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Original Research Article

A retrospective, observational, real-world evidence study to understand the clinical and obstetric characteristics and tolerability profile of women in labor managed with camylofin dihydrochloride injection

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ABSTRACT

Background: To determine the clinical and obstetric characteristics and tolerability profile of pregnant women in the active phase of labor who were managed with Camylofin dihydrochloride injection.

Methods: Retrospective data of 210 full-term pregnant women in the active phase of labor who were managed with Camylofin injection doses of 50 mg, 50+25 mg and 50+50 mg were considered in the study. The comparative effectiveness of 3 doses was evaluated using independent T-test and ANOVA at 5% level of significance.

Results: The overall mean maternal age was 25.4 (± 4.14) years with mean gestational age of 38.8 (± 1.04) weeks. In total, 77.1% (n=162) of patients needed 50 mg dose of Camylofin injection for adequate cervical dilatation, and additional doses of 25 mg or 50 mg were required in 16.7% (n=35) and 6.2% (n=13), of patients, respectively to accelerate the labor. The mean cervical dilatation rates increasing dose viz 2.8 cm/hr, 4.1 cm/hr and 2.9 cm/hr, respectively. The adverse events were 14.8% (n=23) in 50 mg arm, 34.3% (n=12) in 50+25 arm and 69.0% (n=9) in 50+50 arm. Of the total, 34 events (50.0%) were related to Camylofin dihydrochloride injection, i.e. ADRs.

The means of cervical dilation rate, active phase duration and total duration of labor were statistically significant (p-value <0.001) for 50 mg versus 50+25 mg.

Conclusions: The study infers Camylofin injection usage with consideration of dose escalation in the routine clinical management of labor. Both mother and neonate had shown comparable tolerability profile across the three dosage arms with minimal events.

Keywords: Real-world evidence, Camylofin, Labor management, Patient outcomes

INTRODUCTION

Labor is a multifactorial process that involves myometrial contraction, cervical effacement and dilatation and the expulsion of the fetus and placenta in an orderly manner.¹ The progress of labor is assessed by progressive dilatation and effacement of the cervix and the descent of the presenting part.² Normal labor has been defined as when an infant is born within 12 hours of active labor.³ The most vexing issue faced by obstetricians is the deviation of normal labor.

Prolonged (obstructed) labor affects 3-6% of women in labor globally⁴ and contributes to an estimated 2.8% of maternal mortality worldwide.^{5,6} In developing countries, it ranges from 4 to 70% of all maternal deaths along with high prenatal mortality rate.⁴ Obstructed labor is seen between 0.56-1.89% of all deliveries in the referral hospitals of India.⁷ Recent studies from India have reported the incidence of prolonged pregnancies were anywhere from 4.62%⁸ to 8.9%.⁴

Active management of labor is now a part of modern obstetrics and has shown to decrease the occurrence of prolonged labor when compared to physiological or expectant management.⁹ A Cochrane review found that active management significantly shortened the duration of labor by 1.27 hours, while the first stage of labor was significantly reduced by 1.56 hours.¹⁰ Interventions to shorten labor, such as antispasmodics, can be used as a treatment strategy in order to decrease the incidence of prolonged labor.

Antispasmodics are drugs that have either musculotropic or neurotropic effects and are used to relieve spasms of smooth muscle tissue.⁹ Smooth muscle constitutes about 15% of the cervix, which is mainly found just below the internal OS.^{11,12} Administering antispasmodics during labor could lead to faster and more effective dilatation of the cervix.¹³

Camylofin dihydrochloride a selective phosphodiesterase (PDE-4) enzyme inhibitor, has both musculotropic and neurotropic effects and has been recommended for use in acceleration of labor for more than six decades.¹⁴ Camylofin dihydrochloride primarily acts on the smooth muscles (intestine, ureter and cervix). It is a preferential cervical dilator, with no interference on the uterine contractions. In addition, its pharmacological effect on glands, eyes, heart, and circulation is minimal.¹⁴ Moreover, Camylofin dihydrochloride does not interfere with uterine contractility due to its PDE-4 iso-enzyme selectivity. Owing to this preferential cervical dilating action, Camylofin dihydrochloride has been widely recommended for use in accelerating the first stage of labor.¹⁴

There is a growing body of evidence to support the effectiveness and tolerability of Camylofin dihydrochloride in the active management of labor.^{1,14-17} Camylofin dihydrochloride has a fast onset and a long duration of action, coupled with superior effectiveness compared to other agents like Drotaverine, Hyoscine, and Valethamate.¹⁴ The results from various studies have demonstrated its effectiveness in the acceleration of labor in young women, both primigravida, and multigravida.¹⁴ Camylofin has been in use for over 60 years,^{18,19} with multiple citations in academic textbooks of repute,²⁷⁻³² treatment protocol and multiple research publications.^{14,26,27} However, there is a lack of consensus on appropriate usage of the dosage regimen of Camylofin dihydrochloride injection in the acceleration of labor.

The present multicenter, retrospective real-world evidence study was designed to understand the clinical and obstetric characteristics and tolerability profile of women in labor managed with three doses (50, 50+25 and 50+50 mg) Camylofin dihydrochloride injection. Additionally, was also evaluated the comparative effectiveness of the three dose regimens of Camylofin dihydrochloride injection in terms of duration of active phase, cervical dilatation rate

and total duration of labor across primigravida and multigravida women.

METHODS

This was a retrospective, observational, real-world evidence multicenter study designed to understand clinical and obstetric characteristics of pregnant women in the active phase of labor who were managed with Camylofin dihydrochloride injection in a real-world clinical practice setting. There was no prospective assessment or study specific procedures with patients during the study. The treatment and collection of the data were according to the real-world clinical practice.

The study was conducted in conformity with the principles of the declaration of Helsinki, international council for harmonization-good clinical practices (ICH-GCP) guidelines, Indian council of medical research, Indian GCP guidelines, and as per the approved protocol. The process of data analysis was only initiated after approval from the independent ethics committee. Since this was a retrospective data collection study, informed consent (ICF) was not required and accordingly, ICF waiver approval was taken from the ethics committee. Patient confidentiality was maintained during the data entry and analysis process.

The pregnant women who were previously managed with Camylofin dihydrochloride injection either with single dose 50 mg or an additional dose of 25 mg (50+25 mg) or 50 mg (50+50 mg) during the labor time were considered for the study. A time gap 1-hour interval between the two doses (50+25 mg and 50+50 mg) of Camylofin dihydrochloride injections was maintained during the management. The decision to escalate the dose was entirely to the clinical discretion of the investigators. The data of pregnant women treated in the period of five years, starting from May 2014 to June 2019 was considered for this retrospective analysis. The study was conducted at two Indian centers, Agra, Uttar Pradesh and Pune, Maharashtra including 105 pregnant women from each center.

The inclusive criteria was all adult pregnant women (gestational age 37 to 40 weeks) in labor who were managed with Camylofin injection. The exclusion criteria were women with multiple pregnancies, any comorbidities or condition managed with antihistaminics, tricyclic antidepressants, phenothiazines, disopyramide, pethidine having drug interaction with Camylofin and patients with incomplete hospital records.

The following data at respective antenatal (ANC) visits was collected -

Baseline data from ANC visit - The data collated for treatment initiation visit consisted of demographic details (age, weight, height), past pregnancy details (gravidity, parity, history of previous deliveries), and expected date of delivery.

ANC follow-up visits – data collected in follow-up visits comprised details of first trimester, second and third trimester, presence of any complications, general and systemic examinations, abdomen inspection, palpation, history of comorbidities and medications.

Intrapartum - data during labor included gestational age at admission, time of onset of labor, medication history, details of dosage, frequency and time of Camylofin dihydrochloride injection administered, and recorded cervical dilatation, cervical effacement, uterine contractions and fetal characteristics (heart rate, Apgar score), at regular time intervals. In addition, mode of delivery, any maternal and fetal complications, neonatal condition at birth i.e. birth weight and Apgar score at 1 minute and 5 minutes were also noted.

Following parameters were calculated from the base parameters for every patient: duration of active phase of (1st stage of) labor, duration of 2nd and 3rd stage of labor and total duration of labor.

Postpartum – safety data captured in the form of reported adverse events (AEs) and adverse drug reaction (ADRs) for both maternal and neonatal, post administration of Camylofin injection.

The evidence of effectiveness was evaluated based on the comparative effectiveness of different dose regimens of Camylofin dihydrochloride injection between primigravida and multigravida patients. While the tolerability parameters were from the reported ADRs and AEs across different doses of Camylofin dihydrochloride injection.

Statistical analysis

The categorical data was presented as percentage distribution (e.g., primigravida, multigravida). In the case

of continuous parameters, calculation of mean (\pm SD), median, minimum and maximum (e.g., age, weight, gravidity, parity, gestational age on admission, rate of cervical dilatation and cervical effacement, and fetal characteristics (Apgar score)) was done. The same analysis was repeated for patients managed with three dosages of Camylofin dihydrochloride injection. The frequency count for each dosage arm was calculated. For assessment of safety and tolerability, the proportion of patients reported AEs or ADRs and a list of these events (serious or non-serious), were described in terms of number and percentage of patients (n (%)) for each event. The causality analysis of ADRs as reported by the site PIs was presented in number and percentages.

The comparative assessment of mean active phase of the first stage of labor, mean cervical dilatation rate and mean total duration of labor was done for primigravida and multigravida patients (for three different dose regimens of Camylofin dihydrochloride injection), using independent sample t-test (to compare the duration between the two groups among various doses) and ANOVA at 5% level of significance and the corresponding p-values were presented.

RESULTS

Clinical and obstetric characteristics

The baseline clinical and obstetric characteristics of all enrolled patients are summarized Camylofin doses viz. in Table 1. The maternal characteristics including maternal age, weight, gravidity, parity, gestational age, cervical dilatation and cervical effacement and fetal characteristics comprising APGAR score. The parameters are detailed in terms of count (N), mean (\pm SD), median, minimum and maximum values.

Table 1: Summary of clinical and obstetric characteristics of study populations is given dose viz (n=210).

Category	Variable	N (%)	Mean	\pm SD	Median	Min	Max	
Camylofin Injection 50 mg	Maternal age (in years)	162 (77.1)	25.4	4.33	25.0	18.0	38.0	
	Weight (in kgs)	162 (77.1)	63.3	6.56	63.0	48.0	86.0	
	Gravidity	Primigravida	69 (42.6)	1.0	0.00	1.0	1.0	1.0
		Multigravida	93 (57.4)	2.5	0.80	2.0	2.0	7.0
		Total	162 (77.1)	1.9	0.97	2.0	1.0	7.0
	Parity	162 (77.1)	1.3	0.83	1.0	0.0	3.0	
	Gestational age (in weeks)	162 (77.1)	39.0	1.06	39.0	37.0	40.0	
	Cervical dilatation rate (cm per hour)	162 (77.1)	2.8	1.55	2.4	0.3	9.3	
	Cervical effacement rate (% per hour)	162 (77.1)	18.0	10.96	15.2	0.0	66.7	
	APGAR Score at 1 min	162 (77.1)	8.6	1.10	8.0	6.0	10.0	
	APGAR Score at 5 min	162 (77.1)	9.3	0.53	9.0	8.0	10.0	
	Maternal age (in years)	35 (16.7)	25.0	3.13	25.0	19.0	33.0	
	Weight (in kgs)	35 (16.7)	63.3	7.57	62.0	50.0	80.0	

Continued.

Category	Variable	N (%)	Mean	±SD	Median	Min	Max	
Camylofin Injection 75 mg (50+25)	Gravidity	Primigravida	11 (31.4)	1.0	0.00	1.0	1.0	
		Multigravida	24 (68.6)	2.3	0.48	2.0	3.0	
		Total	35 (16.7)	1.9	0.74	2.0	1.0	3.0
	Parity	35 (16.7)	0.7	0.75	1.0	0.0	2.0	
	Gestational age (in weeks)	35 (16.7)	38.4	0.77	39.0	37.0	39.0	
	Cervical dilatation rate (cm per hour)	35 (16.7)	4.1	1.14	4.4	1.7	7.0	
	Cervical effacement rate (% per hour)	35 (16.7)	27.1	9.01	29.6	0.0	50.0	
	APGAR Score at 1 min	35 (16.7)	9.9	0.47	10.0	8.0	10.0	
	APGAR Score at 5 min	35 (16.7)	9.9	0.24	10.0	9.0	10.0	
	Camylofin Injection 100 mg (50+50)	Maternal age (in years)	13 (6.2)	26.1	4.21	27.0	19.0	35.0
Weight (in kgs)		13 (6.2)	66.2	6.00	65.0	55.0	75.0	
Gravidity		Primigravida	0 (0.0)	0.0	0.0	0.0	0.0	0.0
		Multigravida	13 (100)	2.2	0.44	2.0	2.0	3.0
		Total	13 (6.2)	2.2	0.44	2.0	2.0	3.0
Parity		13 (6.2)	0.7	0.63	1.0	0.0	2.0	
Gestational age (in weeks)		13 (100)	38.5	1.13	38.0	37.0	40.0	
Cervical dilatation rate (cm per hour)		13 (6.2)	2.9	0.35	2.8	2.3	3.5	
Cervical effacement rate (% per hour)		13 (6.2)	27.1	6.63	23.1	20.0	38.5	
APGAR Score at 1 min		13 (6.2)	10.0	0.00	10.0	10.0	10.0	
APGAR Score at 5 min	13 (6.2)	10.0	0.00	10.0	10.0	10.0		
Camylofin Injection Overall	Maternal age (in years)	210 (100)	25.4	4.14	25.0	18.0	38.0	
	Weight (in kgs)	210 (100)	63.5	6.71	63.0	48.0	86.0	
	Gravidity	Primigravida	80 (38.1)	1.0	0.00	1.0	1.0	1.0
		Multigravida	130 (61.9)	2.3	0.73	2.0	2.0	7.0
		Total	210 (100)	1.9	0.91	2.0	1.0	7.0
	Parity	210 (100)	1.2	0.84	1.0	0.0	3.0	
	Gestational age (in weeks)	210 (100)	38.8	1.04	39.0	37.0	40.0	
	Cervical dilatation rate (cm per hour)	210 (100)	3.0	1.53	2.8	0.3	9.3	
	Cervical effacement rate (% per hour)	210 (100)	20.1	11.09	20.0	0.0	66.7	
	APGAR Score at 1 min	210 (100)	8.9	1.12	9.0	6.0	10.0	
APGAR Score at 5 min	210 (100)	9.5	0.54	10.0	8.0	10.0		

Of the total enrolled patients (N=210), 162 patients (77.1%) were given Camylofin injections 50 mg dose, 35 patients (16.7%) required additional injection of 25 mg dose (75 mg (50+25)) and 13 patients (6.2%) needed additional injection of 50 mg dose (100 mg (50+50)) to manage the labor.

The maternal age of study population was distributed in a range from 18 to 38 years with overall mean of 25.4 (± 4.14) years. The mean maternal weight was comparable between 50 mg (63.3 kgs) and 75 mg (50+25) (63.3 kgs) categories whereas in 100 mg (50+50) category, the mean was slightly higher (66.2 kgs).

Table 2: Overall group analysis.

Groups considered	Parameter	Active phase of 1 st stage duration (in minutes)	Cervical dilatation rate (cm per hour)	Total duration of labor (in hours)
Camylofin Injection 50 mg vs 75 mg (50+25)	50 mg (N=162) mean (\pm SD)	167.5 (\pm 96.32)	2.8 (\pm 1.55)	3.1 (\pm 2.47)
	50+25 (N=35) mean (\pm SD)	84.6 (\pm 37.75)	4.1 (\pm 1.14)	1.8 (\pm 0.56)
	Mean difference 95% C.I	63.29 - 102.44	-1.82 - -0.9	0.84 - 1.69

Continued.

Groups considered	Parameter	Active phase of 1 st stage duration (in minutes)	Cervical dilatation rate (cm per hour)	Total duration of labor (in hours)
	SE	16.6	0.3	0.4
	<i>p</i> -value	<0.0001	<0.0001	<0.0001
Camylofin Injection 50 mg vs 100 mg (50+50)	50 mg (N=162) mean (±SD)	167.5 (±96.32)	2.8 (±1.55)	3.1 (±2.47)
	50+50 (N=13) mean (±SD)	118.8 (±19.59)	2.8 (±0.35)	2.5 (±0.30)
	Mean difference 95% C.I	30.19 - 67.26	-0.41 - 0.21	0.20 - 1.03
	SE	26.8	0.4	0.7
	<i>p</i> -value	<0.0001	0.5349	0.0042
Camylofin Injection 75 mg (50+25) vs 100 mg (50+50)	50+25 (N=35) mean (±SD)	84.6 (±37.75)	4.1 (±1.14)	1.8 (±0.56)
	50+50 (N=13) mean (±SD)	118.8 (±19.59)	2.8 (±0.35)	2.5 (±0.30)
	Mean difference 95% C.I	-51.07 - -17.21	0.83 - 1.70	-0.91 - -0.40
	SE	11.0	0.3	0.2
	<i>p</i> -value	0.0002	<0.0001	<0.0001

*The p-value and 95% C.I were assessed using an independent t-test

Table 3: Tests of significance (ANOVA) for exploratory endpoints.

Camylofin dose (mg)	LS Mean	SE	95% C.I		p-value		
			Lower	Upper	50 vs 75 (50+25)	75 (50+25) vs 100 (50+50)	50 vs 100 (50+50)
Active phase of 1st stage duration (in minutes)							
50	167.5	6.8	154.10	180.88			
75 (50+25)	84.6	14.6	55.82	113.43	<0.0001	0.4450	0.1260
100 (50+50)	118.8	24.0	71.50	166.03			
Overall	150.7	6.3	138.19	163.14	<0.0001		
Cervical dilatation rate (cm per hour)							
50	2.8	0.1	2.54	2.99			
75 (50+25)	4.1	0.2	3.64	4.60	<0.0001	0.0214	0.9706
100 (50+50)	2.9	0.4	2.07	3.65			
Overall	3.0	0.1	2.54	3.15	<0.0001		
Total duration of labor (in hours)							
50	3.1	0.2	2.75	3.43			
75 (50+25)	1.8	0.4	1.10	2.56	0.0063	0.6303	0.5968
100 (50+50)	2.5	0.6	1.28	3.68			
Overall	2.8	0.1	2.54	3.15	0.0077		

Table 4: Primigravida vs Multigravida within the treatment arms.

Category	Statistical variable	Active phase of 1 st stage duration (in minutes)	Cervical dilatation rate (cm per hour)	Total duration of labor (in hours)
Camylofin 50 mg	Primigravida (N=69) Mean (±SD)	201.4 (±100.24)	2.3 (±1.16)	3.4 (±2.07)
	Multigravida (N=93) Mean (±SD)	142.3 (±85.48)	3.1 (±1.71)	2.9 (±2.72)
Primigravida Vs Multigravida	Mean difference 95% C.I	29.46 - 88.69	-1.29 - -0.40	-0.20 - 1.29
	SE	14.6	0.2	0.4
	<i>p</i> value	0.0001	0.0002	0.1513

Continued.

Category	Statistical variable	Active phase of 1 st stage duration (in minutes)	Cervical dilatation rate (cm per hour)	Total duration of labor (in hours)
Camylofin 75 mg (50+25)	Primigravida (N=11) Mean (±SD)	90.4 (±39.73)	3.9 (±1.03)	1.9 (±0.47)
	Multigravida (N=24) Mean (±SD)	82.0 (±37.37)	4.2 (±1.19)	1.8 (±0.60)
Primigravida Vs Multigravida	Mean difference 95% C.I	-21.29 - 38.28	-1.20 - 0.44	-0.28 - 0.49
	SE	13.9	0.4	0.2
	P value	0.5570	0.3431	0.5808
Camylofin 100 mg (50+50)	No patient data for 100 mg (50+50) primigravida			
Primigravida Vs Multigravida				

*The p-value and 95% C.I were assessed using an independent t-test

Table 5: Primigravida vs Multigravida across the treatment arms.

Camylofin dosage arm	Gravida	Statistical variable	Active phase of 1 st stage duration (in minutes)	Cervical dilatation rate (cm per hour)	Total duration of labor (in hours)
50 mg vs 75 mg (50+25)	Primigravida	50 mg (N=69) mean (±SD)	201.4 (±100.24)	2.3 (±1.16)	3.4 (±2.07)
		75 mg (50+25) (N=11) Mean (±SD)	90.4 (±39.73)	3.9 (±1.03)	1.9 (±0.47)
		Mean difference 95% C.I	76.44 - 145.46	-2.31 - -0.85	0.93 - 2.08
		SE	30.7	0.4	0.6
		P value	<0.0001	0.0004	<0.0001
50 mg vs 75 mg (50+25)	Multigravida	50 mg (N=93) Mean (±SD)	142.3 (±85.48)	3.1 (±1.71)	2.9 (±2.72)
		75 mg (50+25) (N=24) Mean (±SD)	82.0 (±37.37)	4.2 (±1.19)	1.8 (±0.60)
		Mean difference 95% C.I	37.13 - 83.62	-1.72 - -0.51	0.46 - 1.68
		SE	17.9	0.4	0.6
		P value	<0.0001	0.0005	0.0007
50 mg vs 100 mg (50+50)	Primigravida	No patient in 100 mg (50+50) group			
50 mg vs 100 mg (50+50)	Multigravida	50 mg (N=93) Mean (±SD)	142.3 (±85.48)	3.1 (±1.71)	2.9 (±2.72)
		100 mg (50+50) (N=13) Mean (±SD)	118.7 (±19.59)	2.9 (±0.35)	2.5 (±0.30)
		Mean difference 95% C.I	2.89 - 44.24	-0.14 - 0.66	-0.20 - 0.96
		SE	23.9	0.5	0.8
		P value	0.0260	0.1967	0.1966
75 mg (50+25) vs 100 mg (50+50)	Primigravida	No patient in 100 mg (50+50) group			
75 mg (50+25) vs 100 mg (50+50)	Multigravida	75 mg (50+25) (N=24) Mean (±SD)	81.9 (±37.37)	4.2 (±1.19)	1.8 (±0.60)
		100 mg (50+50) (N=13)	118.7 (±19.59)	2.9 (±0.35)	2.5 (±0.30)

Continued.

Camylofin dosage arm	Gravida	Statistical variable	Active phase of 1st stage duration (in minutes)	Cervical dilatation rate (cm per hour)	Total duration of labor (in hours)
		Mean (\pm SD)			
		Mean difference 95% C.I	-55.83 - -17.8	0.85 - 1.92	-0.99 - -0.39
		SE	11.2	0.3	0.2
		P value	0.0004	<0.0001	<0.0001

Table 6: Reported AEs as coded using MedDRA by SOC, HLT, and PT across the three Camylofin dosage arms

MedDRA Coding SOC, HLT, PT	50 mg (%) (N=162)	75 mg (50+25) (%) (N=35)	100 mg (50+50) (%) (N=13)	All Subjects (%) (N=210)
Maternal AEs	23 (14.8)	12 (34.3)	9 (69.2)	44 (21.0)
General disorders and administration site conditions	15 (9.2)	6 (17.1)	4 (30.8)	25 (11.9)
Mucosal findings abnormal				
Mucosal dryness	13 (8.0)	6 (17.1)	4 (30.8)	23 (10.9)
Febrile disorders				
Post procedural fever	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.9)
Gastrointestinal disorders				
Nausea and vomiting symptoms	13 (8.0)	5 (14.3)	5 (38.5)	23 (10.9)
Vomiting				
Injury, poisoning and procedural complications				
Neurological and psychiatric procedural complications	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)
Compensatory sweating				
Pregnancy, puerperium and perinatal conditions	6 (3.7)	3 (8.6)	1 (7.7)	10 (4.7)
Maternal complications of pregnancy NEC	4 (2.5)	(0.0)	(0.0)	4 (1.9)
Inferior vena cava syndrome				
Postpartum complications NEC				
Postpartum hemorrhage	2 (1.2)	3 (8.6)	1 (7.7)	6 (2.8)
Neonatal AEs	6 (3.7)	0	0	6 (2.9)
Respiratory, thoracic and mediastinal disorders				
Neonatal hypoxic conditions	2 (1.2)	(0.0)	(0.0)	2 (0.9)
Neonatal asphyxia				
Pregnancy, puerperium and perinatal conditions				
Amniotic fluid and cavity disorders of pregnancy NEC	4 (2.5)	0 (0.0)	0 (0.0)	4 (1.9)
Meconium stain				

Table 7: Distribution of patient ADRs is given across treatment arms using medical dictionary, MedDRA coding (SOC, HLT, PT).

MedDRA coding SOC, HLT, PT	50 mg (%) (N=162)	75 mg (50+25) (%) (N=35)	100 mg (50+50) (%) (N=13)	All subjects (%) (N=210)
Number of subjects with at least one ADRs				
Maternal	21 (12.9)	11 (31.4)	6 (46.1)	38 (18.1)
Neonatal	3 (1.8)	0 (0.0)	0 (0.0)	3 (1.4)
Maternal ADR				
Skin and subcutaneous tissue disorders	10 (6.2)	2 (5.7)	1 (7.7)	13 (6.2)

Continued.

MedDRA coding SOC, HLT, PT	50 mg (%) (N=162) (%)	75 mg (50+25) (%) (N=35)	100 mg (50+50) (%) (N=13)	All subjects (%) (N=210)
Rashes, eruptions and exanthems				
NEC	0 (0.0)	2 (5.7)	1 (7.7)	3 (1.4)
Skin rashes				
<i>Probable</i>	0 (0.0)	2 (5.7)	1 (7.7)	3 (1.4)
<i>Possible</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin vasomotor conditions				
Flushing	10 (6.2)	0 (0.0)	0 (0.0)	10 (4.8)
<i>Probable</i>	6 (3.7)	0 (0.0)	0 (0.0)	6 (2.9)
<i>Possible</i>	4 (2.5)	0 (0.0)	0 (0.0)	4 (1.9)
Injury, poisoning and procedural complications				
Neurological and psychiatric procedural complications	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.9)
Compensatory sweating				
<i>Probable</i>	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.9)
<i>Possible</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions				
Mucosal findings abnormal	16 (9.9)	6 (17.1)	4 (30.8)	26 (12.4)
Mucosal dryness				
<i>Probable</i>	14 (8.6)	6 (17.1)	4 (30.8)	24 (11.4)
<i>Possible</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile disorders				
Post procedural fever	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.9)
<i>Probable</i>	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.9)
<i>Possible</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders				
Headaches NEC	0 (0.0)	2 (5.7)	1 (7.7)	3 (1.4)
Headache				
<i>Probable</i>	0 (0.0)	2 (5.7)	1 (7.7)	3 (1.4)
<i>Possible</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastro-intestinal disorders				
Nausea and vomiting symptoms	2 (1.2)	1 (2.9)	0 (0.0)	3 (1.4)
Vomiting				
<i>Probable</i>	1 (0.6)	1 (2.9)	0 (0.0)	2 (0.9)
<i>Possible</i>	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)
Neonatal	3 (1.8)	0 (0.0)	0 (0.0)	3 (1.4)
Respiratory, thoracic and mediastinal disorders				
Neonatal hypoxic conditions	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.9)
Neonatal asphyxia				
<i>Probable</i>	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)
<i>Possible</i>	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)
Pregnancy, puerperium and perinatal conditions				
Amniotic fluid and cavity disorders of pregnancy NEC	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)
Meconium stain				
<i>Probable</i>	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)
<i>Possible</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Multigravida patients were comparatively higher in 50 mg (57.4%) and 75 mg (50+25) (68.6%) dose categories than

the primigravida. However, in 100 mg (50+50) category, there were no primigravida patients. The mean cervical

dilatation rate (cm per hour) is comparable between 50 mg (2.8 cm/hr) and 100 mg (50+50) (2.9 cm/hr) dose categories. The rate is slightly increased in 75 mg (50+25) dose category (4.1 cm/hr), which is higher than the overall average rate of dilatation (3.0 cm/hr).

The mean cervical effacement rate was 18.0% per hour in 50 mg and 27.1% per hour in 75 mg (50+25) and 100 mg (50+50) arms, which is higher by about 50%.

The mean Apgar score for the treatment arm 50 mg was 8.6 (1 min) and 9.3 (5 min). The mean Apgar scores at 1 and 5 minutes were almost the same for 75 mg (50+25), 9.9 and 9.9, and 100 mg (50+50) arms, 10.0 and 10.0, respectively. The overall score was good for 1 min (8.9) and 5 min (9.5) with no noted complications.

No obvious differences with means of maternal age, gravida, gestational age and Apgar score were observed across the three dose categories.

Efficacy

The significance analysis of three treatment arms for exploratory parameters was analyzed using independent t-test (two arms) and ANOVA test (three arms). The resulted mean with 95% C.I and p-values are given in Tables 2 and 3.

In the significance analysis of overall groups, 50 versus 75 mg (50+25) and 75 mg (50+25) versus 100 mg (50+50) were resulted as statistically significant (p-value <0.0003) for all three endpoints, duration of active phase, cervical dilatation rate and total duration of labor.

While, in group 50 versus 100 mg (50+50), only mean duration of active phase and mean total duration of labor were statistically significant (p-value <0.005) and mean cervical dilatation rate was not statistically significant (p-value 0.5349).

The ANOVA test for three arms wise came significant (p-value <0.01) for 50 versus 75 mg (50+25) mean duration of active phase, mean cervical dilatation rate, and mean total duration of labor. While dose increase from 50 to 100 mg (50+50) was not significant for all three parameters (p-value >0.05). For 75 mg (50+25) versus 100 mg (50+50), only rate of cervical dilatation was significant (p-value <0.05) whereas the other two parameters were not significant (p-value >0.05).

Primigravida versus multigravida analysis

The significance analysis of primigravida versus multigravida within the treatment arms is shown in Table 4 and across the treatment arms is given in Table 5.

Within the treatment arms

In dose category, 50 mg, the mean duration of active phase and mean cervical dilatation rate were significant ((p-value

<0.0003) between primigravida and multigravida whereas mean total duration of labor was not significant (Table 4). For dose arm 75 mg (50+25), none of the parameters were significant (p-value >0.05). While in 100 mg (50+50) category there were no primigravida patients to compare with multigravida patients.

The mean cervical dilatation rate was increased by 0.8 cm, mean duration of active phase was reduced by 60 mins and mean total duration of labor was reduced by 0.5 hours from primigravid to multigravida in 50 mg arm. However, the change was not very considerable for 75 mg (50+25) with 0.3 cm, 8 mins, and 0.1 hours, respectively.

Across the treatment arms

For dosage groups, 50 mg versus 75 mg (50+25), both primigravida and multigravida and group 75 mg (50+25) versus 100 mg (50+50), multigravida, the differences between mean duration of active phase, mean cervical dilatation rate and mean total duration of labor were significant (p-value <0.001) (Table 5). For group 50 mg versus 100 mg (50+50) multigravida, only mean duration of active phase of labor was significant (p-value <0.05) and the other two parameters were not significant. There were no primigravida patients in 100 mg (50+50) arm to compare the significance with the other two groups.

Safety

Safety assessments consist of all AE and/or ADRs reported across the three Camylofin dosage arms captured during post-delivery follow-up visits. AE analyses were performed for all patients who received at least one dose of Camylofin injection during the maintenance therapy. AEs were broken down as maternal (anticholinergic (dryness of mouth, fever, and sweating), hypotension, PPH and vomiting) and neonatal (birth asphyxia and meconium stained liquor). The results from the safety analysis of the treatment arms are provided in Table 6.

Overall, 68 AEs, 62 maternal and 6 neonatal, were documented for 44 patients (21.0%) and 6 neonates (2.9%) across all three treatment arms. Of these total AEs, no serious AE (SAE) and treatment emerging (TE) deaths were reported (Table 6). Amongst, 69.2% was reported in 100 mg (50+50) arm, followed by 34.3% in 75 mg (50+25) and 14.8% in 50 mg. While neonatal events were reported only in 50 mg arm.

All ADRs were assessed with respect to their causal relationship to study medication, i.e. 'related' or 'not related' to the administration of Camylofin dihydrochloride injection. The five categories used to assess the causal relationship in the safety database (probable, possible, probably not, not related, not assessable). ADRs assessed as related to occurring in patients in all three arms, broken down by MedDRA SOC, HLT and PT are presented in Table 7. Total 38 patients (18.1%) were reported maternal ADRs wherein 50 mg

arm, 7 patients had reported 2 ADRs and 2 patients reported 3 ADRs. Two patients in 50 mg arm had both maternal ADR and neonatal ADR.

The incidences of AEs were 14.8% (n=23) in 50 mg arm, 34.3% (n=12) in 75 mg (50+25) arm and 69.0% (n=9) in 100 mg (50+50) arm. Of the total 68 AE events, 34 events (50.0%), as catered to maternal - dryness of mouth, fever, sweating and vomiting, and neonatal - birth asphyxia and meconium stain, were related to administration of Camylofin dihydrochloride injection, i.e. ADRs.

Out of the total 52 ADRs (34 AEs + 18 ADRs), 49 were reported for maternal and 3 for neonates. The causality assessment of these ADRs had suggested that 46 ADRs, (44 maternal and 2 neonate) had 'probable' and 6 ADRs (5 maternal and 1 neonate) had 'possible' relation with the Camylofin injection.

Mucosal dryness as underlying disease was the leading AE in the total cases of the study patients followed by vomiting, postpartum hemorrhage, inferior vena cava syndrome, post-partum fever, and compensatory sweating in at least 1 case. While for neonates, meconium stain and neonatal asphyxia were the commonly reported events.

DISCUSSION

Camylofin dihydrochloride injection was studied in 210 pregnant women in labor to collect clinical and obstetric data that represents the real-world clinical practice to the extent possible.

Primary objective is to determine the clinical and obstetric characteristics of women in active phase of labor who were managed with Camylofin injection and secondary objective is to evaluate the tolerability profile of the patients treated with the injection. The exploratory objectives are to evaluate the comparative effectiveness of different doses of Camylofin injection in mean duration of active phase of 1st stage of labor, mean cervical dilatation rate and mean total duration of labor in primigravida and multigravida patients.

Overall data from the study indicated that Camylofin injections has been a drug of choice in managing the active phase of labor by accelerating cervical dilatation for both primigravida and multigravida patients. Also, dose escalation of the injection was considered to a moderate extent in multigravida patients.

The 50 mg dose of Camylofin injection was sufficient enough to bring in the necessary cervical dilatation in 162 patients (77.1%) whereas 35 patients (16.7%) needed additional dose, i.e., 25 mg of Camylofin injection and 13 patients (6.2%) required the same dose for second time, i.e., 50 mg of Camylofin injection. Overall, irrespective of the gravidity, the dose escalation from 50 mg to 75 mg (50+25) was effective in accelerating the labor with increase in the rate of cervical dilatation. At the same time,

further increase in dose to 100 mg (50+50) does not appear to be significant with respect to cervical dilatation rate and in turn reducing the total duration of labor time.

Camylofin has been reported to possess neurotropic action via anti-cholinergic effect and hence known to cause anticholinergic effects (dryness of mouth, fever, sweating), besides other side effects like hypotension, PPH, vomiting and maternal tachycardia. In the current study none of the study population had reported tachycardia in mother and/or neonate. The symptoms associated with the higher dose, specifically dry mouth and rashes, were (percentage wise) high in two injection groups, 100 mg (50+50) and 75 mg (50+25), than the single injection, 50 mg (Table 6 and 7). The APGAR score was normal for all neonates. In all three arms, comparable patterns of AEs as well as ADRs were presented, which is mainly consistent with the safety profile known for the population examined, including the occurrence of rare cases of severe events. Moreover, ADRs found in this study were already known and reported for Camylofin dihydrochloride injection in management of acceleration of labor. Other known side effects such as severe cases of infusion-related events or allergic hypersensitivity reactions were not observed in the current study. Even though the pattern of events was comparable among all three arms patients, the AE incidence was comparatively high in 100 mg (50+50) arm, then 75 mg (50+25) arm than 50 mg arm. No treatment emerging death, serious adverse event and death case in patients, were reported during the study period. The outcomes of the study are compared with the values reported in the literature. All of the reported studies had used single Camylofin injection (50 mg) and hence the corresponding values from the current study were only compared to assess the results.

In a placebo-controlled study, the reported mean rate of cervical dilatation was 1.92 cm/hour and the mean total duration was 4 hours 42 minutes in 50 mg Camylofin dose.¹⁴ In comparator-studies, a single-center study where Camylofin injection (50 mg) was compared in 100 pregnant women, mean duration of active phase of 1st stage of labor was 141.4 (± 55.41) minutes and the mean rate of cervical dilatation was 3.3 (± 1.03) cm/hours and mean duration of delivery was 172.0 (± 60.82) minutes.¹ In another randomized comparative study conducted on 63 primigravida women, the cervical dilatation rate was 1.78 cm/hour and mean duration of active phase of 1st stage was 332.5 minutes with 50 mg Camylofin injection.¹⁴ A randomized controlled study, 50 primigravida women, the cervical dilatation rate with 50 mg Camylofin injection was, 3.14 cm/hour.¹⁴ In the current study, the corresponding values (50 mg) are 167.5 (± 96.32) minutes and 2.8 (± 1.55) cm/hour, 186.0 (± 148.2) minutes (3 hours 6 minutes), respectively. There are no reported studies using multiple (two) injections of Camylofin drug (in the Indian population) and therefore, no comparisons are drawn with any literature reports.

Limitations

The gravida analysis included groups with different sample sizes (e.g. Multigravida patients in 50 mg – 93 patients versus 100 mg – 13 patients), for this reason, the evaluation and the reported p-values across the groups limited to the respective groups. The results from within the groups, 50 mg, primigravida versus multigravida and 75 mg (50+25), primigravida versus multigravida can be considered owing to comparable sample sizes. However, within the group analysis would not offer information about the effectiveness of escalation of dose from 50 mg to 50+25 mg or 50+50 mg. Importantly, no primigravida patients in the 100 mg (50+50) dosage arm further limits the extendibility of the resulted gravida analysis.

Considering all the above reasons, drawing the gravida analysis observations and inferences, if any, would rather be taken with extra caution particularly for 100 mg (50+50) dose.

CONCLUSION

The study infers Camylofin injection usage with consideration of dose escalation in the routine clinical management of labor. Both mother and neonate had shown comparable tolerability profile across the three dosage arms with minimal events.

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