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Original Article

To compare and evaluate the efficacy and safety of drotaverine and valethamate bromide

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Abstract

Objectives: To comparatively evaluate the efficacy and safety of drotaverine and valethamate bromide in shortening the duration of labor. *Methods:* The study was conducted over 200 selected uncomplicated primi and second gravidae with term pregnancy in established labor, at 3 or 4 cm cervical dilatation with adequate uterine contraction. In group I, 100 cases were given injection drotaverine IM, 40 mg every 2 hours up to a maximum of 3 injections, and in group II, the remaining 100 cases received intravenous infusion of valethamate bromide (16 mg in 540 ml of 5% dextrose) at a rate of 16 drops per minute till full dilatation. Duration of first, second and third stage of labor, cervical dilatation rate, injection delivery interval, mode of delivery, side effect if any and neonatal outcome were noted. *Results:* Injection to full dilatation interval was significantly shorter in group I (113.5±74 min.) in contrast to group II (177.4±105.68 min.) (P<0.05). Irrespective of gravidity, injection to full dilatation duration was shorter in group I being 134.2±80.02 min. vs 189.58±109.24 min. in primi and 82.93±52.09 min. vs 143.56±67.05 min. in second gravidae in group I and group II respectively (P<0.05). Mean cervical dilatation rate was faster in group I as compared to group II in primi as well as in second gravidae (2.89 vs 2.01 cm/hr in primi and 4.55 vs. 2.72 cm/hr in second gravidae). Over all mean cervical dilatation rate was also significantly higher in group I (3.38 cm/hr) as against group II (2.17 cm/hr (P<0.05). Mean injection delivery interval was significantly shorter in group I (135.87±85.94 min vs. 200.19±115.04 min in group II) (P<0.05). There was no significant difference in second and third stage of labor and neonatal outcome. Adverse effects like tachycardia and dryness of mouth was more commonly associated with group II (P<0.001). *Conclusion :* Intramuscular drotaverine is safe and more effective than valethamate bromide in reducing the duration of first stage and total delivery time.

Key words : drotaverine, valethamate bromide, cervical dilatation, labor

Introduction

In the modern era of day care obstetrics, a smooth timely delivery and early return to the routine activity is desired by everyone. With the wide acceptance of active management of labor, concern over the problem of functional cervical dystocia has justifiably grown over the years. More and more clinical trials have been devoted to acceleration of labor to prevent the risk of prolonged labor like exhaustion, dehydration, infection, and ketoacidosis. All these causes increased physiological burden for the mother and these events may eventually cause complications in the 2nd stage and the puerperium. A short 1st stage of the labor is

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naturally of dual advantage, both to the obstetrician and the patient.

Several drugs like antispasmodics, tranquillizers, prostaglandins and psychotherapeutic methods have been tried in the past to facilitate cervical dilatation, but the majority of these were found to have ill effect on the mother and the fetus.

Blasko found that type IV Phosphodiesterase (PDE) enzyme is present in increased concentration in the third trimester in myometrium, suggesting its contribution in regulating uterine motility. Hence like drotaverine selective PDE IV inhibitors may help to facilitate dilatation of cervix[1]. Drotaverine, an isoquinoline derivative is a superior smooth muscle relaxant which acts specifically on spastic sites and corrects the cAMP and calcium balance relieving smooth muscle spasm[2]. This inhibitory action is detectable only in lower uterine segment during labor since muscle fibers in upper uterine segment are strongly affected by contractile effect of oxytocin. Use of drotaverine during pregnancy is free of any teratogenic and embryotoxic effects[3]. Valethamate bromide is an ester with a quaternary N atom, time tested extensively used drug by virtue of its anticholinergic parasympatholytic and musculotropic action, which relieves spasm of smooth muscles of cervix. The present study has been done to observe the effect of IM drotaverine on duration of the first stage of labor and to compare it with valethamate bromide in uncomplicated primi and 2nd gravidae.

Methods

This study was conducted over carefully selected 200 women with uncomplicated term gestation, admitted for labor during the period November 1999 to November 2000.

A detailed history of the cases was taken regarding age, occupation and socioeconomic status. Their presenting complaints were recorded like period of amenorrhea, duration since the onset of labor pain, leaking per vaginum and other complaints if any. Obstetric history was elicited regarding outcome of previous pregnancies, any history of prolonged labor, retained placenta, abortion, preterm labor or still births. Past and family history regarding any major illness or systemic diseases was also taken.

A thorough general and systemic examination was done. Per abdomen examination was done to note height of the uterus, presentation, frequency and intensity of contractions. Fetal well being was monitored by noting the rate, rhythm and regularity of fetal heart sounds. By per vaginum examination cervical dilatation, effacement and consistency and station of the presenting part were noted. Pelvic assessment was done to exclude any pelvic contraction or cephalopelvic disproportion etc.

Routine investigations were advised including Hb, BT, CT, Blood grouping, blood sugar, sickling and VDRL, urine for routine and microscopic examination.

Following inclusion and exclusion criteria were considered for selection of the uncomplicated patients.

Inclusion criteria

- Primigravida and second gravida
- Age between 18-30 year.
- Intact fetal membranes with vertex presentation.
- Regular established uterine contraction at the rate of at least 2/10 minute, each contraction lasting for at least 20 seconds.
- Cervical dilatation of 3-4 cms.
- No evidence of maternal or fetal distress.

Exclusion criteria

- Malpresentation
- Twin pregnancy
- Cervical surgery in the past or history of cervical injury
- Induced labor
- Maternal systolic pressure below 100mm Hg or above 150 mm Hg.
- Patients on antihypertensive therapy
- Known hypersensitivity to drotaverine or valethamate bromide
- If any other spasmolytic agent had been used within 48 hours

After obtaining a homogenous group based on inclusion criteria, cases were randomly assigned by computer generated number to group I (drotaverine and group II (valethamate). The drug administration was done in patients with established labor i.e. at 3 or 4 cm cervical dilatation with regular uterine contractions of >2 per 10 min each lasting 20 seconds. In group I (n=100) cases received I/M drotaverine 40mg, in supine position. Injection was repeated after 2 hours as per requirement

(cervical dilations ≤7 cm) to a maximum of 3 injections.

In group II (n=100), cases received intravenous infusion of valethamate bromide 16 mg, in 540 ml of dextrose at an infusion rate of 16 drops/minute.

Continuous monitoring of maternal and fetal condition was done. Any abnormality if detected was managed accordingly. Evaluation of uterine activity was done ½ hourly to assess the frequency and duration of contractions. Any relation with drug administration to uterine contraction was specially noted.

Per vaginum examination was done at the beginning of labor, at the time of administration of drotaverine or valethamate bromide infusion hourly, during labor and at further doses of the drugs, if required. State of the cervix was noted during each examination for the following points:

- Length of cervix – Unchanged, partially effaced or fully effaced.
- Dilatation of cervix-in centimeters or in finger breadth.
- Consistency-firm, medium or soft.

Time of membrane rupture, position of presenting part and time of full dilatation was also noted. Adverse effect if present like headache, vertigo, nausea, palpitation, hypotension, dryness of mouth, blurred vision were also noted and treated accordingly.

All events of labor were graphically recorded in the form of partogram. If labor did not end within 12 hours spontaneously, it was considered as failure of acceleration of labor and other methods of termination of pregnancy were looked for. Other outcome variables like injection delivery interval, total doses of drug required, route of delivery, incidence of operative interference, duration of first, second and third stages of labor, amount of blood loss, complications of the third stage like cervical tear, retained placenta, post partum hemorrhage etc. were noted. Fetal outcome in terms of live or stillbirth, weight, apgar scoring at 1 min and 5 min were recorded. Both mother and the baby were followed up for at least 48 hours.

Analysis of the results

Results were analyzed by using various statistical techniques like percentage, mean, standard deviations, Z test, t test, test of significance x^2 which ever were found necessary.

Observation

In the present study epidemiological factors of cases in both the groups were same. The groups were statistically matched as far as age, gravidity (60% primi and 40% second gravida), gestational age, initial cervical dilatation and effacement is concerned (P>0.5) (Table 1). Both the groups were similar with regards to antenatal booking, educational level and socio economic status. Drug administration was started either at 3 cm dilatation (41% of the women in group I and 43% in group II, P>0.05) or 4 cm dilatation (59% of the women in group I and 57% in group II, P>0.05). Position of the cervix was posterior in 17%, central in 32%, anterior in 51% of the women in group I while it was posterior in 16%, central in 22% and anterior in 62% of the women in group II.

Injection to full dilatation interval was significantly shorter in group I as compared to group II (P<0.05). In group I, 84% of the cases entered in second stage within 3 hours while only 66% of the cases in group II entered the second stage in same duration. Only one patient entered in second stage after five hours in group I, while in group II there were 6 such patients (Table 2). Irrespective of the dilatation at which drug administration was started i.e. 3cm or 4cm, group I showed shorter mean duration of injection to full dilatation interval (Table 3).

Table 1. Parameters at the time of inclusion.

Factor	Group I	Group II	P Value
Mean age of patients (years)	22.76±2.71	23.25±3.17	>0.5
Mean gestational age (weeks)	39.33±1.07	39.19±1.02	>0.5
Mean initial cervical dilatation (cm/hr)	3.59±0.49	3.58±0.48	>0.5
Mean effacement (%)	65.7±19.51	60.7±17.48	>0.05
Primigravidae (%)	60	60	-
Second gravidae (%)	40	40	-

Table 2. Distribution of cases according to injection to full dilatation interval (duration of 1st stage).

Injection full dilatation interval (min.)	Group I (% cases)	Group II (% cases)	P Value
0-60	37	6	<0.001
61-120	29	24	<0.05
121-180	18	36	<0.02
181-240	7	17	<0.01
241-300	7	10	<0.04
301-360	0	1	-
>360	1	5	<0.001
Mean	113.51±74.23	177.4±105.683	<0.05

Similarly injection to full dilatation interval was shorter in group I whether the patient was primi or second gravida P<0.05 (Table 3).

Mean cervical dilatation rate was significantly greater in group I (3.38 cm/hrs) as against group II (2.17 cm/hrs) (P<0.05). When the rate of cervical dilatation was separately evaluated according to the initial 3 and 4 cm dilatation at which the drug was first administered, cervical dilatation rate was higher in group I. Similarly on comparing primi and second gravidae, group I had higher cervical dilatation rate as against group II. However second gravidae showed higher cervical dilatation rate as compared to primi whether the labor was accelerated by drotaverine or valethamate bromide (Table 3).

The mean injection delivery interval (IDI) was 135.87±85.94 min in group I and 200.13±115.04 min in group II which was statistically significant (P<0.05). The duration of 2nd stage and 3rd stage were statistically not different in group I and group II (P>0.05). Average blood loss in third stage was also same (Table 4).

Table 3. Comparative evaluation of mean duration of injection to full dilatation and cervical dilatation rate.

Name of factor			Group I (%)	Group II (%)	P. value
Mean duration of	(i)	Overall mean	113.51±74.23	177.4±105.68	<0.05
1st stage (injection to	(ii)	3cm initial dilatation	129.7±76.29	199.3±118.1	<0.05
full dilatation) (min)	(iii)	4 cm initial dilatation	102.54±71.36	152.85±71.13	<0.05
	(iv)	Primi	134.23±80.02	189.58±109.24	<0.05
	(v)	2nd gravida	82.93±52.09	143.56±67.05	<0.05
Mean cervical dilatation	(i)	Over all mean	3.38	2.17	<0.05
rate (cm/hr)	(ii)	3 cm initial dilatation	3.23	2.10	<0.05
	(iii)	4 cm initial dilatation	3.51	2.35	<0.05
	(iv)	Primi	2.89	2.01	<0.05
	(v)	2nd gravida	4.55	2.72	<0.05

Table 4. Comparative evaluation of mean duration of IDI, 2nd stage, 3rd stage and mean 3rd stage blood loss.

Name of factor	Group I (%)	Group II (%)	P. value
Mean injection delivery interval (min)	135.87±85.94	200.13±115.04	<0.05
Mean duration of 2nd stage (min)	21.05±17.97	21.39±14.59	>0.5
Mean duration of 3rd stage (min)	4.62±1.46	4.92±1.50	>0.05
Mean 3rd stage blood loss (cc)	104.79±53.41	119.4±99.38	>0.05

In group I, 84% of the cases required only single I/M injection; however in 14% of the cases repeated dose was required and only in 2% cases 3rd dose was needed for full dilatation. Thus average dose of drotaverine required was 1.18±0.43 injections. In group I, 3% of the cases required additional oxytocin infusion for proper contraction while in group II, 13% cases required oxytocin. No decrease in uterine contractions was noted after the administration of both the drugs.

Comparison of the effect of cervical effacement on mean duration of active first stage was also noted in both the groups. In group II, average duration of the first stage was inversely proportional to the effacement of cervix; but in group I, it was not related to the percentage of initial effacement (Table 5).

Minimal minor adverse effects were noted in group I like nausea (3%), vomiting (1%) maternal tachycardia (3%) and dryness of mouth (4%), while comparatively higher incidence of nausea (5%), vomiting (2%), maternal tachycardia (22%), fetal tachycardia (9%), dryness of mouth (22%) and flushing of face (2%) was found in group II which was statistically significant (Table 5).

As far as the mode of delivery is concerned, 99% of the cases in both the groups progressed to second stage and delivered vaginally. Only one case in each group delivered by caesarian section; the indication being fetal distress in group I and arrest dilatation and descent in group II.

Out of the 99% vaginal deliveries, 93% were spontaneous and 6% were assisted by forceps application in both the groups. May be by chance but the indications for forceps applications were exactly the same in both the groups i.e. fetal distress in 5 cases and prolonged second stage in 1 case in each group.

Majority of the patients in both the groups were not having any 3rd stage complications. Mean 3rd stage blood loss and incidence of maternal morbidity was not significantly different in both the groups. Mean apgar score at 1 min and 5 min were almost similar in both the groups (9.76±0.81 in group I 9.63±0.93 in group II, P>0.05). Total neonatal morbidity was 10% in group I and 9% in group II (P<0.5). In group I, four cases were admitted in nursery for neonatal jaundice, three for birth asphyxia, one for low birth weight (LBW), one for coronary heart disease (CHD) and one for congenital malformation, while in group II maximum admissions were for birth asphyxia (6%) and 1 each for Jaundice, LBW and congenital malformation.

Table 5. Comparison of effect of effacement of cervix on mean duration of active 1st stage.

Effacement (%)	Drotavarine group Mean (min)	Valethamate bromide group (n=100) Mean (min)	p value
0–30	116.57±73.14	204.09±94.57	<0.05
40–50	108.77±79.90	184.4±120.77	<0.05
60–70	110.55±67.88	171.97±99.91	<0.05
≥80	119.16±88.77	166.19±101.15	>0.05
Total mean±SD	113.51±74.23	177.4±105.68	<0.05

Table 6. Comparative evaluation of cases according to adverse effect of drug.

Adverse effect	Drotavarine group (n=100)		Valethamate bromide group (n=100)		P value
	No	%	No	%	
Nausea	03	03	05	05	<0.001
Vomiting	01	01	02	02	<0.001
Maternal tachycardia	03	03	22	22	<0.001
Fetal tachycardia	00	00	09	09	-
Hypotension	00	00	00	00	-
Dryness of mouth	04	04	22	22	<0.001
Fever	00	00	00	00	-
Rash	00	00	00	00	-
Flushing of face	00	00	02	02	-

Table 7. Comparative evaluation of previous studies.

S. No	Authors /yr	Drotaverine dosage	Cx. dil. rate (cm/hr)	Dur of 1st stage (min)	IDI (min)	S/E	Valethamate bromide dosage	Cx dil rate (cm/hr)	Dur of 1st stage (min)	IDI	S/E
1.	Baser[4] (1993)	-	-	-	-	-	16mg I/V in D 5% at 16 dr/min at 2.5-3.5 cm cx. dil. at 2-3 contr.	-	204	-	-
2.	Kaur[5] (1995)	-	-	-	-	-	In D 5% at 16 dr/min at 3-4cm cx. dil. at 2-3 contr.	1.94	220 (3.67 hr.)	-	-
3.	Purwar[6] (1996)	-	-	-	-	-	In D 5% at 20 dr/min at 3-4cm cx. dil. after amniotomy	2.90±1.74		183 (3.05 ±1.33 hr)	T, V, DM, F
4.	Blasko[7] (1998)	40mg I/M at 4 cm cx. dil. at 2-3 contr.	-	183.6 ±121.1	209.0	None	-	-	-	-	-
5.	Singh[8] (2000)	40mg i/m at ≥ 3cm dil, 3 hrly max. upto 3 doses	-	165	-	None	-	-	-	-	-
6.	Sharma[9] (2001)	40mg i/m at 4cm cx. dil. at 2-3 contr. 2 hrly, max-3	2.04	-	194	H-4% T-4%	8m g I/M hrly for 3 doses	1.87	-	220.7	DM 10% T 20%, F 41%
7.	Mishra[10] (2002)	40mg I/V 2 hrly, max-3	Primi 2.05, multi 3.68	Primi 205, multi 105	-	2% cases	8mg ½-1 hrly I/V, max-6	Primi-1.53, multi-2.00	Primi-255, multi 210	8% -	cases
8.	Kaur[11] (2003)	40 mg 2/m at 3-4 cm cx. dil. 2 hrly, max-3	3.99 ±2.21	116.34 ±59.44	149.82 ±63.75	H 3.2% T 4.0%	8mg I/M at 3-4cm 1 hrly upto max-3	2.74±1.72	158.78 ±58.98	191.32 ±60.47	H-2%, DM-10%, T28%, F-6%
9	Pai et al[12] (2003)	40mg I/M at 3-4cm cx. dil.	-	Primi-194.3 ±116.3, multi-165.8 ±107.4	-	None	-	-	-	-	-
10	Khosla[13] 2003	40mg I/M at 4cm cx. dil. 2 hrly, max upto 3	-	175.92 ±90.56	-	None	8mg I/M at 4 cm cx dil 1/2 hrly for 3 doses	-	132.64 ±60.24	-	Min mat S/E
11.	Present study 2000	40mg I/M at 3 or 4 cm cx dill, can be repeated after 2 hrs if cx dil ≤ cm, max-2	Total 3.38 Primi-2.89 multi 4.55	113.51 ±74.23	135.87 +85.94	N-3% V-1% T-3% DM-4%	V,br,16mg I/V in D 5% at 16 drugs/min.	Total 2.17 primi 2.01 multi 2.72	177.4 ±105.68	200.13 ±115.04	N-5% V-2% Mat T22% F, T9% DM 22% F2%

Discussion

Acceleration of labor is considered to be an important factor in reducing maternal morbidity as well as the neonatal complications. Since long back valethamate bromide is used to relieve cervical spam. It can be given intramuscularly or as slow intravenous infusion and its efficacy is proved to be more with intravenous infusion [4-6].

A newer drug, drotaverine is an isoquinoline derivative. It is safe and very effective in shortening the duration of labor. It acts by increasing the intracellular concentration of substrate camp, which produces cervical dilatation. The smooth muscle cone of the uterine cervix which remains normally contracted during pregnancy till early labor, starts relaxing near term when cervix is taken up. Once contraction sets in, this cone is situated above the equator of the fetal head. This pulling up process requires adequate relaxation of the smooth muscle cells of muscle cone. Dilatation of the smooth muscle cone helps the rest of the ground substance of the cervix to respond to uterine contractions [12].

In the present study, IV continuous infusion of valethamate bromide was given and the results were compared with IM drotaverine. Cervical dilatation rate in the present study with valethamate bromide infusion is comparable with previous studies. Purwar [6] reported a slightly higher cervical dilatation rate but they have given IV infusion at the rate of 20 drops/min instead of 16 drops.

Intramuscular administration of drotaverine in the dilatation of cervix in uncomplicated pregnancies significantly reduces the duration time of dilatation and the total delivery time. It reduces the number of cervical tears. The drug is safe, and does not alter the delivery parameters[7]. In the present study, duration of the injection to full dilatation is significantly shorter in the drotaverine group i.e. 113.51±85.94 min which is very similar to the results of Kaur [5]. Blasko [7] has reported 183.6±121.1 min average duration of first stage which is higher in comparison to the results of the present study but they have given only single injection to 97% of the cases, while in the present study 16% of the cases were considered for repeat dose if dilatation was ≤7cm after 2 hours of first injection. Oxytocin infusion wad added as and when needed as per obstetrician's judgment.

Singh et al [9] repeated the injection after 3 hours instead of 2 hours of the 1st dose, and reported 1st stage duration of 165 min. Drotaverine improves the cervical dilatation rate which is supported by various previous studies (Table 7). In the present study, cervical dilatation rate was significantly higher in drotaverine group in comparison to valethamate bromide. Results are similar to the results of the study done by Kaur[11].

Drotaverine is associated with higher cervical dilatation, shorter 1st stage duration and very less adverse effect in therapeutic doses as compared to valethamate bromide [9-11]. In the present study also, drotaverine group had higher cervical dilatation rate, shorter duration of labor and minimal minor side effects as compared to valethamate bromide infusion, whether given in primi gravidae or second gravidae, whether given at 3 cm or 4 cm initial dilatation. However the cervical dilatation rate and 1st stage duration was shorter when either of the drugs was administered at 4 cm dilatation and in multigravidae

Valethamate is associated with higher incidence of adverse effect due to its anticholinergic properties[6,9-11]. Drotaverine does not produce any adverse effects in therapeutic doses (40-80mg)[7]. The present study also shows significantly higher incidence of minor adverse effect associated with valethamate bromide infusion like maternal and fetal tachycardia, dryness of mouth and flushing of face. Duration of the 2nd stage, 3rd stage, operative interference, maternal complications and neonatal outcome were similar in both drotaverine and valethamate bromide.

Conclusion

Drotaverine is a superior cervical dilatation agent as compared to valethamate bromide. Its timely administration helps in a smooth and faster progress of labor by virtue of faster cervical dilatation with minimal side effects.

References

1. Blasko G. Pharmacology, mechanism of action and clinical significance of a convenient antispasmodic agent: drotaverine. J Am Med Assoc Ind. Physicians' Update 1998;1:63-9.
2. Gupta K. Emerging role of drotaverine in emergency medicine: A review. J Am Med Assoc Ind Physicians' Update 1999;2:57-64.
3. Czeizel AE, Rockenbauer M. The evaluation of Drotaverine intake during pregnancy on fetal development. Prenat Neonatal Med 1996;1:137-45.

4. Baser A, Desai SV, Daftari SN. Acceleration of labor by epidosin. J Obstet Gynecol India 1993;43;217-20.

5. Kaur D, Saini AS, Lata S. Effect of intravenous infusion of epidosin on labor. J Obstet Gynecol India 1995;45:708-10.

6. Purwar M, Balsara R. Acceleration of labor by intravenous epidosin in primigravidae. A randomized controlled trial. Indian J Clin Pract 1996;6:71-2.

7. Blasko ST, Demeter J. The effect of intramuscularly administered drotaverine on dilatation stage of uncomplicated deliveries. Obstet Gynecol Today 1998;3:723-37.

8. Singh P, Singh A. The effect of intramuscular injection drotaverine on the first stage of labor in uncomplicated vaginal deliveries. Abstract Book of VII conference of Bihar Obstetrics and Gynecology Society 2000;89-90.

9. Sharma JB. Pundir P, Kumar A. et al. drotaverine hydrochloride vs Valethamate bromide in acceleration of labor. Int J Gynaecol Obstet 2001;74:255-60.

10. Mishra SL, Toshniwal A, Banjerjee R. Effect of drotaverine on cervical dilatation. A comparative study with epidosin (Valethamate bromide). J Obstet Gynecol India 2002:52:76-9.

11. Kaur D, Kaur R. Comparison of drotaverine and epidosin in first stage of labor. J Obstet Gynecol India 2003;53:449-52.

12. Pai M.V., Shree Kumar S, Gupta K, et al. Effect of drotaverine on the active phase of labor. A controlled clinical trial. Obstet Gynecol Today 2003;8:611-4.

13. Khosla AH, Bala I, Dahiya K, et al. A comparative study of the efficacy of valethamate bromide with drotaverine in normal labor. J Obstet Gynecol India 2003:53:568-70.