Original Article

Effectiveness and safety of drotaverine hydrochloride on first stage of cervical dilatation and in labor pain management — A Meta-analysis

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Labor is a complex process that involves many factors such as myometrial contraction, cervical ripening, dilatation and the expulsion of the fetus and placenta. Prolonged labor increases the incidence of maternal distress, PPH, birth canal injury and puerperal sepsis. Fetus is also exposed to higher risk of infection, asphyxia, intracranial stress and increased incidence of operative delivery. Therefore, providing relief from labor pain and shortening duration of labor is a challenge for obstetricians. There are various agents now in use as smooth muscle relaxants which inhibit spasm that impairs cervical dilatation. They include hyoscine,valethamate bromide and drotaverine hydrochloride. The purpose of the meta-analysis was to assess efficacy, safety and potency of drotaverine hydrochloride in terms of duration of first stage of labor, incidence of cervical tears, maternal and fetal outcomes and cervical dilatation rate. Literature search was made using inclusion and exclusion criteria and comprehensive meta-analysis was carried out. All the studies carried out in comparing the efficacy of drotaverine and valethamate consistently showed that there is a significant decrease in first stage labor, pain duration and a significant increase in cervical dilatation rate with drotaverine as compared to valethamate. Drotaverine has definitely proven to be superior in shortening the duration of first stage of labor and significantly increases cervical dilatation rate as compared tovalethamate bromide thus providing a convenient, shorter, physiological and uncomplicated delivery without any adverse effects on maternal and neonatal outcome.

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Key words **: Labor, Cervical dilatation, Spasmolytic, Drotaverine, Valethamate, Meta-analysis.**

Agony and stress experienced by women due to labor pain is beyond description. Shortened duration, reduction of pain in labor and early return to the routine activity are cherished dreams of every woman in labor and also desired by the majority of obstetricians. Prolonged labor pain leads to increased incidence of maternal distress, which is one of the causes for the incidence of operative delivery[1]. The most common cause of prolongation of first stage of labor is cervical spasm leading to cervical dystocia[2]. Effacement and subsequent dilatations of the cervix are markers of the progress and duration of labor. Progress of labor is assessed by progressive dilatation of the cervix and progressive descent of presenting part[3]. It has been proven that the cervical dilatation is one of the important factors, which determines the duration of labor and uterine activity. The dilatation stage has a variable time course determined by the initial stage of the uterine orifice, the intensity of labor pains, constitutional characteristics of the parturient and by the fact, whether parturient is a primipara or multipara.Inhibitory impulses in the form of spasm often impair the dilatation of cervix and prolong the duration of labor despite good uterine contractions[2].

Providing pain relief during labor reduces maternal stress and results in shortening of labor with improved maternal and fetal outcome during delivery. Many clinical trials have been carried out on the acceleration of labor to prevent the risks of prolonged labor such as maternal exhaustion, infection, dehydration and ketoacidosis. Since all these causes increase physiological burden for the mother, these events may eventually cause complications in the second stage of labor and puerperium. Thus a short firststage of the labor is naturally of dual advantage for both obstetricians and pregnant women[4].

Ideal pharmacological agent for management of labor :

An ideal pharmacological agent should help in dilatation and effacement of cervix thereby shortening the duration of first stage of labor without interfering with myometrium activity, second and third stage of labor; with no harmful effects to mother and fetus. Commonly used pharmacological agents in the management of labor are tran-

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quilizers or prostaglandins, which are associated with harmful effects on both mother and fetus. Anticholinergic agents like hyoscine and valethamate bromide are also used but these have side effects like dry mouth, tachycardia, blurred vision etc, and are contraindicated in women with glaucoma, severe hypertension, paralytic ileus and ulcerative colitis. Most commonly used agent is drotaverine hydrochloride, which is an isoquinoline derivative having a powerful spasmolytic action on smooth muscle cells. Drotaverine acts through PDE-IV inhibition having PDE-IV isoenzyme selectivity, calcium blocking effect, low anti-aggregatory effect and sodium channel antagonistic effect. Further, drotaverinelacks cardio toxic effect due to its PDE IV isoenzyme selectivity, sodium channel antagonistic effect and calcium channel antagonistic effect[5]. Therefore, an attempt has been made to analyze the results of drotaverine from various studies in terms of efficacy, safety and potency against comparators using comprehensive meta-analyses.

Materials and Methods

Literature search was made using following inclusion and exclusion criteria —

Inclusion criteria :

(a) Randomized trials of comparative studies of drotaverine in the management of labor.

(b) Regular established uterine contractions at the rate of at least two contractions per 10 minutes, each contraction lasting for at least 40-45 seconds.

Exclusion criteria :

(a) Induced labor.

(b) If any spasmolytic agent had been used within 48 hours.

As per the inclusion and exclusion criteria, eligible studies published in bibliographic electronic databases such as MEDLINE, EMBASE, CINAHL and LILACS were searched up to March 2015. Eligible studies were analyzed on the following clinical endpoints:

(a) duration of first stage of labor

(b)incidence of cervical tears

(c) maternal and fetal outcomes and

(d) cervical dilatation rate.

Meta-analysis methods :

Meta-analysis was performed in two stages. In the first stage measures of treatment effect with its 95% confidence interval (CI) was calculated for each individual study. In the second stage an overall treatment effect was calculated as a weighted (inverse of the variance of the treatment effect) average of the individual summary statistics. Treatment effect of mean scores were assessed by standardized mean difference (SMD), which was calculated based on study size, mean score and level of significance. For a dichotomous outcome measure the treatment effect was assessed based on odds ratio (OR) and Mantel-Haenszelrisk ratio.

Since each study was carried out with different samples, the sampling error variability is likely to be high in a meta-analysis. The other source of heterogeneity might be due to characteristics of the samples, variations in the treatment, in the design quality and so on. Therefore, assessing the heterogeneity in meta-analysis is a crucial issue because the presence versus the absence of true heterogeneity (between studies variability) canaffect the statistical model. The presence of true heterogeneity has been tested using Q test, which follows a chi-square distribution with k–1 degrees of freedom, k being the number of studies. When not rejecting the homogeneity hypothesis a fixed-effects model was adopted. However, the strength of the Q statistic depends on the number of studies that will be included in the meta-analysis. Therefore, I^2index obtained by dividing the difference between the result of the Q test and its degrees of freedom by the Qvalue itself was also used in percentage values along with Tau-square, which indicates the degree of heterogeneity. Comprehensive meta-analysis software (evaluation version), which incorporated all the above statistical procedures was used for the present meta-analysis. Studies with at least 25 subjects were included for analysis and for statistical significance $P<0.05$ was considered. The treatment effect and its 95% CI of each study and over effect were shown in forest plots.

Ethics : The Nature of manuscript is based on Meta-analysis from the published articles. Therefore, the issue of ethics doesn't arise.

Results

Duration of first stage of labor:A total of 18 randomized studies were identified as per the inclusion and exclusion criteria. The mean duration (minutes) of first stage of labor was available for 15 studies (Table 1). Out of these 15 studies 12were carried out with drotaverine drug (Group

Table 1 — *Clinical studies on drotaverine and its role in reduction in duration of 'first stage of labor*

Studies	No. of Subjects	Mean duration of first stage labor (in minutes)		
		Drotaverine(n)	Valethamate(n)	Control(n)
NagariaT*et al*[4]	200	113.5 (100)	177.4 (100)	-
Roy A*et al*[6]	200	148.9 (100)	-	331.6 (100)
Singh KC *et al*	100	265.4 (44)	-	312.3 (40)
Pai MV *et al*[7]	281	156 (141)	-	222 (140)
Sharma JB *et al*[1]	150	194 (50)	220 (50)	412.8 (50)
Sankar M *et al*[8]	300	174.5 (100)	196 (100)	344.7 (100)
Poornima RR *et al*[9]	200	190 (100)	-	250 (100)
Kaur D *et al*[2]	300	116 (250)	158 (50)	-
Mishra SL *et al*[10]	150	205 (50)	275 (50)	373 (50)
JayashreeS *et al*[13]	200	123.1 (100)	160 (100)	-
Dahal P *et al*[14]	300	178.3 (100)	254.3 (100)	346.3 (100)
Ibrahim MI *et al*[15]	352	120.7 (176)	-	200.8 (176)
Demeter J *et al*[16]	200	183.6 (100)	-	236.2 (100)
Kalhon P *et al*[19]	100	331.4 (50)	-	145.1 (50)
Ashraf S *et al*[20]	450	179.1 (150)	198.6 (150)	299.0 (150)

A) involving 1,161subjects with drotaverine drug (Group A) and 1,156 subjects with control (Group B). All the above trials had shown that the 'duration of first stage of labor' was significantly lower (P value <0.05) in the patients who were given drotaverine compared to control group.Meta-analysis was carried out using these 12 studies results by assuming that all the studies had similar effect with similar kind of study subjects (Fixed effect model). The forest plot of meta-analysis is shown in Fig 1. All the studies showed that there was a significant (P value <0.05) decrease in pain score due to drotaverine as compared to control. The overall effect size (95% C.I) for favoring the drotaverine is estimated to be 0.283 (95%C.I: 0.201-0.365) and it is statistically significant (Z=6.78; P value <0.001).Heterogeneity test (Tau-square=0.00, Chi-square=2.38;df=11; P value=0.997; I2=0) indicate that there is no heterogeneity among the studies and confirming that the fixed effect assumption is valid. The conclusion is that all the studies consistently showed a significant decrease in pain duration due to drotaverine drug compared to control group.

A total of eight studies (Table 1) were conducted in comparing the efficacy of drotaverine (Group A) with that of valethamate (Group B) involving 900 and 700 subjects in the respective drug groups. The forest plot of meta-analysis is depicted in Fig 2 and the treatment effect of all the trials were found to be statistically significant (P<0.05).

Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Roy A et al	-0.285	0.142	0.020	-0.564	-0.007	-2.007	0.045
Singh KC et al	-0.445	0.221	0.049	-0.878	-0.011	-2.011	0.044
Pai MV et al	-0.240	0.120	0.014	-0.475	-0.006	-2.006	0.045
Sharma JB et al	-0.406	0.202	0.041	-0.802	-0.010	-2.010	0.044
Sankar M et al	-0.285	0.142	0.020	-0.564	-0.007	-2.007	0.045
Poornima RR et al	-0.285	0.142	0.020	-0.564	-0.007	-2.007	0.045
Mishra SL et al	-0.406	0.202	0.041	-0.802	-0.010	-2.010	0.044
Dahal P et al	-0.285	0.142	0.020	-0.564	-0.007	-2.007	0.045
Ibrahim MI et al	-0.214	0.107	0.011	-0.424	-0.005	-2.006	0.045
Demeter J et al	-0.285	0.142	0.020	-0.564	-0.007	-2.007	0.045
kalhon P et al	-0.406	0.202	0.041	-0.802	-0.010	-2.010	0.044
Ashraf S et al	-0.232	0.116	0.013	-0.460	-0.005	-2.006	0.045
	-0.283	0.042	0.002	-0.365	-0.201	-6.783	0.000

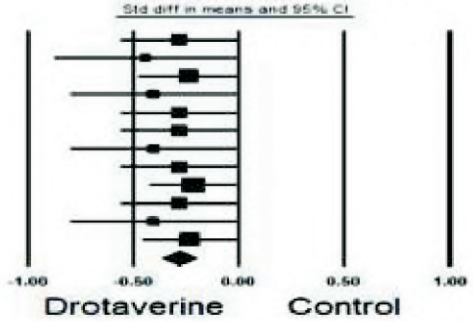

Fig 1 — Impact of Drotaverine drugs on duration of first stage labor compared to control

The overall effect size (95% CI) favoring the drotaverine drug was estimated to be 0.294 (95%C.I: 0.191-0.397) and it is statistically significant (Z=5.60;P value <0.001). Heterogeneity test (Tau-square=0.00, Chi-square=0.93; df=7; P value=0.996; I^2=0) indicate that there is no heterogeneity among the studies and the conclusion is that all the studies consistently showed a significant decrease in pain duration due to drotaverine compared to valethamate.

Incidence of cervical tears (%): A total of seven studies (Table 2) were carried out in comparing the incidence of cervical tears due to drotaverine (Group A) with that of control (Group B) involving 716 subjects in each drug groups. The forest plot of meta-analysis is shown in Fig 3 and the treatment effect of individual study results showed that only one study (Demeter J, *et al*) differed significantly between the drotaverine drug and control. However, the overall effect size (95% C.I) 0.102 (95%C.I: 0.053-0.198) favoring the drotaverine drug was found to be significant (Z=6.80; P value =0.000). Heterogeneity test (Tau-square=2.93, Chi-square=19.83; df=6; P value =0.003; I^2=69.73) indicated that there was a heterogeneity among the studies. However, while fitting random effect model the overall effect size (95% C.I) 0.232 (95% C.I: 0.048-1.115) was not statistically significant (P>0.05). The conclusion is that even though individual study results (except one) did not show significant difference, the overall effect size derived from fixed effect model showed a significant decrease in cervical tears incidence rate due to drotaverine compared to control group.

Out of four studies, which reported incidence of cervical tears for both drotaverine (Group A) and valethamate (Group B), two studies showed zero incidence in both the drug groups. Based on the remaining two studies involving 210 subjects in each group forest plot of meta-analysis is shown in Figure 4.The overall effect size (95% CI) for favoring the drotaverine drug was estimated to be 0.246 (95% CI: 0.027-2.22) and it is not statistically significant (Z=1.25; P=0.212). The conclusion is that there is no strong evidence to state that the cervical tears incidence rate due to drotaverine is significantly less as compared to valethamate.

Maternal and fetal outcome: All mothers who received drotaverine injection gave birth to babies having APGAR score of 8-10 for about 90% of children compared to comparator(s), which had also recorded almost similar score (Table 3). Therefore, meta-analysis for APGAR score could not be carried out due to the fact that in more than 90% of study subjects treated with either of the drugs (drotaverine/valethamate) or acted as control, the APGAR score was shown to be between 8 and 10 in

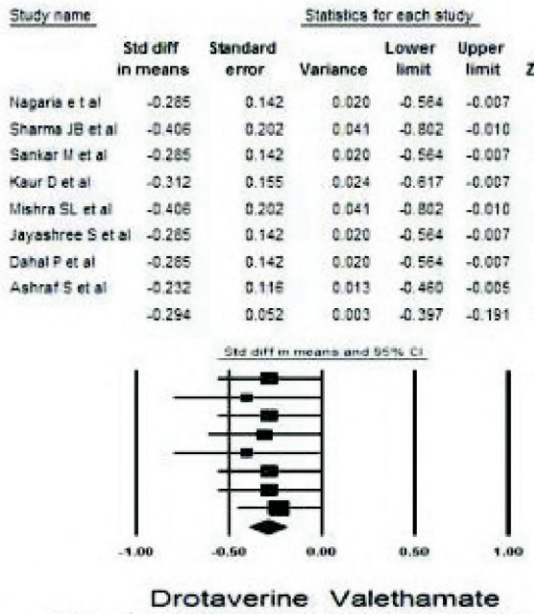

Fig 2 — Impact of Drotaverine and Valethamate drugs on duration of first stage labor

majority of the studies. Further, based on range of values of APGAR score no meaningful meta-analysis could be carried out.

Cervical dilatation rates (%) : Out of 13 clinical studies (Table 4) only seven were found to be eligible for meta-analysis in comparing the cervical dilation rates (%) between drotaverine (group A) and control (group B) involving 625 and 624 study subjects in the respective drug groups. The forest plot of meta-analysis is shown in Fig 5 and all the seven studies showed a significant (P value <0.05) increase in cervical dilatation rate due to drotaverine compared to control. The overall effect size (95% C.I) for favoring the drotaverine drug was estimated to be 0.291 (95%C.I: 0.179-0.403) and it is statistically significant (Z=5.11; P value =0.001).Heterogeneity test (Tau-square=0.00, Chi-square=2.09; df=6;P value =0.910; I^2=0) indicated that there is a homogeneity among the studies and the conclusion is that all the studies are consistently showing the significant increase in cervical dilatation rate due to drotaverine as compared to control.

A total of 10 studies (Table 4) reported cervical dilatation rate for both drotaverine (Group A) and valethamate (Group B) involving 1,009 and 809 study subjects in the respective drug groups. The forest plot of meta-analysis is shown in Fig 6. The overall effect size (95% CI) for favoring the drotaverine drug was 0.305 (95%C.I: 0.209-0.401) and statistically significant (Z=6.23; P value =0.001). Heterogeneity test (Tau-square=0.00, Chi-square=1.53; df=9; P value =0.99; I^2=0) indicated that there is no heterogeneity among the studies and the conclusion is that all the studies are consistently showing the significant increase in cervical dilatation rate due to drotaverineas compared to valethamate.

Discussion

Labor is a multifactorial process, which involves myometrial contraction, cervical ripening, dilatation and the expulsion of the fetus and placenta. Providing relief from labor pain is always a challenge for gynecologists and obstetricians. Shortening of labor pain results in improved maternal and fetal outcome because in prolonged labor, the incidence of maternal distress (dehydration, ketoacidosis), PPH, birth canal injury and puerperal sepsis are more with resultant increase in maternal morbidity. Fetus is also exposed to higher risk of infection, asphyxia, intracranial stress (due to excessive cranial moulding) and increased incidence of operative delivery[1]. There are various agents now in use as smooth muscle relaxants, which inhibit spasm that impairs cervical dilatation. They include anticholinergic agents like hyoscine, valethamate bromide, and directly acting antispasmodics like drotaverine hydrochloride. The anticholinergic agents have side effects like dry mouth, tachycardia, blurred vision etc, and are contraindicated in women with glaucoma, severe hypertension, para-

Table 2 — *Clinical studies on Incidence of cervical tears*

Studies	Incidence of cervical tears (%)		
	Drotaverine (n)	Valethamate (n)	Control (n)
Pai MV *et al*[7]	0.7 (140)	-	2.3 (140)
Roy A *et al*[6]	Reduced incidence (100)	- (100)	
Mishra SL *et al*[10]	0 (50)	0 (50)	2 (50)
Sankar M *et al*[8]	0 (100)	0 (100)	2 (100)
Poornima RR *et al*[9]	1 (100)	-	1 (100)
Jayashree S *et al*[15]	0 (100)	1 (100)	-
Ibrahim MI *et al*[13]	1.9 (176)	-	1.3 (176)
Demeter J *et al*[16]	3 (100)	-	61 (100)
Ghosh A[17]	0 (110)	2 (110)	-
Kalhon P *et al*[19]	0 (50)		8 (50)

Table 3 — *Clinical studies on APGAR Score of new born babies*

Studies	APGAR Score (at 5 minutes)		
	Drotaverine	Valethamate	Control
Pai MV *et al*[7]	9 for 99.25%, 8 for 0.75 %, <8 none (141)	-	9 for 96.80 % and 8 for 2.34 %, <8 for 0.78 % (140)
Mishra SL *et al*[10]	8/10 for 100 % (50)	8/10 for 98 % (50)	8/10 for 98 % (50)
Sankar M *et al*[8]	7-10 for 98 % (100)	7-10 for 92 % (100)	7-10 for 92 % (100)
Poornima RR *et al*[9]	6-8 in 4% and 8-10 in 88% (100)	-	6-8 for 4% and 8-10 for 88% (100)
Nagaria T *et al*[8]	9.76 (100)	9.63 (100)	-
Singh KC *et al*[18]	9.96 (44)	-	9.93 (40)
Palii SB *et al*[12]	8-10 in 92% (50)	8-10 in 86% (50)	-
Ibrahim MI *et al*[13]	9 (176)	-	9 (176)
Demeter J *et al*[16]	9.68 (100)	-	9.32 (100)
Ashraf S *et al*[20]	9.1 (150)	9.2 (150)	9.2 (150)

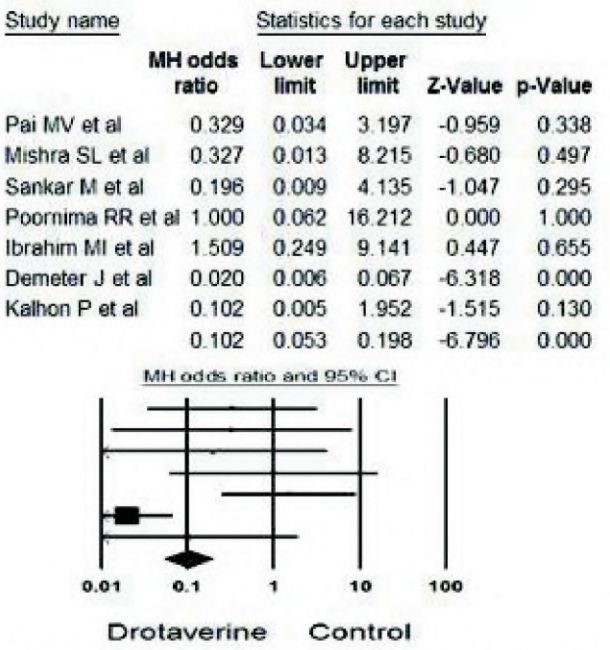

Fig 3 — Impact of Drotaverine drug on incidence of cervical tears (%) compared to control

lytic ileus and ulcerative colitis.

Smooth muscle constitutes approximately 10% of the cervix[21] which forms the physiological background for the use of various smooth muscle relaxants in the stage of dilation of labor to produce good effect on the consistency and dilation of cervix.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. Drotaverine, a well-established therapeutic agent that directly acts on smooth muscles through selective inhibition of phosphodiesterase-IV isoenzyme may help to facilitate dilatation of cervix and is free from anticholinergic side effects. It is a superior smooth muscle relaxant which acts specifically

Table 4 —*Clinical studies on role of drotaverine on 'cervical dilatation'*

Studies	Cervical dilatation rates (cm/h)		
	Drotaverine	Valethamate	Control
Madhu C *et al*[11]	3 (49)	2.4 (49)	1.9 (48)
Nagaria T *et al*19	3.3 (100)	2.1 (100)	-
Sharma JB *et al*[5]	2.04 (50)	1.87 (50)	1 (50)
Kaur D *et al*[12]	3.99 (250)	2.74 (50)	
Singh KC *et al*[18]	1.2 (44)	-	-
SankarM *et al*[8]	2.71 (100)	2.39 (100)	1.35 (100)
Mishra SL *et al*[10]	2.05 (50)	1.53 (50)	1.13 (50)
Palii SB *et al*[12]	1.92 (50)	1.44 (50)	-
Jayashree S *et al*[13]	3.31 (100)	2.58 (100)	-
Ibrahim MI *et al*[15]	2.7 (176)	-	1.8 (176)
Ghosh A[17]	3.45 (110)	1.3 (110)	-
Kalhon P *et al*[19]	2.3 (50)	-	1.3 (50)
Ashraf S *et al*[20]	2.6 (150)	2.3 (150)	2.0 (150)

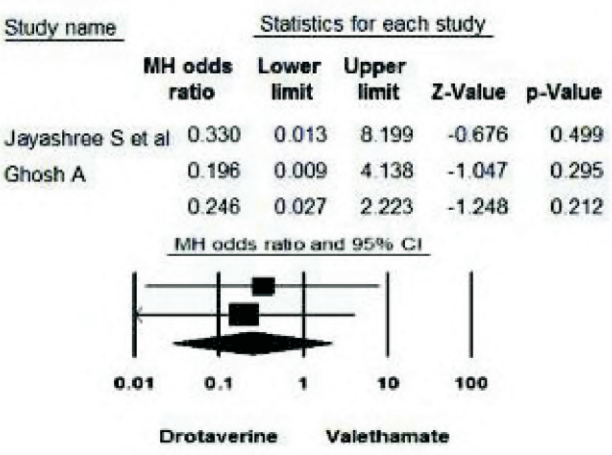

Fig 4 — Impact of Drotaverine and Valethamate drugs on incidence of cervical tears (%)

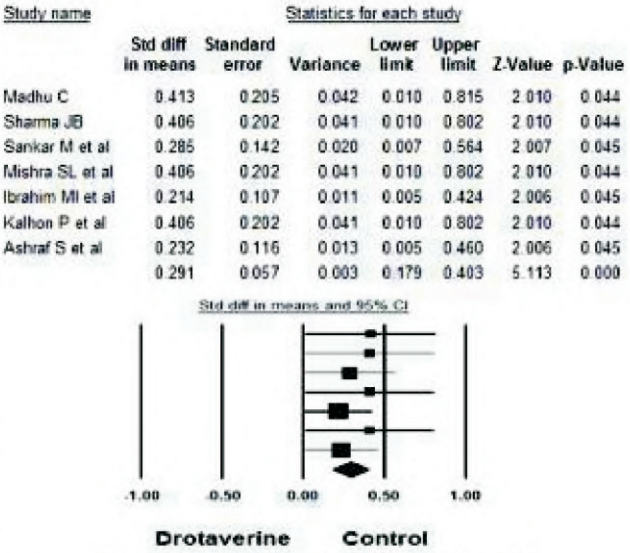

Fig 5 — Impact of Drotaverine drug on cervical dilation compared to control

on spastic sites and corrects the cAMP and calcium balance relieving smooth muscle spasm.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. 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 sub-

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Madhu C	0.410	0.204	0.042	0.010	0.810	2.010	0.044
Nagaria T	0.285	0.142	0.020	0.007	0.564	2.007	0.045
Sharma JB	0.406	0.202	0.041	0.010	0.802	2.010	0.044
Kaur D et al	0.312	0.155	0.024	0.007	0.617	2.006	0.045
Sankar M et al	0.285	0.142	0.020	0.007	0.564	2.007	0.045
Mishra SL et al	0.406	0.202	0.041	0.010	0.802	2.010	0.044
Palli SB et al	0.406	0.202	0.041	0.010	0.802	2.010	0.044
Jayashree S et al	0.285	0.142	0.020	0.007	0.564	2.007	0.045
Ghosh A	0.272	0.135	0.018	0.006	0.537	2.007	0.045
Ashraf S et al	0.232	0.116	0.013	0.005	0.460	2.006	0.045
	0.305	0.049	0.002	0.209	0.401	6.229	0.000

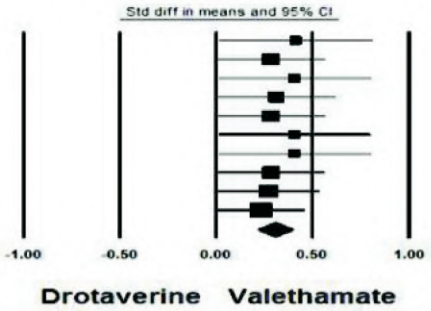

Fig 6 — Impact of Drotaverine and Valethamate drugs on cervical dilation

stance of the cervix to respond to uterine contractions. Use of drotaverine during pregnancy is free of any teratogenic and embryotoxic effects[4].

The use of drotaverine in the first stage of labor for hastening cervical dilatation, reducing duration of labor and consequently providing significant pain relief is well established by various trials done in India and internationally. Further, in one of the studies[7] carried out in India the effect of drotaverine is more in multigravida than in primigravida. Thus, due to its efficacy and safety drotaverine is widely used in first stage of labor for cervical dilatation and labor pain management, which is safe for mother as well as fetus. In the present meta-analysis it has been established that all the studies consistently showed a significant treatment effect in favor of drotaverineas compared to valethamate and control group. In addition to reduction in duration of first stage of labor, drotaverine is found to be promising candidate in increasing the dilatation rate that is essential for uncomplicated pregnancies. All mothers who received drotaverine injection gave birth to babies having APGAR score of 8-10 for about 90% of children compared to comparator(s), which had also recorded almost similar scores. Further, the combined study results suggested that drotaverine significantly ($P<0.05$) reduces the incidence of cervical tears.

Conclusion

Around 20 clinical trial studies with more than 3900 women have concluded that drotaverine has definitely proven to be superior in shortening the duration of first stage of labor and significantly increase cervical dilatation rate as compared to valethamate bromide and hyoscine thus providing a convenient, shorter, physiological and uncomplicated delivery without any adverse effects on maternal and neonatal outcome. It does not cause fetal asphyxia. Drotaverine is free from fetal and maternal anticholinergic side effects which are commonly seen with anticholinergic agents like hyoscine and valethamate bromide and it is a safe drug to augment labor, resulting in better maternal and fetal outcome as compared to comparator(s). Hence drotaverine can be used as first line of drug for cervical dilatation and augmentation of labor.

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Authors' contribution : JB Sharma conceptualized the idea, collected data for meta-analysis and wrote the manuscript. P.Vanamail carried out meta-analysis, incorporated the statistical aspects and involved in writing the manuscript. Both the authors have read and approve the final version of the manuscript.

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