International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Agarwal SN et al. Int J Reprod Contracept Obstet Gynecol. 2024 Jun;13(6):1452-1458
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20241425

Original Research Article

Randomized control comparative study to evaluate the effect of camylofin dihydrochloride and valethamate bromide in active phase of first stage of labour

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Received: 18 March 2024
Revised: 30 April 2024
Accepted: 01 May 2024

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ABSTRACT

Background: Numerous drugs have been used to shorten the active phase of labor. Do they really shorten the duration of labor? What adverse effects do they have on the baby and the mother? These questions were the basis to perform the present study of comparing two of such drugs, injection Camylofin dihydrochloride and injection Valethamate bromide with control subjects. Aim of the study was to assess the effect of camylofin dihydrochloride and valethamate bromide on active phase of first stage of labour.
Methods: This is an open label randomized controlled study of 120 eligible women with spontaneous onset of labour at SSG hospital, Vadodara, India. Women were randomized to receive either a single intra-muscular Camylofin, 3 doses of intra-venous Valethamate or third as control group. The main outcome measure was duration of active phase of first stage of labour and rate of cervical dilatation. The study was conducted over a period of 9 months from May 2022 to January 2024.
Results: Mean duration of active phase of labour was 4.33±1.32 hours, 6.74±1.26 hours and 6.83±1.65 hours in Camylofin, Valethamate and control group respectively with p value <0.0001. Mean rate of cervical dilatation was 1.47±0.41 cm/hour, 0.91±0.23 cm/hour and 0.87±0.18 cm/hour in three groups respectively. There was no significant difference in maternal side effects and neonatal outcome among them.
Conclusions: Considering the results of this study, it can be concluded Camylofin is superior to Valethamate in decreasing total duration of active phase of first stage with higher cervical dilatation rate.

Keywords: Labour, Camylofin dihydrochloride, Valethamate bromide, Cervical dilatation rate, Active phase of labour

INTRODUCTION

Labour is one of the important and memorable events in a woman's life. The painless and short labour has been a cherished desire of every woman and goal of obstetrics is a pregnancy that resulted in healthy infant and minimally traumatized mother.[1] Labour is a multi–factorial process that involves myometrium contraction, cervical ripening and in dilatation, and then expulsion of the fetus and placenta in an orderly manner. The first stage of labour in a primigravidae lasted for 12–16 hours and in a parous woman usually 6–8 hours. There is a general consensus of opinion to classify labour lasting over 24 hours as prolonged labour. The progress of labour is assessed by progressive dilatation and effacement of the cervix and the descent of the presenting part.[2] The problems and hazards of prolonged labour, both for mother and fetus have been recognized for many years. Therefore, attempts to accelerate labour and thereby shorten the duration of labour, without jeopardizing maternal or fetal interests would have been warranted.

There are many causative factors associated with prolonged dilatation stage of labour, such as initial state of

cervix, rate of cervical dilatation, intensity of uterine contractions, presentation, cephalopelvic disproportion, constitutional characteristics, and parity of the parturient. During pregnancy there is a pronounced softening of cervix, caused by increased vascularity and edema of the entire cervix, together with hypertrophy and hyperplasia of cervical glands.[3]

The concept of "active management of labour" was introduced by Professor O"Driscoll at the National Maternity Hospital; Dublin.[4] Following this, obstetricians have changed their outlook regarding first stage of labour. Attempts to accelerate labour and thereby shorten its duration without jeopardizing maternal or fetal outcome are welcome to both the patient and the obstetrician.

There are various mechanical and pharmacological methods by which the cervical dilatation can be facilitated e.g., sweeping of membranes and stretching of the cervix causes local release of prostaglandins resulting in reduction in the need for formal induction of labour, amniotomy, cervical application of relaxin, estradiol and hylase, prostaglandins in various formulations for induction of labour, especially PGE2 gel for cervical ripening. Oxytocin is proven to induce and augment labour. Buscopan (Hyoscine butyl-N-bromide) and Scopolamine have been used for pain relief and shortening of labour. Epidosin (Valethamate bromide) has neurotropic and musculotropic actions, resulting in relaxation of cervical musculature leading to quick dilatation of cervix and shortened labour. Drotaverine hydrochloride shortens duration of the dilatation stage of labour. Anafortan (Camylofin dihydrochloride) is a selective PDE-4 enzyme inhibitor which facilitates cervical effacement and dilatation, accelerates labour, regulates the autonomic system and thereby prevents disordered progress of labour.

In this article, we will study the effect of Camylofin dihydrochloride and Valethamate butyl bromide on active phase of first stage of labour, their comparison regarding shortening of labour, maternal and neonatal side effects and any complications.

Aim and objectives

Aim of the study was to assess the effect of camylofin dihydrochloride and valethamate bromide on active phase of first stage of labour.

Objectives of the study were: to study the effects of two drugs on duration of active phase of 1st stage of labour; rate of cervical dilatation; and to assess the side effects of two drugs.

Camylofin dihydrochloride

Camylofin dihydrochloride is an anti-spasmodic drug available in India and other Latin American and African countries, for the treatment of abdominal colic and for acceleration of labor.[5]

Camylofin dihydrochloride is 3-methyl butyl 2-(2-diethyl amino ethyl amino)-2-phenyl acetate hydrochloride. It belongs to the group of spasmolytic, anticholinergic and gastro intestinal sedative drugs. It has a molecular formula of $C_{19}H_{32}N_{207}$.2HCl and a molecular weight of 393.4. Its structure is depicted in Figure 1.[6]

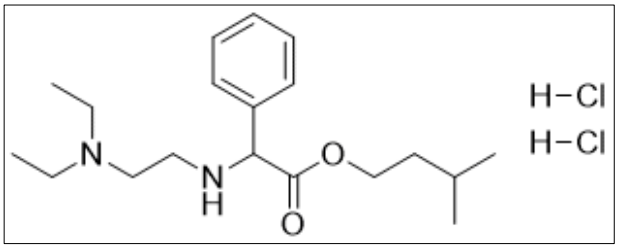

Figure 1: Structure of Camylofin dihydrochloride ($C_{19}H_{32}N_{202}$.2HCl).

Here again, camylofin primarily acts on the smooth muscles of the cervix. This action of camylofin is unique since, it is a preferential cervical dilator, i.e. it has no interference on the uterine contractions.

Although camylofin possesses a musculotropic action, it does not interfere with uterine contractility due to its PDE IV isoenzyme selectivity. Owing to this unique preferential cervical dilating action, camylofin can be recommended for use in accelerating the first stage of labour.[7,8]

Valethamate bromide

It is an ester with a quaternary ammonium compound.

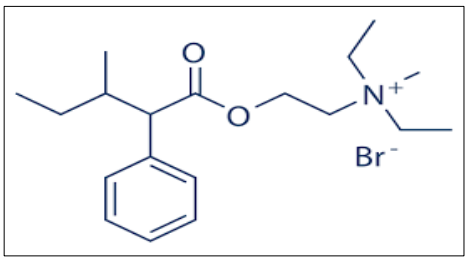

Figure 2: Structure of Valethamate bromide ($C_{19}H_{32}BrNO_2$).

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. 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.[9]

Liggins has stated that any hypothesis for the initiation of labour is incomplete unless it includes the satisfactory

explanation for the structural changes in the cervix.[10] Cervical dilatation is one of the important factors which determines the duration of labor and is the resultant of all the driving forces of uterine contraction acting against passive tissue resistance.[11]

METHODS

Study type

It was a randomized controlled comparative study.

Study place

The study was conducted at the Department of Obstetrics and Gynecology, Shree Sayajirao Gaekwad General Hospital, Vadodara, Gujarat, India.

Study duration

The duration of the study was from May 2023 to January 2024.

Sample size

As this study is time bound, considering the average number of patients who delivered vaginally, the total sample size of 120.

Study sample

Inclusion criteria

All patients in labour room who are being given trial of normal vaginal delivery were included with criteria being primi gravida, singleton pregnancy with cephalic presentation, 37 completed weeks and spontaneous labour onset.

Exclusion criteria

Patients delivered during the process of labour by cesarean section for various maternal or fetal indications. Patients admitted with advanced spontaneous labour with or without ruptured membranes (patients who on admission had 8 cm cervical dilation). Multiple pregnancy and other than cephalic presentation. Patient having drug allergy to any of the mentioned drugs were also excluded from the study.

Ethical approval

The study was approved from ethics committee for biomedical and health research, Medical College and SSG Hospital.

Analytical tool

The analytical tool used for the study was Jamovi software.

Randomisation

The selected women were randomized into three groups by simple randomization using an opaque sealed envelope, into - group A: patient given Camylofin dihydrochloride, group B: patient given Valethamate bromide, and group C: control group with no drug.

Randomization will be done by the doctor in labour room. Detailed history of the patient will be taken. Thorough general physical examination followed by abdominal and per vaginal examination will be performed. Women will be divided into group A, B and C and respective drugs will be introduced after 4 cm cervical dilatation in group A and B.

Methods

All eligible women admitted in labour room for delivery will be enrolled in the study taking inclusion and exclusion criteria in consideration. Participants will be briefed about the nature of the study, details of the treatment and a written informed consent will be obtained after being explained about the risks and benefits of the study.

In group A, after 4 cm dilatation a single intra-muscular dose of 2 ml Camylofin will be given (25 mg/ml: total=50 mg).

In group B, after 4 cm dilatation, 3 doses of 1 ml intravenous Valethamate every 15 minutes (8 mg/ml: total=24 mg).

In group C, patients will not be given any drug.

Final outcome

The final outcome was assessed by the following: duration of active phase of first stage of labour; rate of cervical dilatation; maternal side effects like blood loss, any adverse drug reaction to mother, cervical/vaginal tear, atonic tear, retained placenta; and neonatal assessment by Apgar score at 1 and 5 minutes and meconium stained liquor.

RESULTS

This was a randomised control trial conducted in our hospital in which a total of 120 women with spontaneous onset of labour and those satisfying the inclusion and exclusion criteria were enrolled and randomized into three groups by using envelope method.

In group A, Camylofin 2 ml (25 mg/ml) single intra-muscular dose was given. In B group, Valethamate 1 ml (8 mg/ml) 3 doses at 15 minutes interval by intravenous route. Group C was control group.

Different parameters were tabulated and statistical tests were applied accordingly.

Table 1 shows age wise distribution of all the candidates. In group A- maximum nummber of female (38%) were in age group 25-29 years, in group B- maximum nummber of female (53%) were in age group 25-29 years and in group C- 55% females were in same age group. Very few females 15%, 5%, 8% were below the age of 20 years in group A, B, C respectively. Only 1 female was above 35 years of age in group A. Age difference in all the groups were statistically insignificant with Chi-square value 8.875 and p value 0.35 (>0.05) at CI 95%.

Table 2 shows distribution of candidates according to their gestational age. All the females in study were divided in different groups regarding gestational age to see effect of same on our results. Maximum females were in the age group of 39 weeks to 39 weeks 6 days with 38% in group A, 43% in group B. In group C, 30% females were in group 38 weeks to 38 weeks 6 days and 40 weeks to 40 weeks 6 days. 5 females that is 13 % were between 37 weeks to 37 weeks 6 days in group A and C . In group B, 4 females that is 10 % were in same gestational age group. Chi-square test was applied to the data at 95% CI with value 2.334 and p value was 0.88 which is statistically insignificant (>0.05).

Table 3 shows time duration from injecting the drug to full dilatation of cervix that is end of active phase of first stage. Data were plotted in terms of duration in hours for three groups. In Camylofin group 38% females fell in 4-5 hours, 35% in <4 hours and 28% in 6-7 hours. None of the candidate was in group for more than 7 hours. In Valethamate group 1 female was in <4 hours group and maximum 22 females which was 55% were in 6-7 hours group. 10%, 48%, 5% females were in group 4-5 hours, 7-8 hours and >8 hours respectively. In control group C, none of the females showed full cervical dilatation within 4 hours. 14 females (35%) were in group 6-7 hours and 16 (40%) were in group 7-8 hours. Chi-square test was applied to the data and value was 63.62 at CI 95% with p value <0.0001 which is statistically significant (<0.05).

Table 4 shows rate of cervical dilatation in cm/hour for 3 groups in terms of mean and standard deviation and comparison of the groups.

The main objective of the study is to determine the difference in the duration of active phase of first stage of labour. This can be achieved by calculating the cervical dilatation rate in three groups. All the data were studied and mean of cervical dilatation rate was measured. Mean was 1.47 cm/hour in group A, 0.91 cm/hour in group B and 0.87 cm/hour in group C. As seen highest rate was achieved in camylofin group compared to both groups. Differences in three groups were measured and p value were calculated. While comparing camylofin and valethamate p value was <0.0001 which is statistically significant (<0.05).

P value while comparing Valethamate with control group C was found to be 0.38 on the other hand Camylofin with control group C was found to be <0.0001 (<0.05). These results were showing high efficacy of Camylofin in increasing cervical dilatation thus accelerating labour.

Table 5 shows different side effects of drugs in study. Female in no-drug group (group C) developed no significant events in labour except one female who developed nausea and vomiting, for which symptomatic treatment was given. In Camylofin group total 6 females (15%) females developed side effects. On detailing, 2 (5%) had tachycardia, 3 (7.5%) had nausea/vomiting and 1 (2.5%) had drowsiness. None of them were very severe and troublesome to parturients. Females to whom Valethamate was given, 7 had side effects that is 18% of total 40 females who received the drug. Out of those 7 females, 2 had blurring of vision, 1 had nausea/vomiting and 4 had dry mouth. These side effects are mainly because of anti-cholinergic effects of Valethamate. These data were calculated at 95% CI and tested as statistically insignificant with Chi-square value 13.71 and p value 0.18 (>0.05).

Table 6 shows labour related complications associated with the drugs. It is very important to study the complications in labour especially cervical tear, atonic PPH, retained placenta particular to the injected drug. One from females in spontaneous labour had cervical tear. 4 females in Camylofin group and 2 in Valethamate group developed such complications. In camylofin group, 3 females that is 7.5% had cervical tear. One female had atonic PPH in same group. While in Valethamate group, one had cervical tear and one had atonic PPH. Overall complications were less and manageable. None of the females had retained placenta. Data were analysed at 95% CI with Chi-square value 0.875 and p value 0.64 (>0.05) which is statistically insignificant.

Table 7 shows effects of drugs in study to neonates. Injecting drugs in active labour can produce significant side effects in neonates as in mother. Studying neonatal side effects is equally important as in mother to give birth to healthy neonate. In Camylofin group, 2 of the 40 neonates had meconium stained liquor that is 5% of total. Initial resuscitation was given to both of them. Shifted to NICU for observation and on 2nd day babies were handed over to mother. Low APGAR was seen in 1 neonate, baby was kept under observation for 24 hours and then handed over to mother. Similar to this, in Valethamate group, 1 neonate had meconium stained liquor and managed conservatively. 2 neonates had low APGAR and kept for observation. All of the neonates were healthy and discharged uneventfully. As we can say neither of the drugs causes significant neonatal complications. Data were analysed at 95% CI with Chi-square value 1.55 and p value 0.45 (>0.05) which is statistically insignificant.

Table 1: Age wise distribution of females.

Age distribution (years)	Group A		Group B		Group C	
	N	%	N	%	N	%
<20	6	15	2	5	3	8
20-24	11	28	11	28	13	33
25-29	15	38	21	53	22	55
30-34	7	18	6	15	2	5
35-39	1	3	0	0	0	0

Chi-square=8.875 (CI=95%), p=0.3530

Table 2: Gestational age.

Gestational age	Group A		Group B		Group C	
	N	%	N	%	N	%
37 weeks – 37 weeks 6 days	5	13	4	10	5	13
38 weeks – 38 weeks 6 days	11	28	9	23	12	30
39 weeks – 39 weeks 6 days	15	38	17	43	11	28
40 weeks – 40 weeks 6 days	9	23	10	25	12	30
41 weeks – 41 weeks 6 days	0	0	0	0	0	0

Chi-square=2.334 (CI=95%), p=0.8865

Table 3: Duration of active phase of first stage.

Duration of active phase of first stage	Group A		Group B		Group C	
	N	%	N	%	N	%
<4	14	35	1	3	0	0
4-5	15	38	4	10	9	23
6-7	11	28	22	55	14	35
7-8	0	0	19	48	16	40
>8	0	0	2	5	7	18

Chi-square=63.624 (CI=95%), p<0.0001

Table 4: Cervical dilatation rate.

Cervical dilatation (cm/hour)	Mean	SD
Group A (Camylofin)	1.47	0.41
Group B (Valethamate)	0.91	0.23
Group C (control)	0.87	0.18
Comparison	Difference	P value
Group A versus group B	0.55	<0.0001
Group B versus group C	0.04	0.3890
Group A versus group C	0.59	<0.0001

Table 5: Maternal side effects.

Maternal side effects	Group A		Group B		Group C	
	N	%	N	%	N	%
Dry mouth	0	0	4	10	0	0
Tachycardia	2	5	0	0	0	0
Giddiness	0	0	0	0	0	0
Nausea/vomiting	3	7.5	1	2.5	1	2.5
Drowsiness	1	2.5	0	0	0	0
Blurring of vision	0	0	2	5	0	0
Total	6	15	7	18	1	2.5

Chi-square=13.714 (CI=95%), p=0.1864

Table 6: Labour related complications.

Labour related complications	Group A		Group B		Group C	
	N	%	N	%	N	%
Atonic PPH	1	2.5	1	2.5	0	0
Cervical tear	3	7.5	1	2.5	1	2.5
Retained placenta	0	0	0	0	0	0
Total	4	10	2	5	1	2.5

Chi-square=0.875 (CI=95%), p=0.6456

Table 7: Neonatal complications.

Neonatal complications	Group A		Group B		Group C	
	N	%	N	%	N	%
Meconium stained liquor	2	5	1	2.5	1	2.5
Low APGAR	1	2.5	2	5	0	0

Chi-square=1.556 (CI=95%), p=0.4594

DISCUSSION

Similar to our study other studies also proved beyond doubt that Camylofin is superior to Valethamate and placebo in reducing duration of active phase of first stage of labour.[9,10]

There are very limited study directly comparing Camylofin and Valethamate. Different studies are there for both of them individually.

Our study findings proved that Camylofin being preferential cervical dilator rapidly dilates the cervix and causes significant shortening of first stage. In similar study by Mehra et al, mean duration of active phase of first stage of labor was shorter in anafortan group (313.17 minutes) than in epidosin group (356.3 minutes) and it was found to be statistically significant with p value of 0.024.[12]

Cervical dilatation rate is more with Camylofin. In study by Mehra et al, mean cervical dilatation rate observed in anafortan group (2.02 cm/hour) was more than that in epidosin group (1.81 cm/hour) and was found to be statistically significant with p value of 0.024.[12]

Table 8: Comparison of different studies for duration of active phase of labour.

Study	Study group (min)	Control group (min)
Asholter et al (1953)[15]	232	372
Warke et al (2003)[16]	215	334
Mehra (2021)[12]	313	356
Present study	259	400

Our study shows no significant maternal side effects with any of the drugs. In study by Sharma et al, there were no major maternal or fetal adverse effects in any group, but minor side effects were more common in the valethamate group.[13] In study done by Dayama et al in Camylofin group maternal minor side effects were present in 14% cases while in Hyoscine group in 16% cases.[14]

Table 9: Difference of duration of active phase of first stage of labour.

Group	No. of cases	Mean duration (hours)	Difference of mean (hours)	Difference in percentage
A	40	4.33	2.50	36
B	40	6.74	0.09	1
C	40	6.83	-	-

Summary

This study was conducted to compare the efficacy of Camylofin dihydrochloride and Valethamate bromide on active phase of first stage of labour, cervical dilatation in active labour, and adverse effects on maternal and fetal outcome.

The demographic characteristics were comparable with respect to maternal age and gestational age. The outcome measures compared were duration of active phase of first stage of labour (which was the primary outcome), meconium stained liquor, neonatal APGAR score, maternal complications and side effects.

Mean duration of active phase of labour in control group was 6.83±1.65 hours, in Camylofin group it was 4.33±1.32 hours and 6.74±1.26 hours in Valethamate group.

Both Camylofin dihydrochloride and Valethamate had no effect on the uterine contractions.

There was significant shortening of 2nd and 3rd stage of labour in Camylofin group.

The incidence of cervical tears was 7.5% in Camylofin group and 2.5% in Valethamate and control group which is statistically not significant.

Both group A and B had 1-1 female for Atonic PPH.

No case of retained placenta noted in all 3 groups.

Incidence of maternal side effects with Camylofin mainly mild nausea/vomiting was 15% and Valethamate mainly anti-muscarinic was 18%.

There was no significant increase in incidence of meconium stained liquor in the drug groups compared to control.

1 newborn in Camylofin group and 2 in Valethamate group had low APGAR initially but all newborns in all 3 groups had Apgar score >7 at 5 minutes.

There were no intrapartum or early neonatal deaths in all the study groups.

Limitations

Only primigravidae are included in study, so effects of drugs in multigravida cannot be studied. Study duration is less. Sample size 120 is limited.

CONCLUSION

Considering the results of this study, it can be concluded that, Camylofin dihydrochloride 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 Camylofin dihydrochloride may be given to low risk women in active labour. The promising beneficial effects of camylofin dihydrochloride 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 and helps woman in giving happy birth experience.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Agarwal SN, Shah VH, Gokhale AV, Amin JV. Randomized control comparative study to evaluate the effect of camylofin dihydrochloride and valethamate bromide in active phase of first stage of labour. Int J Reprod Contracept Obstet Gynecol 2024;13:1452-8.