COMPARATIVE EFFICACY OF DROTAVERINE HYDROCHLORIDE AND VALETHAMATE BROMIDE ON CERVICAL DILATATION IN ACTIVE LABOUR

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BONAFIDE CERTIFICATE

This is to certify that the study entitled "**Comparative Efficacy of Drotaverine Hydrochloride and Valethamate Bromide on Cervical Dilatation in Active Labour**" is the bonafide work done by **Dr.B.Farhana Sulthana,** at the Institute of Obstetrics and Gynaecology and Govt. Hospital for Women and children, attached to Madras Medical College, Chennai during the period of her Post Graduate study for MD Branch II Obstetrics and Gynaecology, from 2003 – 2006 under the guidance of **Prof.Dr.Latha Jawahar, M.D. DGO.,**

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CONTENTS

INTRODUCTION

Labour is a natural physiological phenomenon of child birth. It is a multifactorial spontaneous process which involves myometrial contractions, cervical ripening and dilatation, and expulsion of the fetus and placenta in an orderly manner. In the process of labour, polarity of the uterus is maintained by active contraction of upper uterine segment. The driving forces of uterine contraction act upon the cervix which plays the role of innocent obstruction due to passive tissue resistance. It has been proved that cervical dilatation is one of the important factors which determine the duration of labour

Sometimes it is observed that although uterine contractions are good, the cervix fails to dilate or dilates very slowly or partially. The most common cause of prolonged first stage of labour is cervical spasm due to the overactivity of the circular muscle fibres of cervix, which may be increased in presence of inflammation injury or fibrosis of cervix or due to fear tension pain syndrome. Prolonged labour results in maternal exhaustion. At this crucial juncture, some medication which overcomes the functional overactivity of the circular muscles of

cervix, without giving rise to complications would help the patient and the obstetrician.

Active management of labour was introduced into clinical practice in 1963 at National Maternity Hospital, Dublin. It's aim was to reduce maternal and fetal distress, shorten the duration of labour and anticipation and management of complications. Cervical smooth muscle relaxants are well accepted addendum to the principle of active management of labour. The present study was done to compare the efficacy of Drotaverine hydrochloride and Valethamate bromide on cervical dilatation in active labour in relation to a control group.

AIM OF STUDY

The study is a prospective study design which aims

1. To find out the average duration of Active phase of labour in normal term parturient in primigravidae and multi gravidae.

2. To compare the effects of drugs Drotaverine Hydrochloride and Valethamate Bromide in

a. Shortening the duration of active phase of labour

b. Side effects on mother and fetus if any.

REVIEW OF LITERATURE

HISTORICAL ASPECTS :

Valethamate bromide was described by ***Steinmann*** in ***1953***. It causes reduction in duration of labour by 18-30 % as described by ***Beck*** in ***1956***, ***Schildbach 1954*** and ***Kishore N*** and ***Agarwal 1962***.

It normalizes the irregular uterine contractions and improves the process of cervical dilatation as described by ***Walter 1957***.

Prof. Anjaneyulu et al 1973 observed the shortening of Ist stage due to faster cervical dilatation compared to control group by 35 % but did not observe any effect on second or third stage of labour

Bhau et al 1979 claimed that average time taken for full cervical dilatation becomes shorter after injection of Valethamate bromide, irrespective of the initial cervical dilatation and parity of the patient.

Shrivastava et al 1979 did not find any change in the basal tone and in the intensity of uterine contractions by tachometric assessment. The same team found 45 % reduction in first stage of labour in primi and 46 % in multi and no change in

second stage of labour.

Prof. Bhattacharjee et al in ***1983-84*** observed 89 % cases of spontaneous vaginal deliveries 4 % cases of abdominal deliveries and 5 % forceps deliveries with Valethamate.

A. E. Czeizel and ***M. Rocker Baurer (1989-90)*** studied about Drotaverine hydrochloride in detail, and its teratogenic effect on the fetus as this was developed mainly for threatened abortion initially.

Shepard TH – John Hopkins University (1992) also studies the effect of this drug in hastening cervical dilatation and found favorable results.

Dr. Jones Demeter (1996) did extensive analysis of this drug in first stage of labour and found 50 – 60% reduction in the duration of labour.

Goswami B, Sarkar M, and Biswas B, who presented the efficacy of Drotaverine in the active management of labour, at the XVI FIGO World Congress of Gynecology and Obstetrics at Washington, September 2000, concluded that Drotaverine shortens the first stage by 2.8 hours as compared to a control group, and also hastens cervical dilatations by 1.3 to 2.04 cm per hour as compared to a control group.

A meta-analysis of 14 prospective, randomized controlled clinical studies that compared Drotaverine with placebo and/or Valethamate, presented at the XVII FIGO World Congress in 2003, concluded that the decrease in mean duration of first stage of labour with Drotaverine is 109 minutes compared with placebo, and 37.62 minutes compared with Valethamate. The difference in mean rate of cervical dilatation with Drotaverine showed that, compared to Valethamate and placebo, Drotaverine achieved faster rates of cervical dilatation, which was statistically significant.

THE CERVIX IN PREGNANCY AND LABOUR

The cervix is a thick walled, cylindrical connective tissue structure that tapers at its inferior extremity, which is relatively inert and firm during most of pregnancy, and becomes soft and ripe as time for parturition approaches. During parturition, it loses its elasticity, plasticity and viscosity resulting in full cervical diltation ***(STYS 1986)***. Some of the these changes are evident quite early in pregnancy ***(Anthony et al 1982)***

There are 3 main structural components of the cervix,

- Smooth muscle
- Collagen

- Connective tissue ground substance containing glycosaminoglycans.

According to ***Rorie and Newton***, the muscle contents as determined by planometry is

Corpus – 69 %	Middle 1/3 – 18 %
Cervix Upper 1/3 – 29 %	Lower 1/3 – 6 %

Collagen dominates the cervical stroma. Collagen types I and III are the main types found in the human cervix. ***Kleissl et al*** found 62-80 % type I collagen and 20-38 % type III collagen. The glycosaminoglycans constitute about 1 % of dry tissue, dermatan sulphate being the most common (52-73%). Hyaluronic acid 8-22 % and heparin sulphate 6-13 % being found in smaller amounts

Changes that take place in collagen and the connective tissue matrix are the primary factors in cervical ripening. These features are incorporated into the scoring system described by Bishop as an index of the proximity of spontaneous labour, and included cervical position, consistency, dilatation, and length or effacement. During cervical ripening 2 complementary changes take place.

1. Collagen breakdown and rearrangement of the collagen fibres (**Harness** and **Harness 1959, Dan Forth et al)**

2. Alterations in the relative amounts of the various glycosaminoglycans – There is a striking increase of hyaluronic acid with a concomitant decrease in dermatan sulphate. Hyaluronic acid itself has a high water binding capacity.

The collagen fibres loosen when the mucopolysaccharide substance between them becomes hydrated and the whole cervix is softened. Hydroxyproline is an indicator of the amount of collagen, and ***Uldjerg et al,*** showed that low concentrations of cervical hydroxyproline are associated with faster rates of cervical dilatation. These changes usually take place late in pregnancy and are influenced by various hormones esp. estrogen.

It is widely accepted that prostaglandins have discrete softening and effacement effects on cervix even without uterine contractions ***(Hiller and Wallis 1981 – Gao schen et al 1985).*** Cervical tissues have the ability to generate prostaglandins ***(Ellwood et al 1980)*** The administration of progesterone receptor antagonist RU486 for induction of abortion was associated with cervical ripening ***(Wolf et al 1989 Elger et al 1990, Silvestre et al 1990)*** Human cervical tissues possess estrogen receptors ***(Honnelier et al 1989)*** and estrogen including dehydroepiandrosterone sulphate have shown to be accumulated in ripening cervix ***(Ishikawa and Shimizu, 1989)*** Relaxin, an ovarian polypeptide hormone, increases significantly in cervix towards end of pregnancy ***(Von Maillot et al***

1979).

Prolonged labour is a problem especially prolonged I stage when incomplete cervical dilatation appears to be the only cause holding back descent of the presenting part. This led to an increased use of anti spasmodies for the past 15-20 years. Drugs containing belladonna alkaloids are often used for this purpose, but they have considerable adverse effects.

Hans Ulrich Beck 1956 first reported about the use fullness of Valethamate bromide in accelerating cervical dilatation and shortening the duration of labour by 18-30 % and normalization of irregular uterine contraction.

AE Czeizel and M. Rockenbauer (1980-81) first reported about the usefulness of Drotaverine Hydrochloride in threatened abortion and later, on its usefulness in accelerating cervical dilatation in labour.

Indeed, pharmacological manipulation of the cervix to produce dilatation without inducing myometrical activity would be similar to surgically removing the resistance of the cervix.

PATTERNS OF LABOUR

Labour is divided into 3 stages.

First stage : From the onset of true labour pains to complete dilatation of the cervix (10 cm)

Second stage : Begins with complete dilatation of the cervix and ends with delivery of the infant.

Third stage : Denotes time interval from delivery of the infant to delivery of the placenta.

Ist stage has 2 phases.

1. Latent phase
2. Active phase

Latent phase : commences with maternal perceptions of regular contractions and ends at between 3 and 4 cm of dilatation

a. Cervix shortens from 3 cm to 0.5 cm length (effacement)

b. Cervix dilates to 3-4 cm

Duration :

Primigravida – 20 hrs } (95^{th} percentile – statistical maximum)

Multigravida 14 hrs

Factors that affect duration of latent phase :

- Excessive sedation or conduction analgesia
- Poor cervical condition (eg. Thick, uneffaced, undilated)
- False labour.

Active phase : Cervical dilatation of 3-4 cm or more, in the presence of uterine contractions reliably represent the threshold for active labour. It has 3 components.

a. Acceleration phase : Cervical dilatation 3-4 cm

b. Phase of maximum slope : cervical dilatation 4-9 cm

c. Deceleration phase : cervical dilatation 9-10 cm

Rate of cervical dilatation

Nullpiara – 1.2 cm / hr. } (minimum normal)

Multipara – 1.5 cm / hr.

Mean duration

Nullipara – 4.9 hrs.

Descent begins in the later stage of active dilatation, commencing at about 7.8 cm in nullipara and becoming most rapid after 8 cm.

Slope of descent of presenting part :

Greater than 1 cm / 1 hr – nullipara

Greater than 2 cms/ hr – multipara

Deceleration phase duration should not exceed

Nullipara – 3 hours

Multipara – 1hour.

The characters of the active phase are usually predictive of the outcome of a particular labour. Friedman considers the maximum slope as a good measure of the overall efficiency of uterine contractions, whereas, the deceleration phase is more reflective of fetopelvic relationships.

Friedman developed the concept of three functional divisions of labour.

a) Preparatory division

- Little cervical dilatation
- Considerable changes in the connective tissue components of cervix
- Sensitive to sedation and conduction analgesia.

b) Dilatational division

- Dilatation at its most rapid rate

- Unaffected by sedation or conduction analgesia

c) Pelvic division

- Commences with deceleration phase of cervical dilatation.

- Cardinal fetal movements in mechanism of labour take place

ABBORMALITIES OF LABOUR

LABOUR PATTERNS	Diagnostic criteria Nullipara	Multipara
PROLONGATION DISORDER		
Prolonged latent phase	> 20 hr	> 14 hr
PROTRACTION DISORDER		
Protracted active phase dilatation	<1.2 cm / hr	< 1.5 cm / hr.
Protracted descent	<1 cm / hr	<2 cm / hr
ARREST DISORDERS		
Prolonged Deceleration phase	> 3 hr	> 1 hr
Secondary arrest of dilatation	> 2 hr	> 2 hr
Arrest of descent	> 1 hr	> 1 hr

Failure of descent – No descent in deceleration phase or second stage.

Causes of labour abnormalities : As per ACOG (1995) abnormalities of labour are classified into 3 categories.

1. Abnormalities of the powers

- Hypotonic dysfunction
- Hypertonic dysfunction
- Poor maternal expulsive efforts

2. Abnormalities of the passenger (fetus)

- Excessive fetal size.
- Malpresentation
- Malposition
- Abnormal attitude
- Congenital abnormalities

3. Abnormalities of the passage (pelvis)

- Cephalopelvic disproportion.
    - Absolute

- Relative

Labour Abnormalities due to cervical causes :

Rigidity of cervix – Hypertrophic rigidity

Cicatricial rigidity

Functional or spasmodic rigidity

Atresia of cervix

Sacculation of cervix

Tumours of cervix

Hypertrophic rigidity :

Causes : Prolapse uterus

Chronic cervictis

Cicatricial rigidity :

Causes : After amputation of cervix

Conisation

Curettage

Long standing prolapse

Atresia of cervix : (reported by **Morgan and Price and Slugett H**)

Causes: Mucosal agglutination due to inflammation.

Ring Biopsy

Sacculation of wall of cervix : very rare

Ballooning out of one or other walls of cervix. The internal os is found tucked away up behind or in front of the presenting part.

Conglutination of the external os presenting as pin hole os.

Tumours of cervix :

- Fibromyoma.
- Carcinoma.

Treatment :

Epidural analgesia was advocated early by ***Arthur*** and ***Johnson***, who showed that this not only gave time for cervix to dilate, but also that the nerve blocking had a specific effect. But ***Stud et al*** showed clearly that epidural

block does not influence rate of cervical dilatation, but the most essential remedy is to ensure adequate uterine contractions. Other methods of overcoming cervical resistance are

1. Vacuum may be applied and uterine forces supplemented by traction during contraction.

2. Duhrssen's incisions of the cervix - pre requisite is cervix should be thin and well applied ***(Cope et al)***

3. Accouchement force – manual dilatation and pushing up the lips of the cervix over the presenting part during contraction.

4. Caesarian section.

The physical state of the cervix determines the rate of cervical dilatation, and in addition modulates uterine wall tension and intra uterine pressure. This effect has been termed the cervical attenuation / augmentation of pressure or **CAP effect**. Therefore a complaint cervix will result in rapid progress in labour, but owing to the compliance of the cervix and lower uterine segment, the wall tension is reduced and the pressure attenuated. Conversely, a non compliant cervix predisposes to slow labour progress and myometrial activity directly translated

into uterine wall tension and high intra uterine pressures.

Full cervical dilatation is one of the important factors for any successful delivery. Cervical spasm may set in either gradually or instantly during the Ist stage of labour, and it may be primary or secondary to any definite etiology. The relaxation of cervical muscle is believed to be an involuntary reflex action coupled with rhythmic contractions of the body of the uterus. The relaxation is also dependent on the presenting part and the bag of membranes which act as a mechanical wedge. A ball valve action of the presenting part especially the vertex is also helpful in dilatation.

Psychological makeup of the patient and apprehension may complicate cervical spasm. Since the cause of cervical spasm is not fully known, it is difficult to treat the spasm with any specific drugs, but broadly the spasm may be due to

- Nervous mechanism
- Hormonal mechanism
- Both

Any drug to relieve the spasm has to act through these mechanisms or act on the smooth muscles directly.

PHARMACOLOGIC REVIEW OF VALETHAMATE BROMIDE AND DROTAVERINE HYDROCHLORIDE

VALETHAMATE BROMIDE

It is an ester with a quaternary ammonium compound. The unique feature of this drug is that it blends the anticholinergic properties of atropine and the musculotropic action of papaverine at the same time. It acts by blocking

1. Cholinergic receptors
2. Ganglia
3. Direct musculotropic action
4. Spasmolytic action

Like atropine it inhibits the conduction of stimuli from the parasympathetic systems to the organs of response. It differs from atropine by its more rapid detoxification and lesser effect on other functions of parasympathetic system. Valethamate bromide relieves cervical spasm due to para sympathetic over excitement, has a good effect on smooth muscles of uterus and helps in cervical dilatation. Its action is selective and that is the reason it does not exhibit the usual side effects of anticholinergic drugs. It does not affect respiratory or circulatory

functions.

Side effects : Drying of all secretins

Flushing of face

Tachycardia

Blurring of vision

Difficulty in swallowing

Constipation / Urinary retention

Glaucoma

Rarely arrhythmias

Contra indications: Glaucoma

Pyloric stenosis

Ulcerative colitis

Paralytic ileus.

Drug interactions: Potentiated by other antispasmodics.

Preparation : Injection – 8 mg in 1 ml

Tablet – 10 mg

Dosage – 8 mg IM / IV once every hour.

DROTAVERINE HYDROCHLORIDE

Leroy et al 1990 found that type IV phosphodiesterase enzyme is present in increased concentration in myometrium at term suggesting its contribution in regulation of uterine motility.

Drotaverine, a benzyl isoquinoline derivative and a phosphodiesterase type IV inhibitor, causes smooth muscle relaxation by increasing the intracellular levels of cyclic adenosine monophosphate (CAMP) secondary to inhibition of phosphate diesterase. Drotaverine produces facilitated relaxation of smooth muscle cells with high concentration of phosphodiesterase IV in the bile duct, ureter and uterus. The pharmacological doses of drotaverine relaxes only the smooth muscle cone of the lower uterine segment and cervix where the concentration of PDE IV per gram of tissue is relatively less. Hence active labour pains are not inhibited by Drotaverine.

Its action does not involve the autonomic nervous system and so side effects are minimal. The drug is generally well tolerated with a good safety profile.

Absorption, fate and excretion.

Absorbed from GIT

Parentral absorption rapid

T ½ - 1 hour 15 minutes. Excreted by kidney.

Side Effects

Too rapid intravenous injection should be avoided to prevent drop in arterial blood pressure. In rare cases, nausea and vertigo may occur after rapid IV injection. A case control study at the Department of human genetics and teratology, National Institute of Public Health (1980-1991) reported that the use of Drotaverine was not associated with any teratogenic effect.

Drug interactions : Levodopa (Antiparkinsonian effect may decrease)

Concurrent use of analgesics, antimuscarinics, or benzodiazepines have additive beneficial effect with drotaverine.

Indications : Spastic conditions of gastrointestinal tract, biliary tract, uterus and urogenital tract, renal colic and irritable bowel disease.

Dosage : Tablet – 80 mgm adults – 4th houly

Injection – 40 mgm 2nd hourly

MATERIALS AND METHODS

This prospective study was conducted in Govt. Hospital for Women and children at the Institute of Obstetrics and Gynaecology attached to Madras Medical College from February 2004 to January 2006.

SELECTION CRITERIA :

INCLUSION CRITERIA :

1. Term pregnancy in active labour – initial cervical dilation of 3 – 4 cms and cervical effacement 75%.

2. Vertex presentation

3. No cephalopelvic disproportion

4. No high risk factors

5. Labour was accelerated with syntocinon whenever needed.

6. All the patients were managed actively

The patients were divided into 3 groups of 100 patients

Group I - Control Group – Normal labour patients – 100 Nos.

Group II - Patients who received Inj. Drotaverine Hydrochloride – 100 Nos

Group III - Patients who received Inj. Valethamate Bromide – 100 Nos.

Primigravidae and multigravidae who fulfilled the above criteria were assigned Group I, Group II, Group III as they arrived, after obtaining an informed consent.

EXCLUSION CRITERIA

1. Medical disorders complicating pregnancy
2. Obstetric complications within high risk category
3. Malpresentation
4. Women with previous caesarian section

History

A detailed history regarding age, parity, socioeconomic status, occupation, booking, gestational age, H/o. any medical disorders or high risk factors was elicited.

CLINICAL EXAMINATION:

A thorough general examination was done followed by detailed obstetric examination to know the height of fundus, presentation and position of the fetus, fetal heart sounds with respect to rhythm, rate and intensity.

Vaginal examination was done in detail to know the position, effacement and dilation of cervix, position and station of presenting part, presence or absence of membranes, and for assessment of pelvis and cephalopelvic disproportion.

MANAGEMENT

All these patients were entered into partograms and the progress of labour, uterine contractions and the fetal heart rate were monitored carefully.

Patients were selected randomly and were allotted to 1 of following groups, regardless of age and parity.

Group I - Control Group

Group II - Received 1 ampoule of Drotaverine Hydrochloride 40 mg intravenously at 2 hourly intervals up to a maximum of 3 doses, starting at 3-4 cms cervical dilatation.

Group III - Received, 1 ampoule of Valethamate bromide 8mg intravenously at hourly intervals up to a maximum of 3 doses, starting at 3-4 cms cervical dilatation.

Per vaginal examination was carried out usually at an interval of 2 hours and findings noted. Artificial rupture of membranes was done soon after

administration of drug at 4 cm cervical dilatation, and duration of active phase of first and second stages of labour recorded. Standard parameters for maternal and fetal well being were monitored as specified by Dawn. If desired rate of contractions were not achieved oxytocin drip was started. Mode of delivery, maternal side effects and fetal outcomes were noted and tabulated. Appropriate non-parametric tests, X^2 test and analysis of variants (ANOVA) were applied for assessment of statistical significance.

OBSERVATIONS

Table – I

DISTRIBUTION OF CASES ACCORDING TO AGE GROUP

Age in years	Group I N = 100	Group II N = 100	Group III N = 100	Percentage
15 – 20	24	31	22	25.9%
21 – 25	49	56	57	54%
26-30	23	13	19	18.3%
31 – 35	4	-	2	2%

$X^2 = 8.21$ P = 0.16 (Not significant)

Patients in age group of 21 – 30 years contributed to 72.3%.

TABLE 2

DISTRIBUTION OF CASES ACCORDING TO GRAVIDITY

Parity	Group I N = 100	Group II N = 100	Group III N = 100	Percentage
Primi	50	50	50	50%
Gravida 2	31	38	34	34.3%
Gravida 3	16	8	12	12%
Gravida 4& 5	3	4	4	3.67%

$X^2 = 3.57$ P = 0.74 (Not significant)

TABLE 3A

DURATION OF ACTIVE PHASE OF LABOUR IN DIFFERENT GROUPS IN PRIMIGRAVIDAE

Group	No.of Cases	Mean Duration (minutes)	Difference of means (minutes	Difference in percentage
I	50	203.4		
II	50	94.6	108.8	53%
III	50	118.6	84.8	41%

Drotaverine Hydrochloride shortened the mean duration of active phase of labour in primigravidae by 108.8 minutes (53% reduction) and Valethamate Bromide by 84.8 minutes (41% reduction) compared to control group.

F = 312.64, (P = 0.001) – Statistically Significant.

TABLE 3B

DURATION OF ACTIVE PHASE OF LABOUR IN DIFFERENT GROUPS IN MULTIGRAVIDAE

Group	No.of Cases	Mean Duration (minutes)	Difference of means (minutes	Difference in percentage
I	50	163.76		
II	50	78.94	84.82	57%
III	50	104.10	59.66	36%

Drotaverine hydrochloride shortened the duration of active phase of labour in multigravidae by 84.82 minutes. (57% reduction) and Valethamate Bromide by 59.66 minutes. (36% reduction) compared to control.

F = 159.35, P = 0.001 – Statistically Significant.

TABLE 4A

RATE OF CERVICAL DILATATION IN ACTIVE PHASE IN PRIMIGRAVIDAE

Group	No.of Cases	Average rate of cervical dilatation (cm /hr)	Difference of Means (cm /hr)
I	50	2.09	
II	50	4.59	2.5
III	50	3.64	1.55

Drotaverine hydrochloride increased the average rate of cervical dilatation by 2.5 cm/hr in primigravidae, and Valethamate bromide by 1.55 cm/hr compared to control group.

F = 196.26, P = 0.001 – Statistically Significant.

TABLE 4B

RATE OF CERVICAL DILATATION IN ACTIVE PHASE IN MULTIGRAVIDAE

Group	No.of Cases	Average rate of cervical dilatation (cm /hr)	Difference of Means (cm /hr)
I	50	2.65	
II	50	5.58	2.93
III	50	4.2	1.55

Drotaverine Hydrochloride increased the average rate of cervical dilatation by 2.93 cm/hr in multigravidae and Valethamate bromide by 1.55 cm/hour compared to control group.

F = 118.67 P = 0.001 – Statistically Significant.

TABLE 5A

DURATION OF II STAGE OF LABOUR IN PRIMIGRAVIDAE

Group	No. of cases	Mean Duration (minutes)	Difference of means (minutes)
I	50	22.30	
II	50	19.62	2.68
III	50	21.08	1.22

There was no significant shortening of II stage of labour with either Drotaverine Hydrochloride or Valethamate Bromide in primigravidae in all 3 groups.

F = 1.23, P = 0.15, Not significant.

TABLE 5B

DURATION OF II STAGE OF LABOUR IN MULTIGRAVIDAE

Group	No. of Cases	Mean Duration (minutes)	Difference of Means (minutes)
I	50	20.68	
II	50	18.86	1.82
III	50	19.82	0.86

The duration of second stage of labour is not significantly different in the 3 groups in multigravidae also.

F = 1.53, P = 0.23, Not significant.

TABLE 6A

ACTIVE PHASE / FIRST INJECTION DELIVERY INTERVAL IN PRIMIGRAVIDAE:

Groups	Gravidity	Active Phase First Injection – Delivery Interval (minutes)	Difference of Means (minutes)	Difference in Percentage
Group I	Primigravidae	225.7		
Group II	Primigravidae	114.62	111.08	49%
Group III	Primigravidae	139.78	85.92	38%

The mean first injection delivery interval was shortened by Drotaverine Hydrochloride in primigravidae by 111.08 mts (49% reduction) and with Valethamate Bromide by 85.92 mts (38% reduction) compared to active phase –

delivery interval in control group.

P = 0.001, Statistically Significant.

TABLE 6B

ACTIVE PHASE / FIRST INJECTION DELIVERY INTERVAL IN MULTIGRAVIDAE :

Groups	Gravidity	Active Phase First Injection – Delivery Interval (minutes)	Difference of Means (minutes)	Difference in Percentage
Group I	Multigravidae	184.44		

Group II	Multigravidae	98.6	85.84	96.5%
Group III	Multigravidae	123.52	60.92	33%

The first injection delivery interval was shortened by Drotaverine in mutigravidae by 85.84 minutes (46.5% reduction) and with Valethamate by 60.92 minutes (33% reduction) compared to active phase delivery interval in control group.

P = 0.001, Statistically Significant

TABLE 7

OXYTOCIN AUGMENTATION

Oxytocin	Group 1 n = 100	Group II n = 100	Group III n = 100
Used	52%	46%	48%
Not used	48%	54%	52%

52%, 46% and 48% required oxytocin augmentation in groups I, II and III respectively. Hence both Drotaverine Hydrochloride and Valethamate Bromide had no effect on uterine contractions.

TABLE 8

C

HARACTER OF AMNIOTIC FLUID

Type of liquor	Group I	Group II	Group III	Fetal outcome
Clear	89	93	90	Good
Thin meconium	7	5	7	Good
Thick Meconium	4	2	3	Good

Patients with thin meconium stained liquor in all three groups were NST Reactive, delivered vaginally and had Apgar > 7/10 at 5 minutes.

All cases of thick meconium were NST Reactive. In control group, 2 were taken up for LSCS, 1 delivered by outlet forceps and 1 delivered vaginally, all had Apgar > 7/10 at 5 minutes.

In Drotaverine group both delivered vaginally – one as face to pubis. Both

were vigorous babies and had Apgar > 7/10 at 5 minutes.

In Valethamate group 1 was delivered by LSCS and 2 by outlet forceps. All had Apgar > 7/10 at 5 minutes.

TABLE 9A

MODE OF DELIVERY IN PRIMIGRAVIDAE

Group	No. of Cases	Normal vaginal Delivery	Forceps Delivery	LSCS
I	50	46	2	2
II	50	49	1	
III	50	48	1	1

There was no increase in instrumental delivery in either of the groups given Drotaverine or Valethamate in Primigravidae. Indications for LSCS in control group were fetal distress and secondary arrest of cervical dilation. Indications for LSCS in drug groups was not pertaining to drug administration.

$X^2 = 6.18$ P = 0.19 Not Significant

TABLE 9B

MODE OF DELIVERY IN MULTIGRAVIDAE

Group	No. of Cases	Normal vaginal Delivery	Forceps Delivery	LSCS
I	50	47	2	1
II	50	49	1	-
III	50	49	1	-

There was no increase in instrumental delivery in either of the groups given Drotaverine or Valethamate in multigravidae. Indication for LSCS in group I was fetal distress. Indications for outlet forceps in all groups were failure of secondary powers.

$X^2 = 6.12$ P = 3.19 Not significant

TABLE 10

RELATIONSHIP BETWEEN DRUGS AND FETAL OUTCOME

Group	No. of Cases	APGAR SCORE			
		1 minute		5 minutes	
		< 7/10	> 7 / 10	< 7 /10	> 7 / 10
I	Primis – 50	2	48	-	50
	Multis – 50	2	48	-	50
II	Primis – 50	1	49	-	50
	Multis – 50	2	48	-	50
III	Primis – 50	3	47	-	50
	Multis – 50	-	50	-	50

3% of newborns in all the 3 groups had Apgar score of < 7 at birth (1mt) and 1 newborn in control group required observation in NICU for 2 hours. All the newborns in all the 3 groups had Apgar score of > 7 at 5 minutes. There was no intrapartum or early neonatal deaths in all the study groups.

$X^2 = 0.5$ P = 0.568 Not significant

TABLE 11

THIRD STAGE COMPLICATIONS

Complications	Drotaverine Group	Valethamate Group	Control
Cervical tears	2%	2%	-
Atomic PPH	-	-	-

Cervical tear was noted in 2% of cases in Group I and Group II. No case of postpartum hemorrhage was observed in any woman.

TABLE 12

COMPARISON OF NUMBER OF INJECTIONS GIVEN IN THE DIFFERENT GROUPS

Group	No. of Cases	No. of Injections			
		1		≥ 2	
Group II	100	Primi (49)	93%	Primi (1)	7%
		Multi (44)		Multi (6)	
Group III	100	Primi (24)	61%	Primi (26)	39%
		Multi (37)		Multi (13)	

The number of injections required in both groups was limited to 3; single injection was required in 93% cases in Group II, while in Group III 61% cases required single injection and 39% cases required 2 or more injections.

$X^2 = 28.91$ OR = 8.5 95% CI = 3 – 22

P = 0.001 Statistically significant

TABLE 13

UNTOWARD MATERNAL EFFECTS AFTER DROTAVERINE HYDROCHLORIDE AND VALETHAMATE BROMIDE

Side effects	Group II	Dose of Drug in mg	Group III	Dose of Drug in mg
Dryness of mouth	1	80	4	16
Vomiting	1	80	1	24
Tachycardia	1	80	3	16

In Drotaverine group, 3% exhibited side effects while in the Valethamate group 8% exhibited side effects. Most common side effects in Valethamate group were dryness of mouth and tachycardia. In both groups side effects were noted after two or more injections hence they are dose related.

TABLE 14

TESTS OF STATISTICAL SIGNIFICANCE

	Group I	Group II	Difference of means (mts)	%	Group III	Difference of means (mts)	%	Anova Test P value & significance
No.of Cases	100	100		100				
Mean Duration of Active Phase (minutes)	183.58 ± 72.28	86.77± 39.82	96.81	52%	113.35 ± 43.32	70.23	38%	F = 34.77 P = 0.001 Significant
Mean rate of cervical dilatation (cm/hr)	2.37 ± 1.04	5.09 ± 2.3	2.72		3.92 ± 1.72	1.55		F = 236.44 P = 0.001 Significant
Mean Active phase / Drug – Delivery Interval (minutes	205.07 ± 75.66	106.61 ± 43.96	98.46	48%	131.65 ± 45.1	73.42	36%	F = 332.86 P = 0.001 Significant

Thus Drotaverine hydrochlomide and Valethamate bromide achieved 52% and 38% reduction in mean duration of active phase of labour respectively compared with control group. The mean rate of cervical dilatation was 2.72 cm/hr faster with Drotaverine and 1.55 cm/hr with epidosin compared to control. The mean drug delivery interval was 48% shortened by Drotaverine and 36% shortened by Valethamate compared to Active phase Delivery interval of Control group.

TABLE 15

COMPARISON OF MATERNAL AND FETAL OUTCOMES

Outcomes		Group I	Group II	Group III
Mode	Vaginal	93	98	97
	Outlets Forceps	4	2	2
	LSCS	3	-	1
Cervical tears		-	2%	2%
Atonic PPH		-	-	-
Meconium stained liquor		12%	7%	10%
Maternal Side Effects		4%	3%	8%
Apgar < 7/10 at 1 mt		3%	3%	3%
Apgar > 7 at 5 mt		100%	100%	100%

Drotaverine hydrochloride and Valethamate Bromide compared favourably with each other with respect to maternal and fetal outcomes, except that Valethamate had a higher incidence of maternal side effect.

DISCUSSION

Various perspective, randomized controlled clinical studies that compared Drotaverine hydrochloride with placebo, and / or Valethamate bromide have been carried out. In the present study, Drotaverine hydrochloride and Valethamate bromide were given intravenously at 3-4cms cervical dilatation in 2 groups of demographically similar women with term pregnancy in active labour, and compared with a control group.

It was noted that the mean duration of active phase of labour in control group was 183.58 ± 72.28 minutes, and 86.77 ± 39.82 minutes in Group II and 111.35 ± 43.32 minutes in Group III, which is comparable to the study conducted by ***Devinder et al (2001)*** (96.34 ± 59.45 minutes with Drotaverine and 128.78 ± 58.99 minutes with Valethamate). Randomised controlled clinical studies presented at the XVII FIGO World Congress held that the decrease in mean duration of Active phase with Drotaverine was 109 minutes compared with placebo, and 37.6 minutes compared with Valethamate. In the present study, the decrease is 96.81 minutes in Drotaverine group compared to control, and 24.58 minutes compared with Valethamate.

The rate of cervical dilatation was 2.37 ± 1.04 cm/hr in Group I, 5.09 ± 2.3cm/hr in Group II, and 3.92 ± 1.72 cm/hr in Group III respectively which is

comparable to the study by ***Devinder et al (2001)*** (4.99 ± 2.21 cm/hr with Drotaverine and 3.74 ± 1.72 cm/hr with Valethamate). ***Goswami et al (2000)*** noted that Drotaverine hastens cervical dilatation by 1.3 to 2.04 cm/hr compared to control. In the present study, cervical dilatation was 2.72cm/hr faster with Drotaverine compared to control and 1.17 cm/hr faster with Valethamate.

Both Drotaverine hydrochloride and valethamate bromide had no effect on the uterine contractions.

The mean first injection delivery internal with Drotaverine is 106.61 ± 43.96 minutes and 131.65 ± 45.1 minutes with Valethamate which is comparable to the study by ***Devinder et al*** (129.82 ± 63.75 minutes with Drotaverine and 151.53 ± 60.47 minutes with Valethamate).

The average duration of II stage of labour was not affected by administration of drugs compared to control group.

93% cases in Drotaverine group required single injection, while 69% cases required single injection and 39% required 2 or more injections in Valethamate group. The incidence of side effects was 3% with Drotarverine compared to 8% with Valethamate. Cervical tears were noted in 2% in both drug groups. No case of atonic PPH was noted in all 3 groups.

Regarding mode of delivery, in control group, 4 cases were delivered by outlet forceps and 3 cases by LSCS. In Drotaverine group, 2 cases were delivered by outlet forceps, and in Valethamate group 2 were delivered by outlet forceps and 1 by LSCS. Thus there was no increase in instrumental delivery in either of the drug groups.

Regarding fetal outcome, thin meconium stained liquor was noted in 8%, 5% and 7% of cases in Group I, II and III respectively. All were NST reactive, delivered vaginally, and had Apgar > 7/10 at 5 minutes. Thick meconium was noted in 4 cases in control group – 2 delivered by LSCS, 1 by outlet forceps and 1 delivered vaginally. Thick meconium noted in 2 cases in Drotaverine group were delivered vaginally, and of the 3 cases of thick meconium in Valethamate group, 1 was delivered by LSCS and 2 by outlet forceps. All cases of thick meconium in all 3 groups were NST reactive and had Apgar > 7/10 at 5 minutes. There was no intrapartum or early neonatal deaths in all 3 groups.

SUMMARY

- This study was conducted to compare the efficacy of Drotaverine Hydrochloride and Valethamate Bromide on cervical dilatation in active labour, and adverse effects on maternal and fetal outcome.
- A total number of 300 parturients were studied

Group I Control Group – Received no drugs

Group II Received intravenous Drotarverine hydrochloride at 3-4 cms cervical dilatation at 2 hourly intervals upto a maximum of 3 doses

Group III Received intravenous Valethamate bromide at 3-4 cms cervical dilatation at hourly intervals upto a maximum of 3 doses

- Mean duration of active phase of labour in control group was 183.58 ± 72.28 minutes. The duration of active phase is reduced by 96.81 minutes (52% reduction) in Drotaverine group which is statistically significant ($p = 0.001$) compared with control and 24.58 minutes faster than Valethamate.
- There was significant difference in rate of Cervical dilatation between the control and other 2 groups ($p = 0.001$) with Drotaverine achieving 2.72cm/ hr faster dilatation and Valethamate achieving 1.55cm/hr faster dilatation compared to control.
- Both Drotaverine Hydrochloride and Valethamate had no effect on the uterine contractions.

- The mean first injections to Delivery interval is significantly reduced in both groups given drugs 48% reductions with Drotaverine and 36% reduction with Valethamate compared to the Active phase delivery internal in Control ($p = 0.001$).
- There was no significant shortening of II stage of labour.
- There was no increase in incidence of instrumental delivery or abdominal delivery in either Drotaverine or Valethamate groups.
- The incidence of cervical tears was 2% in both drug groups.
- No case of atonic PPH noted in all 3 groups
- Incidence of maternal side effects with drotaverine (3%) is significantly less compared to Valethamate (8%).
- There was no significant increase in incidence of meconium stained liquor in the drug groups compared to control.
- All newborns in all 3 groups had Apgar score > 7 at 5 minutes. There was no intrapartum or early neonatal deaths in all the study groups.

CONCLUSION

Drotaverine hydrochloride is a superior cervical dilatation agent significantly reducing the duration of labour without any ill effects on the mother or the fetus. It is significantly better than Valethamate bromide with less side effects due to selective action. Hence it is recommended that Drotaverine Hydrochloride may be given to low risk women in active labour.

The promising beneficial effects of Drotaverine hydrochloride are available in obstetric practice and in this study, it has definitely proven to shorten the duration of labour and provide early relief from distress for the labouring woman.

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PROFORMA

Name : Age : Occupation :
Address: Socioeconomic Class:

Gravida Para Live Abortion :

LMP : EDD : Booked / Unbooked
Immunisation : Yes / No

H/o. Months amenorrhoea

Complaints : Pain since
Discharge Per vaginum

H/o. Present Pregnancy : I Trimester
II Trimester
III Trimester

Pain started at : Once in :

Duration and frequency increasing : Yes / No

Discharge per vaginum : Yes / No
Colourless / Meconium Stained / Blood Stained

H/o. Bowel or Bladder Disturbance :

Menstrual History :

Menarche: Cycles: Pain : Yes / No
LMP : EDP :

Obstetric History :

Married Since : Consanguinity - I^{o}
II^{o}

I Pregnancy - Baby details : III^{o}
II Pregnancy –

Past History :

Known Diabetic : Yes / No Hypertensive : Yes / No

Tuberculosis : Yes / no Rheumatic fever : Yes / No

Personal History :

Diet : Vegetarian / Non Vegetarian / Mixed Appetite : Good/Moderate
Addiction : Smoking / Drugs Sleep : Good / Moderate

Family History :

Mother : Alive / Dead Father : Alive / Dead Siblings :
H/o. Diabetes : Yes / No Hypertension : Yes / No Tuberculosis : Yes / No
Twins : Yes / No

General Examination :

Built : Thin / Moderate / Obese Height : Weight :
Pallov : Yes / No Jaundice : Yes / No Pedal edema : Yes / No
BP : mm of Hg PR : /mt. Breast : Thyroid :
CVS : RVS : Gait :

Abdominal Examination :

Inspection :

Longitudinally enlarged: Yes / No Term : Yes / No
Skin : Normal / Abnormal Strial : Yes / No Linea Nigra: Yes/No
Fetal Movements : Seen / not seen

Palpation :

Height of uterus : SFH : cm Abdominal girth : cm
Acting : Yes / No EFW : kg
Fundal Grip : Breech : Yes/ No Head : Yes/No
Umbilical Grip : Back : Left / Right Limbs : Left / Right
Liquor : Adequate / Diminished
I pelvic grip : head engaged/unengaged
II pelvic grip : Head flexed / deflexed. LOA/ROP/ROA/LOP

Auscultation :

Fetal Heart Rate : / minute Tone :

Vaginal Examination :

Cerix : Position : Posterior / Mid Position / Anterior
Consistency : Firm / Medium / Soft
Dilatation :
Effacement :
Station : Bishop's score
Membranes :
Pelvis :

Drug Used : Dose :

Time of Administration of Drug, Cervical dilatation at time of injection

I dose –
II dose –
III dose –

Membranes ruptured at :
Colour of Liquor : Clear / Thin Meconium / Thick Meconium
Whether augmented with oxytocin : Yes / No

Time from Injection (I dose) to full cervical dilatation
Rate of cervical dilatation : cm/hr

II Stage :
Duration
Mode of Delivery : Normal vaginal / Forceps / Ventouse / LSCS
Indication :
Drug Delivery Interval :

Fetal Outcome :
Baby details :
Apgar : 1mt: 5 mt:
Any resuscitation required :
Admission in NICU : Yes / No

III Stage complications :
Cervical Tears : Yes / No
Atomic post partum hemorrhage : Yes / No

Maternal side effects :
Tachycardia : Yes / No Vomiting : Yes / No
Dryness of mouth : Yes / No

Total number of injections of drugs required : 1 / 2 / 3

PARTOGRAPH

Name ..... Gravida.... Para .. Hospital No
Date of admission ..... Time of admission..... Ruptured membranes..... hrs