78 ± 104.62 minutes respectively whereas that in Valethamate bromide group was 277.58 ± 100.96 , 54.77 ± 15.91 , 5.56 ± 0.99 , 241.22 ± 95.71 and 336.09 ± 112.51 minutes respectively. In our study, duration of all the stages (except second stage) were higher in Valethamate Bromide group as compared to Drotaverine hydrochloride group ($p < 0.05$). Thus, Drotaverine hydrochloride was helpful in significantly reducing the duration of first, third and active stage of labour as well as total duration of labour.

Mode of Delivery

Cesarean section is indicated in cases with prolonged labour. However, standard labour management protocol suggest active management of labour in cases with dystocia.^[7] In our study, as a

result of active management, more than 80% cases were delivered via spontaneous vaginal delivery, whereas LSCS was the mode of delivery in 6.7% cases in Drotaverine hydrochloride group and 10% cases in Valethamate bromide group. Forceps delivery and spontaneous precipitate labour were the mode of delivery in few cases in both the groups. We found no significant difference in mode of delivery between two groups ($p>0.05$).

Side Effects

We compared the side effects of the drugs in both the groups and found no side effects in more than 90% cases in both the groups. However in 6.7% cases in Drotaverine hydrochloride group and 9.2% cases of Valethamate bromide group, certain side effects were seen. Drotaverine hydrochloride was associated with Transient maternal tachycardia and vomiting in 2.5% and 4.2% cases respectively whereas, Valethamate bromide was associated with maternal tachycardia in 9.2% cases. The incidence of vomiting was higher in Drotaverine hydrochloride group whereas the incidence of transient maternal tachycardia was significantly higher in Valethamate bromide group ($p<0.05$).

Complications

All the mothers were monitored for complications, which were observed in 25.8% cases in both the groups. Most common complication in Drotaverine hydrochloride group was tear (10%), followed by PPH (6.7%) and fetal distress (6.7%), whereas complications noted in Valethamate bromide group in decreasing proportions were PPH (10.8%), followed by fetal distress (10%) and tear (5%). We found no significant difference in complications between two treatment arms ($p>0.05$).

Apgar Score

Fetal outcome was assessed in terms of APGAR score at 1 minute and 5 minutes. A single pediatrician was always available to attend the neonate at the time of delivery. In our study, APGAR score was below 7 in 2.5% and 5.8% cases 1 minute in Drotaverine hydrochloride group and Valethamate bromide group respectively whereas it was above 7 in majority of cases in both the groups. At 5 minutes, the APGAR score was above 7 in all the cases in both the groups. We found no significant difference in APGAR score between two treatment groups ($p>0.05$), suggesting both the drugs have no effect on the fetal outcome or may improve the fetal outcome.

CONCLUSION

Valethamate bromide and Drotaverine hydrochloride both are effective antispasmodic agent and have effect on duration of labour. However, Drotaverine hydrochloride is more effective in improving the rate of cervical dilatation and reducing the duration of labour, with minimum side effects. As the requirement of injections are lower in Drotaverine group, it is cost effective

method for reducing the duration of labour. However, the rate of complications and effect on APGAR score in both the drugs is similar.

Summary

The present study entitled "Comparative study of drotaverin hydrochloride and valethamate bromide in management of labour" was conducted to compare the effectiveness, injection delivery time and adverse effects of Drotaverine hydrochloride and Valethamate bromide in management of Labour. A total of 240 females were randomly allocated into two groups,

- patients of Group A received injection Inj. Drotaverine hydrochloride whereas
- patients of group B received Inj. Valethamate bromide.

The findings of present study are summarized as under-

- Majority of cases in both the groups belonged to age range of 21 to 25 years (>60%). The observed difference in age composition of between two groups of women was statistically insignificant ($p>0.05$).
- Majority of the cases of Drotaverine hydrochloride group presented with gestational of 38 to 39 weeks (33.3%), whereas majority of cases in Valethamate bromide group presented in 39 to 40 weeks of gestation ($p>0.05$).
- More than one third of cases belonged to low socioeconomic status in both the treatment arms, and the two groups were comparable with respect to socioeconomic status ($p>0.05$).
- Mean Valethamate bromide injection given to females was 2.53 ± 0.67 whereas mean injections of Drotaverine hydrochloride was 1.67 ± 0.75 .
- Majority of cases in Drotaverine hydrochloride group received 1 injection (50%), whereas 63.3% cases in Valethamate bromide group received 3 injections. The number of injections required was significantly higher in cases with Valethamate bromide group as compared to Drotaverine hydrochloride group ($p<0.05$).
- Mean duration of injection to end of first stage of labor was found to be significantly higher in Valethamate Bromide group (277.58 ± 100.96 minutes) as compared to Drotaverine hydrochloride group (244.96 ± 96.21 minutes) ($p<0.05$).
- Similarly, mean duration following injection to third stage of labour, active stage of labour and total duration of labour (injection to delivery time) was found to be significantly higher in Valethamate Bromide group as compared to Drotaverine hydrochloride group ($p<0.05$).
- Mean rate of cervical dilatation was found to be significantly higher in Drotaverine hydrochloride group (2.05 ± 0.63) as compared to Valethamate bromide group (1.79 ± 0.51) ($p<0.05$).
- Mean APGAR score at 1 minute was 7.60 ± 0.56 and 7.60 ± 0.60 in Drotaverine hydrochloride and Valethamate bromide group respectively.

Similarly, mean APGAR score at 5 minute in Drotaverine hydrochloride was 8.76 ± 0.47 and that in Valethamate bromide group was 8.72 ± 0.52 ($p > 0.05$).

- Side-effects were noted in 6.7% cases in Drotaverine hydrochloride group and 9.2% cases of Valethamate bromide group. TMT and vomiting were the observed side effects in 2.5% and 4.2% cases of Drotaverine hydrochloride group, whereas TMT was only side effects in 9.2% cases of Valethamate bromide group.
- Complications in the form of fetal distress, PPH and tear were reported in 25.8% cases in both the groups. We found no significant difference in complications between two treatment arms ($p > 0.05$).

More than 80% cases in both the treatment group delivered via spontaneous vaginal delivery. However, LSCS was the mode of delivery in 6.7% cases in Drotaverine hydrochloride group and 10% cases in Valethamate bromide group. We found no significant difference in mode of delivery between two groups ($p > 0.05$).

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