The Journal of Obstetrics and Gynecology of India (November–December 2020) 70(6):425–439
https://doi.org/10.1007/s13224-020-01343-3

SYSTEMATIC REVIEWS/META-ANALYSIS

Effectiveness and Safety of Camylofin in Augmentation of Labor: A Systematic Review and Meta-Analysis

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Received: 11 March 2020 / Accepted: 21 June 2020 / Published online: 11 August 2020

Abstract

This systematic review and meta-analysis assessed the effectiveness and safety of camylofin compared with other antispasmodics (drotaverine, hyoscine, valethamate, phloroglucinol, and meperidine) in labor augmentation. A systematic literature search until March 27, 2018, was performed, and data on the cervical dilatation rate (CDR) and duration of stages of labor reported in 39 eligible articles were analyzed using a random-effects model. CDR was significantly higher (0.38 cm/h, 95% confidence interval (CI) 0.10 to 0.67, $p=0.007$), and the duration of the first stage of labor was significantly shorter (− 41.21 minutes, 95% CI, − 77.19 to − 5.22, $p=0.02$) in women receiving camylofin than those receiving other antispasmodics for labor augmentation. CDR was significantly higher with camylofin compared with valethamate (0.6 cm/h, 95% CI 0.4 to 0.9, $p<0.0001$) and hyoscine (20 mg) (0.5 cm/h, 95% CI 0.1 to 0.8, $p=0.02$). The duration of the first stage of labor was significantly shorter with camylofin compared with hyoscine (20 mg) (− 59.9 min, 95% CI, − 117.9 to − 1.8, $p=0.04$). However, CDR and the duration of first stage of labor were not statistically different between camylofin and drotaverine groups. The percentage of women having nausea and vomiting, cervical/vaginal tear, and postpartum hemorrhage were comparable with all antispasmodics, whereas tachycardia was least reported in women receiving camylofin (3, 2.07%) than those receiving other antispasmodics. This meta-analysis demonstrated the benefit of camylofin in labor augmentation with a faster CDR and reduction in the active first stage of labor in Indian women.

Keywords Augmentation · Camylofin · Cervical dilatation rate · Duration of first stage · Systematic review and meta-analysis

Introduction

Prolonged labor is defined as a labor of more than 24 h duration, either due to a prolonged latent phase of > 20 h in a primigravida or > 14 h in a multipara, or due to a "protraction disorder." [1] The overall rate of obstructed labor, prolonged labor, and failure to progress is 110.4 per 1000 deliveries in developing countries including India [2]. Prolonged labor is often associated with increased chorioamnionitis, perineal lacerations, and birth asphyxia [3–5] and is a leading indication for cesarean sections [6–8]

A cervical dilatation rate (CDR) of < 0.5 to 1 cm/h during the active phase is commonly considered as the slow progress of labor and is an indication for active intervention that includes use of oxytocin, amniotomy, etc. [9]. Slow CDR is an indication for cesarean section; however, cesarean deliveries are not devoid of their share of problems. Therefore, less invasive interventions for augmenting labor might be safer and more effective in preventing

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13224-020-01343-3) contains supplementary material, which is available to authorized users.

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risks to mothers and fetuses. Antispasmodic drugs are used in clinical practice to fasten cervical dilation by acting on the smooth muscles of the utero-cervical plexus. Various antispasmodic drugs such as drotaverine hydrochloride (40 mg), camylofin dihydrochloride (50 mg), valethamate bromide (8 mg), and hyoscine butyl bromide (20 and 40 mg) have been evaluated in randomized controlled trials (RCTs). However, the evidence to support their effectiveness in the augmentation of labor is limited [9]. The World Health Organization guidelines for labor augmentation mention the use of antispasmodic agents as an important research priority [9].

Although antispasmodic agents have been used in clinical practice for the last 6 decades, the comparative effectiveness of these agents for cervical dilatation and labor augmentation has not been well-established. Camylofin is safe and effective in shortening the duration of labor compared with other antispasmodic agents such as drotaverine, hyoscine, and valethamate [10]. We conducted a systematic review and network meta-analysis (NMA) to compare the effectiveness and safety of various antispasmodic agents that are widely used for labor augmentation in India.

Methods

A protocol was designed to define the objectives, outcomes to be analyzed, and eligibility criteria for guiding the systematic literature search and selection of relevant articles for this NMA. Observational studies and RCTs published in English, in women with term pregnancies (≥ 37 weeks' gestation), irrespective of parity, receiving an antispasmodic agent or placebo/no intervention (on account of being in the control group) for labor augmentation during any stage, by intramuscular or intravenous route and reporting on at least one of the following outcome measures were considered: duration of labor, CDR, and interval between the first dose of antispasmodic to delivery, i.e., injection to delivery interval (IDI). Studies involving women with obstetric complications and surgical and severe medical complications were excluded.

Literature Search Strategy

A systematic literature search was conducted using search terms "antispasmodics," "effect," and "augmentation" in PubMed, Cochrane Library, and Embase databases irrespective of the publication date. The search strings with keywords are presented in supplementary material (Box 1). Hand searches from the citation lists of relevant publications, conference proceedings, and studies from clinicaltrials.gov database were also screened.

Screening, Data Extraction, and Risk of Bias Assessment

After screening the various databases, full text articles of seemingly eligible studies were retrieved and reviewed by two independent reviewers who finalized the set of articles to be included in the NMA through a consultative process. Data on study characteristics (study design, number of participants, and demographic characteristics), effectiveness parameters (CDR, duration of first, second, and third stages of labor, and IDI), and adverse events (AEs) (tachycardia, nausea, vomiting, flushing of the face, postpartum hemorrhage [PPH], cervical or vaginal tear, fetal tachycardia, fetal bradycardia, and fetal distress) were extracted from the eligible studies by two independent extractors and were matched to resolve discrepancies. The risk of bias assessment was performed using the Cochrane Handbook for Systematic Interventions Reviews [11]. The selected studies were assessed for following areas of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias; the risks were classified as low, high, and unclear.

Statistical Analysis

Following data extraction, a meta-analysis using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen) and NMA using SAS® version 9.4 was performed. Both the studies aimed at comparing the effectiveness of camylofin with other antispasmodics (valethamate, drotaverine, hyoscine, phloroglucinol, meperidine, placebo, and expectant management or no intervention [henceforth referred to as the "control" arm]) on the parameters of CDR, duration of labor (first, second, and third stage and overall duration), and IDI. The random-effects model was adopted because of clinical heterogeneity between the studies. The mean difference and 95% confidence intervals (95% CIs) were estimated for all the parameters across both the arms. For the analysis, a study using other adjuncts with camylofin was considered under the camylofin arm with the assumption that the control group of 'expectant management' might have used the same analgesics and tranquilizers, as well as amniotomy except for camylofin, which would have balanced the confounding effect; [12]. Similarly, studies using valethamate bromide with hyoscine were considered under the valethamate arm, considering its widespread use as an adjunct [13, 14]. Ten studies not reporting standard deviations (SDs) for the means of effectiveness parameters could not be included in the quantitative analysis. Primarily, available data on primigravida women, when reported separately for all outcomes of interest were, included in the analysis; data reported

exclusively for multiparous women were excluded to minimize the bias due to comparatively shorter duration of labor in them. One such study reporting data only for multiparous women was excluded from the NMA. The studies wherein data were not reported separately for primigravida and multiparous women were included in the analysis. The safety parameters were summarized across the different antispasmodics.

Results

Study Selection

A literature search conducted on March 27, 2018, yielded 467 citations. Thirty-nine full text articles were included in this NMA (Fig. 1).

Study Characteristics

Among the 39 studies, 27 were conducted in India. The antispasmodics used in the intervention groups were camylofin (5 studies) [12, 14–17], drotaverine hydrochloride (19 studies) [13, 15, 18–34], valethamate bromide (13 studies) [13, 14, 19, 20, 24–26, 29, 31, 35–38], and hyoscine butyl bromide (10 studies) [16, 22, 33, 34, 39–44]. Seven studies [30, 45–50] evaluated other antispasmodics such as pethidine, phloroglucinol, and tramadol that are not widely used in India. Other adjunct treatments for analgesia and augmentation of labor were reported in 9 studies, which mainly included hyoscine, opioid analgesia, and oxytocin (Table 1). Women receiving camylofin for labor augmentation received maximum 1 dose; those receiving drotaverine and valethamate were given a maximum of 3 doses.

Risk of Bias Within Studies

Figure 2 shows the risk of bias assessment for the included studies. Nineteen of 39 studies had a "high risk" of bias. Eleven studies had a high risk of bias because there was no randomization of the participants or blinding of the participants, investigators, or outcomes. Nine studies had a high risk of bias because of the incomplete data and/or selective

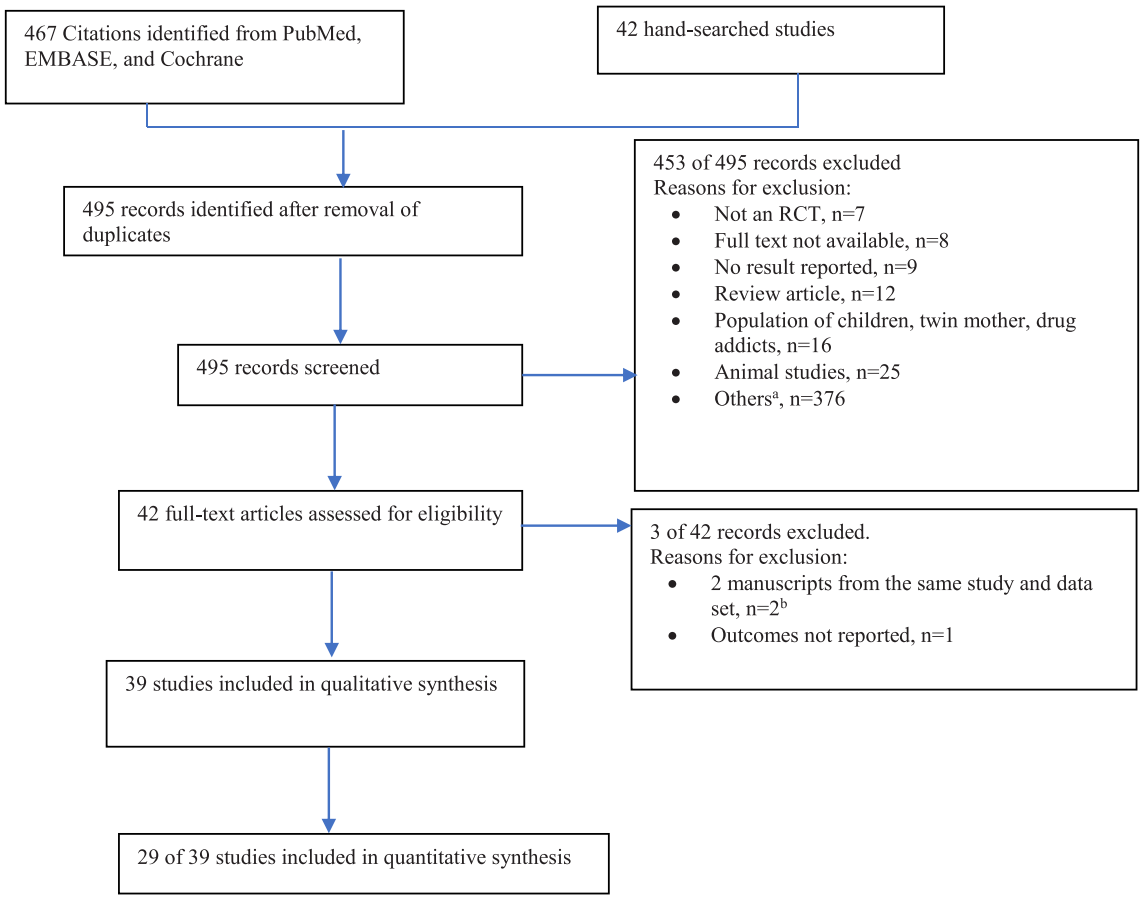

Fig. 1 Selection and inclusion of studies. [a]Others: Studies with anesthetic, analgesic, non-antispasmodics. [b]Parent publications included

Table 1 Summary of included studies

	Study code	References	Study design	Location	Patients randomized (N)	Study population/women analyzed	Arm 1			Arm 2			Arm 3		
							Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)
1	A29	[a]Bachani and Topden [12]	NR	India	1400	P + M/P	Camylofin + Trm/Drt	700	320	NA	NA		exptnt mngnt	700	270
2	A36	Binu [15]	RCT	Bangalore, India	126	P/P	Drt	63	59	Camy	63	59	NA	NA	NA
3	A24	Dayama et al. [16]	RCT	India	150	P/P	Camy	50	50	Hyo	50	50	No medication	50	50
4	A23	Sarbhjit et al. [14]	NR	Patiala, India	200	P + M/P	Camy	100	49	NA	NA	NA	Vlt + Hyo	100	45
5	A41	[¥]Himangi et al. [17]	Double-blind RCT	Mumbai	100	P/Qual	Camy	50	50	NA	NA	NA	Placebo	50	50
6	A39	Aziz [18]	RCT	Bhopal	300	P + M/P	Trm	100	50	Drt	100	50	No medication	100	48
7	A38	*Dahal et al. [19]	Single blind RCT	Dharan, Nepal	300	P + M/P + M	Vlt	100	100	Drt	100	100	No medication	100	100
8	A37	[¥]Changede [20]	Prospective	Mumbai	120	P + M/Qual	Drt	30	15	Vlt	30	15	No medication	60	30
9	A26	[¥]Gaikwad and Gurram [21]	NR	Pune , India	100	P + M/Qual	Drt	50	25	NA	NA	NA	No medication	50	25
10	A6	*Gupta et al. [22]	RCT	India	150	P + M/P + M	Drt	50	49	Hyo	50	47	No medication	50	50
11	A8	[b]Ibrahim et al. [23]	Double-blind RCT	Cairo, Egypt	352	N/N	Drt	176	161	NA	NA	NA	Nrml Sln	176	159
12	A27	[¥]Jogi [24]	RCT	Chattisgarh, India	200	NR/Qual	Drt	100	100	Vlt	100	100	NA	NA	NA
13	A1	*[c]Madhu et al. [25]	RCT	Miraj-Sangli, India	150	P + M/P + M	Drt	50	49	Vlt	50	49	Nrml Sln	50	48

Table 1 (continued)

	Study code	References	Study design	Location	Patients randomized (N)	Study population/women analyzed	Arm 1			Arm 2			Arm 3		
							Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)
14	A40	Nagaria and Jaiswal [27]	NR	Raipur	200	P + M/P	Drt	100	60	Vlt	100	60	NA	NA	NA
15	A33	*Naqvi, et al. [28]	RCT	Karachi	100	P + M/P + M	Phlg	50	50	Drt	50	48	NA	NA	NA
16	A17	[d]Roy et al. [30]	RCT	Kolkata, India	200	P + M/P	Drt	100	40	NA	NA	NA	No medication	100	42
17	A44	Selvaraj and Natarajan [26]	Prospective	Madurai, India	150	P/P	Drt	50	50	Vlt	50	50	No medication	50	50
18	A7	Sharma et al. [29]	RCT	Delhi, India	150	N/N	Drt	50	50	Vlt	50	50	No medication	50	50
19	A43	[¥]Sinhasane and Nishty [31]	NR	Gulbarga, Karnataka	600	P + M/Qual	Drt	200	NR	Vlt	200	NR	Ctrl	200	NR
20	A5	Singh, et al. [32]	Double-blind RCT	Delhi, India	100	P/P	Drt	50	44	NA	NA	NA	Dist-water	50	40
21	A28	Srivastava et al. [33]	Prospective	Lucknow, India	60	N + M/N + M	Hyo	20	20	Drt	20	20	No medication	20	20
22	A31	[¥]Tehalia et al. [34]	RCT	India	100	P + M/Qual	Drt	50	50	Hyo	50	50	NA	NA	NA
23	A47	[¥]Thapa [13]	Prospective	Sinamangal, India	99	P + M/P	Drt	50	31	Vlt + Hyo	49	27	NA	NA	NA
24	A2	Köstü et al. [35]	RCT	Turkey	73	N/N	Vlt	37	30	NA	NA	NA	Nrml Sln	36	32
25	A45	Kuruvila [36]	RCT	Vellore, India	120	N/N	Vlt	57	29	NA	NA	NA	normal saline	53	26
26	A46	[¥]Sreelatha [37]	Prospective	Bangalore, India	200	P/Qual	Vlt	50	50	NA	NA	NA	Ctrl	48	48

Table 1 (continued)

	Study code	References	Study design	Location	Patients randomized (N)	Study population/women analyzed	Arm 1			Arm 2			Arm 3		
							Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)
27	A15	Yilmaz et al. [38]	Double-blind RCT	Ankara, Turkey	160	N	Mepe	53	48	Vlt	53	47	Nrml Sln	54	49
28	A10	[*e]Imaralu et al. [39]	Double-blind RCT	South-western Nigeria	166	P + M/P + M	Hyo	84	80	NA	NA	NA	Nrml Sln	82	80
29	A35	[f]Kirim et al. [40]	Double-blind RCT	Istanbul, Turky	420	P + M/P	Hyo	210	95	NA	NA	NA	Nrml Sln	210	85
30	A19	Maged et al. [41]	Double-blind RCT	Cairo	120	P/P	Hyo (20 mg)	40	40	Hyo (40 mg)	40	40	Nrml Sln	40	40
31	A18	[g]Qahtani and Hajeri [42]	Double-blind RCT	Dammam	110	P/P	Hyo	NR	52	NA	NA	NA	Nrml Sln	NR	45
32	A20	[¥h]Samuels et al. [43]	Double-blind RCT	West Indies	142	P + M/Qual	Hyo	60	29	NA	NA	NA	Nrml Sln	69	34
33	A9	[¥i]Shekhawat et al. [44]	Single-blinded RCT	Yazd, Iran	188	M/Qual	Hyo	94	94	NA	NA	NA	Nrml Sln	94	94
34	A21	Direkvand-Moghadam et al. [45]	RCT	Ilam, Iran	90	N/N	Peth	45	45	NA	NA	NA	Nrml Sln	45	45
35	A34	Anjum et al. [46]	RCT	Rawalpindi	122	P/P	Phlg	61	61	NA	NA	NA	Dist-water	61	61
36	A4	Ara et al. [47]	Double-blind RCT	Quetta	100	P/P	Phlg	50	50	NA	NA	NA	Nrml Sln	50	50
37	A16	*Tabassum, et al. [48]	Double-blind RCT	Peshawar	100	P + M/P + M	Phlg	50	48	NA	NA	NA	Dist-water	50	47

Table 1 (continued)

	Study code	References	Study design	Location	Patients randomized (N)	Study population/women analyzed	Arm 1			Arm 2			Arm 3		
							Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)	Intervention	Randomized (N)	Analyzed (N)
38	A13	Tahir et al. [49]	Double-blind p RCT	Lahore	100	P/P	Phlg	50	50	NA	NA	NA	Dist-water	50	50
39	A32	¥Daftary et al. [50]	Open-label parallel group, mono-centric comparative matching trial	Mumbai	400	P/Qual	Programmed labor protocol (Trm + Drt/Camy/Vlt/Hyo)	200	200	NA	NA	NA	Ctrl treated per prevailing practices	200	200

Mixed data for primigravida and multiparous women were available

Camy, camylofin; Cmp/Ctrl, comparator or control drug; Dist-water, distilled water; Drt, drotaverine hydrochloride; Exptnt mngnt, expectant management; Hyo, hyoscine butylbromide; Mepe, meperidine; M, multiparous; N, number of patients randomized; NR, not reported; Nrml Sln, normal saline; N, nulliparous; Peth, pethidine; Phlg, phloroglucinol; P, primigravida; Qual, qualitatively analyzed; Trm, tramadol; Vlt, valethamate bromide

*Separate data for primigravida women were not available; hence overall data was used for the analysis

¥Not included in quantitative analysis because data were not available the in analyzable form e.g. standard deviation to the mean was not available

[a]Camy group-Opiod analgesia, diazepam, tramadol/drotaverine, amniotomy, and oxytocin of required; Expectant management group-NR

[b]Drt group-Oxytocin augmentation :101, 62.7%, Meperidine hydrochloride: 96, 59.6%; Placebo group-Oxytocin augmentation : 96, 59.6%; Meperidine hydrochloride: 113, 71.1%

[c] Drt group-Oxytocin augmentation: 49,100%, Pethidine 39; Vlt group-Oxytocin augmentation: 49,100%, Pethidine: 40; Nrml Sln-Oxytocin augmentation: 48, 100% Pethidine: 42

[d]Drt group-Oxytocin augmentation: 11; No medication group-Oxytocin augmentation: 11

[e]Hyo group-Oxytocin augmentation: 43; Nrml Sln-Oxytocin augmentation: 47

[f]Hyo group-Oxytocin augmentation: 90, 45.7%; Nrml Sln-Oxytocin augmentation: 88, 47.6%

[g]Hyo group-Opioid analgesia: 22; Nrml Sln-Opoid analgesia: 45

[h]Hyo group-Oxytocin augmentation: 3; Nrml Sln-Oxytocin augmentation: 8

[i]Hyo group-Oxytocin augmentation: 40, 42.6%; Nrml Sln-Oxytocin augmentation: 51, 54.3%

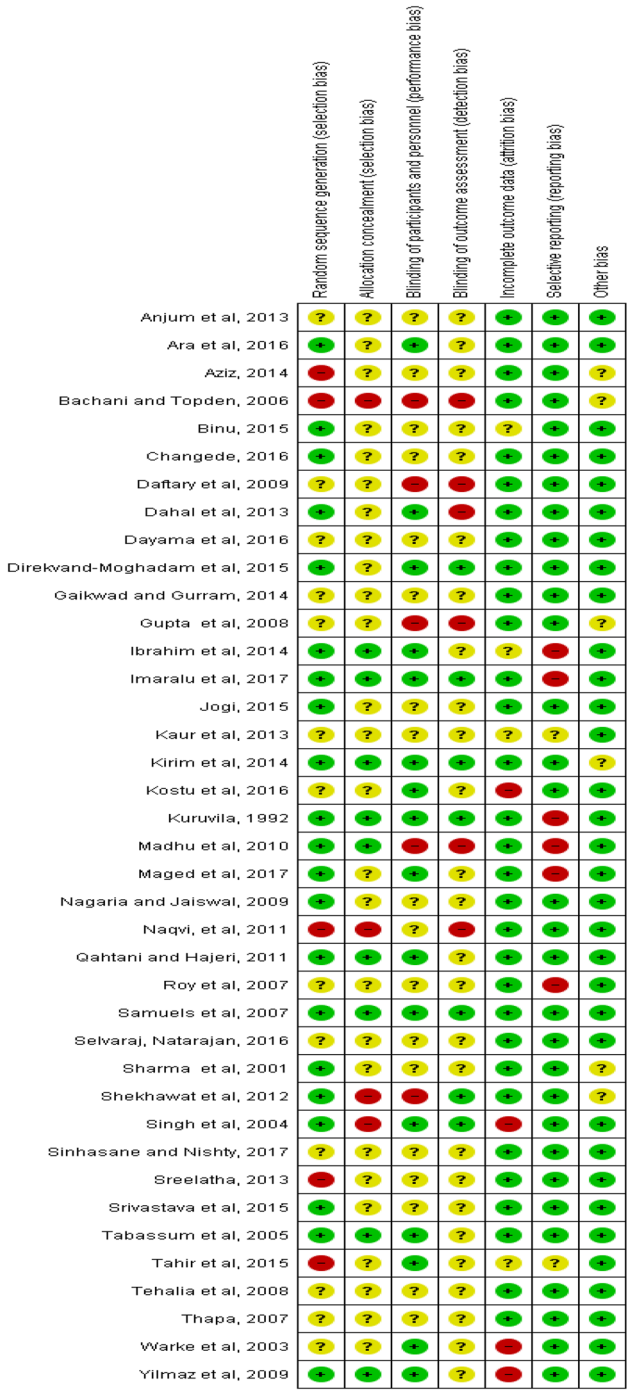

Fig. 2 Risk of bias within studies

reporting of the outcomes. The risk was unclear for one or more parameters for the remaining studies.

Effectiveness of Antispasmodics for Labor Augmentation

Camylofin Versus other Antispasmodics

Figure 3 presents the results of the random-effect meta-analysis comparing camylofin and other antispasmodics.

The difference in the mean duration of the first stage of labor (41.21 minutes, 95% CI, − 77.19 to − 5.22, $p = 0.02$), IDI (− 38.75 minutes, 95% CI, 78.18 to 0.69), and CDR (0.38 cm/h, 95% CI 0.10 to 0.67, $p = 0.007$) between women receiving camylofin and those receiving other antispasmodics significantly favored Camylofin for labor augmentation.

Comparative Effectiveness of Antispasmodics

The number of studies analyzed for each effectiveness parameter are summarized in Table 2.

The network diagrams of various comparisons of antispasmodics are shown in Fig. 4a, b. The results of NMA for 4 antispasmodics available in India are presented in Fig. 5. The results of NMA for all antispasmodics are shown in supplementary Tables 2 to 7.

The difference in mean CDR significantly favored camylofin over valethamate (0.6 cm/h, 95% CI 0.4 to 0.9, $p < 0.0001$) and hyoscine (20 mg) (0.5 cm/h, 95% CI 0.1 to 0.8, $p = 0.02$). The CDR results favored camylofin over drotaverine. The difference in the mean duration of the first stage of labor between camylofin and hyoscine (20 mg) (− 59.9 min, 95% CI, − 117.9 to − 1.8, $p = 0.04$) significantly favored camylofin. There was no statistically significant difference in the mean duration of the first stage of labor between drotaverine and camylofin (9.5 minutes, 95% CI, − 42.5 to 61.5, $p = 0.70$).

The difference in the mean total duration of labor favored camylofin over hyoscine (20 mg) (− 18.1 min, 95% CI − 342.8 to 306.7, $p = 0.60$) and drotaverine (− 25.8 min, 95% CI, − 96.7 to 45.1, $p = 0.32$).

The differences in the mean duration of the third stage of labor between camylofin and drotaverine (− 3.3 min, 95% CI − 5.45 to − 1.10, $p = 0.006$), valethamate (− 3.6 min, 95% CI, − 6.52 to − 0.77, $p = 0.02$), and hyoscine (20 mg) (− 2.9 min, 95% CI, − 5.43 to − 0.38, $p = 0.03$) significantly favored camylofin. The differences in the mean duration of the second stage of labor and IDI were comparable across all the four antispasmodics.

Sensitivity Analysis

One of the studies included in the NMA, Bachani and Topden 2005, had a sample size of 700 women in the intervention arm and thus could have skewed the results. Moreover the other adjunct treatment(s) used with the camylofin arm

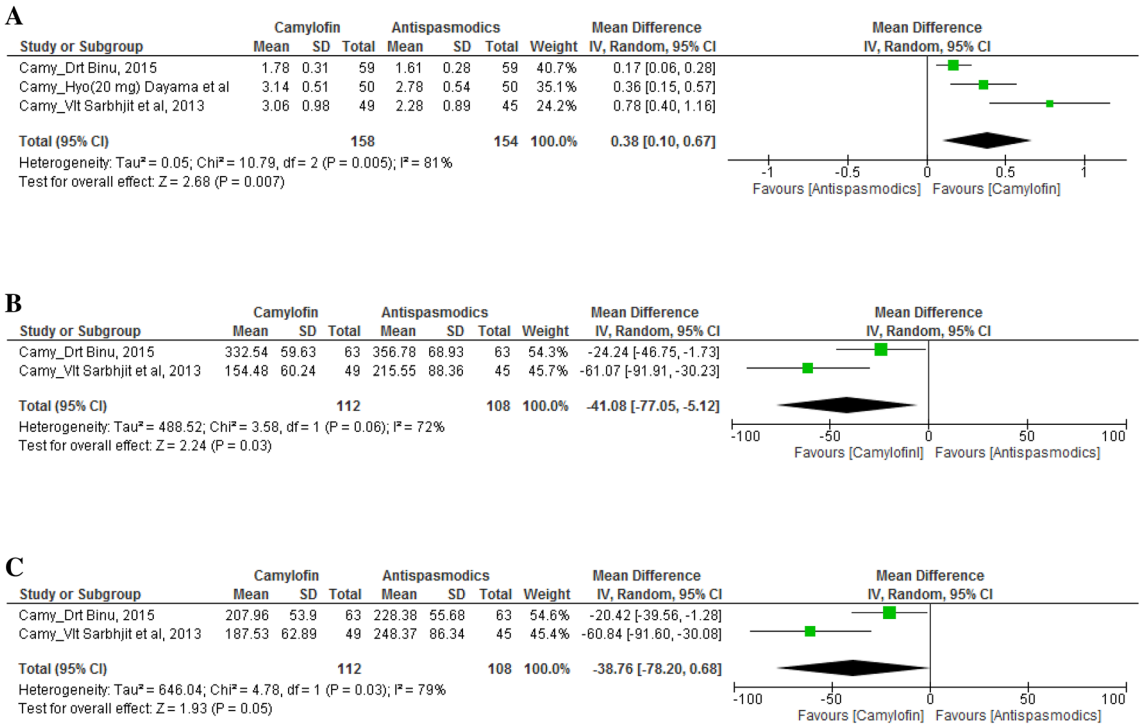

Fig. 3 Comparative effectiveness of camylofin versus other antispasmodics. **a** Cervical dilatation rate. **b** Duration of first stage of labor. **c** Injection to delivery interval

Table 2 Summary of studies analyzed for each effectiveness outcome

Outcomes	Number of studies	Number of participants analyzed
Total duration of labor (minutes)	6 [12, 15, 28, 33, 46, 48]	1083
Cervical dilatation rate (centimeters/h)	10 [14–16, 22, 25, 26, 29, 30, 36, 48]	1202
Duration of the first stage of labor (minutes)	24 [12, 14, 15, 18, 19, 22, 23, 26, 27, 28, 30, 32, 33, 35, 38–42, 45–49	3580
Duration of the second stage of labor (minutes)	20 [12, 15, 18, 22, 23, 26, 27, 28, 32, 33, 38–42, 45–49]	3042
Duration of the third stage of labor (minutes)	17 [12, 15, 18, 22, 23, 29, 32, 33, 39, 40, 45–49]	2681
Injection-delivery interval	11 [12–15, 18, 19, 25, 26, 27–29, 38]	1834

might have also confounded the results [12]. Thus, a sensitivity analysis excluding this study was performed. The sensitivity analysis also showed a similar trend as that of the primary analysis except for the mean difference in the duration of the first stage of labor, which favored camylofin over drotaverine (− 21.3 minutes, 95% CI, − 93.83 to 51.26, $p = 0.55$) (Supplementary Tables 8-12).

Safety of Antispasmodics

A qualitative summary of frequently reported maternal and fetal AEs is presented in Table 3.

Maternal Outcomes

A total of 145 events of tachycardia were reported in the selected studies. The incidence of tachycardia was most commonly reported in women receiving valethamate (106/145, 73.10%) and least reported in women receiving camylofin (3/145, 2.07%). Similarly, dryness of mouth was reported most frequently with valethamate (103/140, 73.57%) and least frequently with hyoscine (10/140, 7.14%). Nausea and vomiting (21/110, 19.09%), cervical/vaginal tear (3/20, 15.00%), and postpartum hemorrhage (2/13, 15.38%) were other events reported with camylofin use.

AEs reported with camylofin were comparatively lower (42 events in 963 women) than reported with drotaverine (80

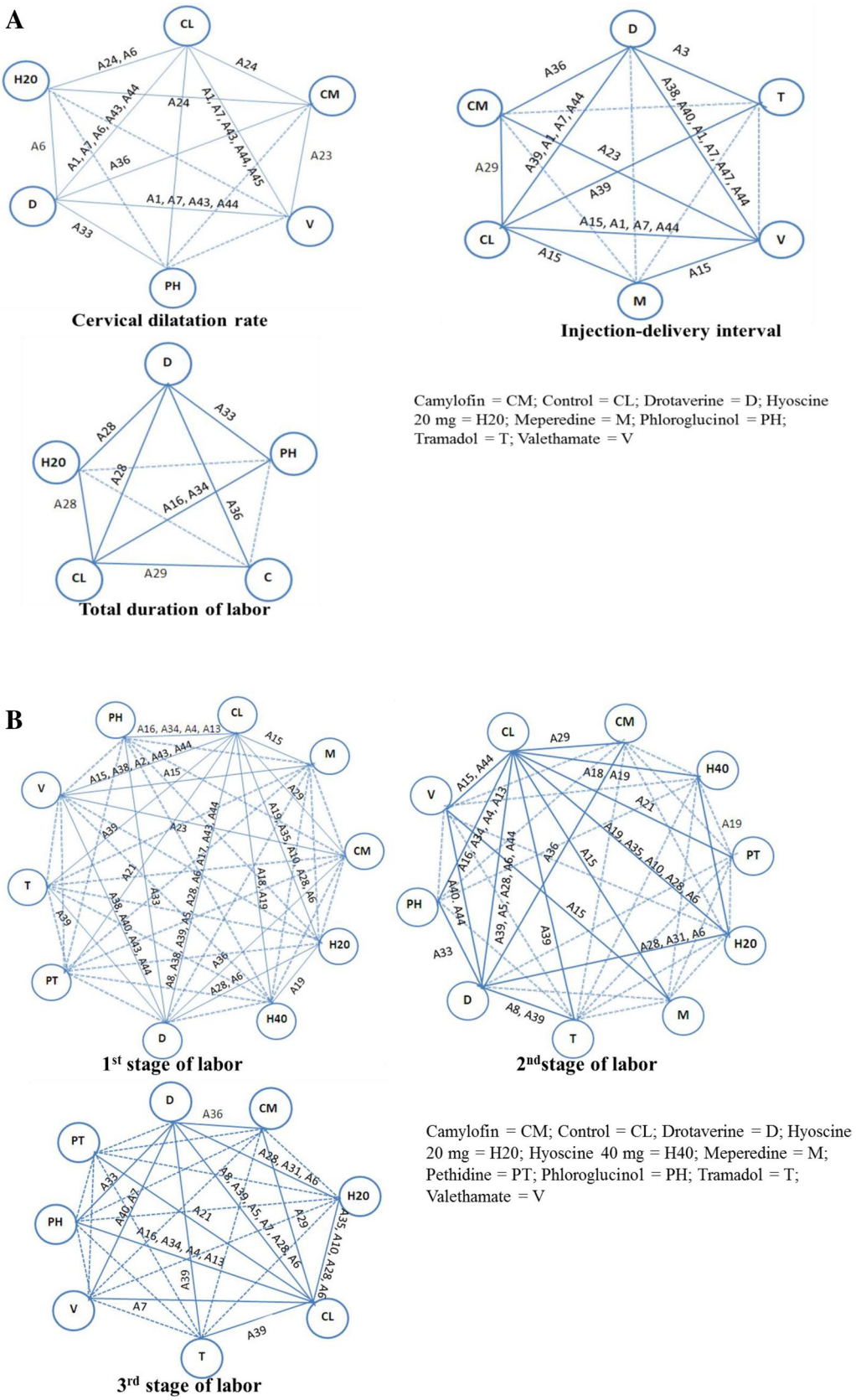

Fig. 4 Network diagrams for assessment of comparative effectiveness of antispasmodics

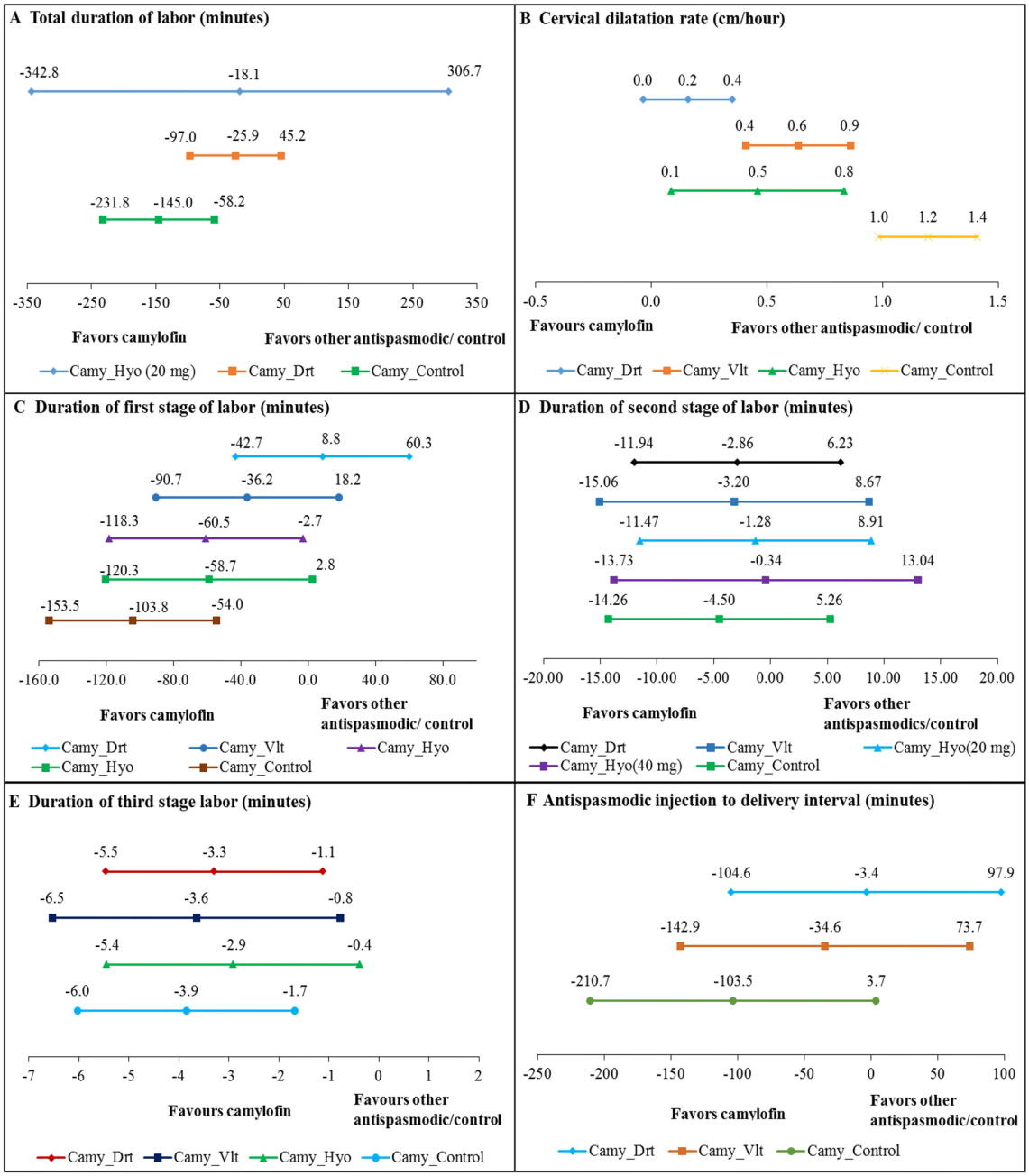

Fig. 5 Results of network meta-analysis of comparative effectiveness of antispasmodics. Camy—Camylofin dihydrochloride; Drt—drotaverine hydrochloride; Hyo—hyoscine butylbromide; Peth—pethidine; Phlg—phloroglucinol; Tra—tramadol; Vlt—valethamate bromide

events in 1069 women), hyoscine (27 events in 476 women), and valethamate (235 events in 770 women). Nausea and vomiting (21/42 events, 50%) and dryness of mouth (13/42, events, 31%) were most frequently reported AEs in women receiving camylofin. Tachycardia was commonly reported in women receiving hyoscine (12/27, 44.4%) and valethamate (106/235, 45.1%). Postpartum hemorrhage and cervical/vaginal tear (2 and 3 events in 963 women, respectively) were rarely reported events in women receiving camylofin compared with women receiving drotaverine (6 and 8 events in 1069 women, respectively).

Fetal Outcomes

Fetal distress was the most commonly observed AE among babies born to women receiving camylofin (238/270, 85.30%). A majority of these events (235) were reported in

Table 3 Maternal and fetal events with antispasmodics

		Camylofin, 5 studies, ($n=963$)		Drotaverine, 19 studies, ($n=1069$)		Hyoscine, 10 studies, ($n=476$)		Valethamate, 12 studies, ($n=770$)	
Event of interest	Total events (N)	Number of events (n)	% Within number of events	Number of events	Events/ Total events	Number of events	Events/ Total events	Number of events	Events/ Total events
Maternal outcomes in patients receiving the intervention									
Tachycardia	145	3	2.07	21	14.48	12	8.28	106	73.10
Dryness of mouth	140	13	9.29	13	9.29	10	7.14	103	73.57
Postpartum hemorrhage	13	2	15.38	6	46.15	1	7.69	0	0.00
Cervical or vaginal tear	20	3	15.00	8	40.00	3	15.00	1	5.00
Nausea and vomiting	110	21	19.09	32	29.00	1	0.91	25	22.73
Total		42		80		27		235	
Event of interest	Total events (N)	Number of events	Events/Total events	Number of events	Events/ Total events	Number of events	Events/ Total events	Number of events	Events/ total events
Fetal outcomes when mothers received this intervention									
Fetal tachycardia/bradycardia	136	0	0.00%	6	4.41	3	2.21	127	93.38
Fetal distress	279	238	85.30	19	6.81	7	2.51	7	2.51
Neonatal morbidity	19	0	0.00	10	52.63	0	0.00	9	47.37

A total of 10 studies did not report on safety. They are not considered in safety (n)

1 study having a high risk of bias, which used drotaverine or tramadol along with camylofin in the intervention arm [12]. Abnormal fetal heart rate (tachycardia/bradycardia) and neonatal morbidities observed with other antispasmodics were not observed with camylofin.

Discussion

This NMA assessed the comparative effectiveness of antispasmodics widely used in women for labor augmentation. Rohwer et al, in their systematic review and meta-analysis reported a significant reduction in the total duration and the duration of the first stage of labor, and increased CDR with the use of antispasmodics compared with the no medication/placebo/sodium chloride, however, the evidence was of low quality [51]. We performed a meta-analysis to compare the effects and safety of camylofin with other antispasmodics. The stress of labor releases catecholamines, which may lead to prolonged labor and compromised fetal oxygenation [52]. Prolonged labor is associated with increased risks for obstetric intervention and poor fetal outcomes [53]. Increased catecholamine secretion can be reduced by the synergistic use of analgesics and antispasmodics in the active phase of labor [52]. Camylofin has both musculotropic and neurotrophic effects, whereby it relaxes smooth muscle by inhibiting the acetylcholine-muscarinic receptor binding. Camylofin primarily acts on the cervical smooth muscles. Although camylofin possesses a musculotropic action, it does not interfere with uterine contractility because of its phosphodiesterase IV isoenzyme selectivity. Because of this unique preferential cervical dilating action, camylofin accelerates the first stage of labor. Camylofin has a prompt action that begins in 15 to 20 min and lasts until 4 to 5 h [17, 54].

In this NMA, the duration of the first stage of labor was significantly shorter by 60 min with camylofin than with hyoscine (20 mg). This reduction was much greater than the 11.7 min observed in the RCT comparing camylofin and hyoscine (20 mg) [16]. The duration of the first stage of labor was also observed to be shorter with camylofin than with high-dose hyoscine (40 mg) and valethamate; however, the differences were not statistically significant. Camylofin performed better than drotaverine in shortening the third stage of labor, although the result was not statistically significant.

In previous reports, CDR was better with camylofin (1.92 cm/h) compared with valethamate-hyoscine combination (0.69 cm/h) [14]. Our results mirrored the trend and demonstrated that camylofin fared better in increasing the CDR compared with valethamate, hyoscine (20 mg). Although not statistically significant, a CDR faster by about 2 mm (0.2 cm)/h was observed with camylofin than with drotaverine. After excluding the study involving the camylofin-drotaverine combination, we found that the duration of the first stage of labor was shorter for camylofin by 21 min than that for drotaverine. The results were similar in a RCT comparing camylofin with drotaverine with significantly better CDR and IDI in the camylofin group [15]. CDR with camylofin was faster by 0.4 cm/h, and the duration of the first stage of labor and IDI were shorter by approximately 40 min compared with other antispasmodics (considered as 1 group) in the present meta-analysis.

As per a recent pan-Indian observational study, labor augmentation occurred in nearly half of the women (44.7%) in primary health centers [55]. Similarly, in Rajasthan, labor augmentation was common (53.5% to 93.0%) [56]. Antispasmodics like drotaverine and valethamate were commonly used drugs after oxytocin and misoprostol for labor augmentation [55, 56]. Our findings showed that the performance of camylofin and drotaverine in augmenting labor was comparable, which might be attributed to the same mechanism of action. Moreover, camylofin is cost-effective as only a single injection is recommended for labor augmentation compared with multiple doses of other antispasmodics [10].

The common AEs with camylofin included nausea and vomiting. Compared with other antispasmodics, camylofin was safer with a low rate of AEs such as tachycardia, dryness of mouth, and PPH in mothers.

Overall, our results show that camylofin was beneficial in labor augmentation, especially in increasing CDR and reducing the active first stage of labor in comparison with all other antispasmodics currently available in India. The duration of the first stage of labor is expected to be reduced with camylofin because of its specific mode of action. Hence, our results may have applicability, especially for primigravida women, in whom the duration of the first stage of labor is often prolonged. The safety profile of camylofin was comparable with that of other antispasmodics..

The major limitation of this NMA was that most studies were from resource-limited settings, conducted in a real-world scenario, and hence had a high risk of bias. The studies were predominantly from India. Since the antispasmodics were used as a part of the active management of labor protocol with a lack of systematic study design, there was a large heterogeneity across studies. Furthermore, few studies did not report data separately for primigravida women. Although a trend towards the benefit of camylofin in reducing the total duration of labor was observed, the inclusion of some mixed data (from primigravida and multiparous women) may have led to this statistically inconclusive result. We used a random-effects model for meta-analysis to minimize the possibility of bias in the results. Pregnancy outcomes are reported in very few studies. Moreover, among the studies, which have reported the pregnancy outcomes, the reasons for cesarean section deliveries and fetal distress are not clearly reported; hence, the failure of augmentation and fetal safety could not be assessed quantitatively. Additionally, safety is underreported in many studies. Nonetheless, the NMA showed a statistically significant reduction in CDR because of camylofin. Although not statistically significant, it has also shown favorable effects of camylofin over other antispasmodics in reducing the total duration of labor, predominantly in primigravida women. These results may help in clinical decision-making practices of obstetricians when using an antispasmodic for augmentation of labor.

Conclusion

Camylofin is being used as an antispasmodic agent since the last 6 decades in Indian women to shorten the active stage of labor; however, there are limited head-to-head comparisons with other antispasmodics such as valethamate, hyoscine, and drotaverine. This NMA provides a comparative evidence of the effectiveness and safety of camylofin with other antispasmodics. The results show that camylofin significantly accelerates CDR and reduces the first stage of labor compared with valethamate and hyoscine. Although not significant, camylofin was also effective in achieving a shorter first stage of labor than drotaverine. The safety profile of camylofin was comparable with that of other antispasmodics. With faster action and lesser side effects compared with other antispasmodics, camylofin proves to be a more suitable option in the armamentarium for labor augmentation in India.

Acknowledgement The authors thank Neelam Joglekar from Covance Scientific Services & Solutions Pvt. Ltd., for performing systematic literature search, synthesizing the literature, and providing medical writing support for the development of the manuscript. The authors also thank Garima Joshi from Covance Scientific Services & Solutions Pvt. Ltd., for providing statistical support and performing meta-analysis.

Funding This meta-analysis was funded by Abbott Healthcare Pvt. Ltd. The views expressed in this article are independent views of the authors and not of Abbott Healthcare Pvt Ltd.

Compliance with ethical standards

Conflict of interest The authors express that there is no conflict of interest.

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