Effect of Intrapartum Hyoscine Butylbromide Administration on Duration of Labor and Mode of Delivery: A Systematic Review and Meta - Analysis

Original Article

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ABSTRACT

Background: Hyoscine Butylbromide (HBB) is a potent parasympatholytic drug with strong antispasmodic action contributing to cervical dilation during labor.

Objective: We aimed to determine if hyoscine butylbromide (HBB) during labor is associated with shortened duration of labor.

Search Strategy: We searched several electronic databases from inception to march 2019 using various search terms.

Selection Criteria: Randomized controlled trials comparing HBB vs. placebo regarding labor duration.

Data Collection and Analysis: After screening and data extraction, mean difference with 95% confidence interval (CI) for continuous data and odds ratio with 95% CI for categorical data were calculated.

Main Results: Fourteen articles (2287 patients) were included. HBB shortens durations of first stage (MD = -60.86, 95% CI [-82.89 to -38.84]), second stage (MD = -3.18, 95% CI [-5.12 to -1.24]) and third stage of labor (MD = -0.84, 95% CI [-1.19 to -0.50]). Indeed, overall rate of cervical dilatation was greater in HBB group (MD= 0.65-minute, 95% CI, 0.51 to 0.80). However, HBB does not affect the rate of vaginal or cesarean deliveries.

Conclusions: Hyoscine Butylbromide shortens the duration of all stages of labor and increases the rate of cervical dilatation. However, it does not affect the mode of delivery

Key Words: Buscopan, cervical dilatation, HBB, labor duration, meta-analysis.

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INTRODUCTION

The slow progress of labor is a common clinical situation in obstetric practice[1]. A longer duration of labor is associated with a reduced chance of spontaneous vaginal delivery and an increased risk of serious maternal or perinatal complications[2]. The rate of cesarean delivery (CD) remains very high in many parts of the world, and the risk of maternal death is around three times higher after CD than a normal vaginal delivery[3,4].

The use of spasmolytics during labor is a common practice in obstetrics after the introduction of active management of labor by O'Driscoll in the 1980s[5,6]. Active management of labor focuses on manipulating the physiological delivery process to ease labor, reduce maternal and neonatal adverse outcomes, and avoid labor complications[7]. Labor is divided into three stages, with the first stage consisting of two phases, a latent phase, which should be less than 8 hours, and an active phase, which starts at 3 cm dilatation and progresses at a rate of one cm/hr. If the progress is slow, waiting four hours is recommended before doing an active intervention[8]. Amniotomy and oxytocin infusion in augmentation of labor is a well-known practice endorsed by the American College of Obstetrics and Gynecology (ACOG)[9].

Hyoscine butylbromide (HBB) is a parasympatholytic medication that acts as an effective antispasmodic drug without the undesired adverse effects of atropine. It has no central action as it does not cross the blood-brain barrier. Additionally, it exerts a spasmolytic action on the smooth muscles of the gastrointestinal, biliary, and genitourinary tracts[10].

HBB blocks the transmission of neural impulses in the intraneural parasympathetic ganglia of abdominal organs, thus relieving spasms in the smooth muscles of

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the gastrointestinal, biliary, urinary tract, and female genital organs, particularly the cervico-uterine plexus, thus helping cervical dilatation[11]. It is not categorized as an analgesic drug for pain relief in the ordinary state, as it does not directly influence the pain pathway; however, it may stop painful cramps and spasms[12].

Pharmacodynamic properties of HBB such as an onset of action of 10 min for intravenous form, time to peak of about 20–60 min, and duration of action of around two hours are identified. It has hepatic metabolism and is excreted through urine and feces (42–61% and 28–37%, respectively)[13]. The injection form of HBB is contraindicated in some conditions like hypersensitivity to the drug, untreated narrow-angle glaucoma, active hemorrhage, paralytic ileus, myasthenia gravis, chronic lung disease (repeated administration), and tachycardia secondary to cardiac insufficiency[14].

There is evidence that the use of HBB in the active management of labor is associated with a more favorable delivery course[15-17]. Reduction in labor duration, effective pain relief, and a decline in the frequency of cesarean sections are all proposed by the literature in favor of the drug. Although HBB cannot cross the blood-brain barrier, a transplacental passage occurs and can cause tachycardia and strong sedation in the neonate. Mode of administration of the drug is variable, with intramuscular or intravenous being the most common modality. The effect of suppository forms of the drug was also studied[18,19].

We conducted the present systematic review and meta-analysis to summarise and discuss the evidence from randomized controlled trials (RCTs) regarding the effects of HBB on the duration of labor and the mode of delivery. The results of the meta-analysis might be useful for health providers counseling patients on the conduct of labor.

MATERIALS AND METHODS

Search strategy

We prepared this systematic review and meta-analysis following the PRISMA guidelines. We searched PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Virtual Health Library, World Health Organization, Pobline, New York Academy of Medicine, Open Grey, from their inception to March 2019. Two investigators conducted the searches independently using the following search strategy: ("hyoscine butyl bromide" OR "scopolamine butyl bromide" OR buscopan OR "butyl scopolammonium bromide") AND (labor OR delivery OR "first stage" OR "labor duration" OR "cervical dilatation" OR "labor pain") AND ("randomized controlled trial" OR "clinical trial"). The reference lists of retrieved articles were checked for other relevant publications.

Eligibility criteria and study selection

Studies which satisfied the following criteria were eligible for inclusion: (1) Population: All nulliparous or multiparous women with full-term pregnancies ≥37 gestation weeks with spontaneous onset or induction of labor; low and high-risk pregnancies, (2) Intervention: Hyoscine butylbromide during labor by all doses and routes of administration(oral, rectal, intramuscular, and intravenous route), (3) Comparator; Placebo or no medication(standard care), (4) Outcome: The primary outcome is the duration of labor, and secondary outcomes are the rate of cervical dilatation, mode of delivery (vaginal or cesarean deliveries) and rate of instrumental deliveries, (5) Study design: Randomized controlled trials (RCTs).

We excluded the following: (1) Non- randomized studies, quasi-randomized trials, and cluster trials, (2) Trials using a cross-over design, (3) Non-English study, (4) Studies with inadequate data for calculation of effect size, (5) Observational studies, animal studies, commentaries, editorial, letters, personal communication.

Duplicates were removed using endnote software, and two investigators independently screened the titles and abstracts of articles found in the search results and excluded studies that were irrelevant. For unclear studies, they retrieved the full text and assessed whether the trials met the inclusion criteria. Any disagreements were resolved through discussion, and a consensus was reached by a third reviewer.

Data extraction and Risk of bias assessment

Relevant data were extracted by two independent reviewers from eligible studies using an Excel sheet form that had been specifically designed for this purpose. Any discrepancies were settled through discussion and consensus among reviewers. The following data were extracted from included studies: the first author's name, year of publication, study location, interventions, baseline characteristics of participants (number of participants in each group, parity, and gestational age), and the outcome parameters of interest. Personal contact was made with the authors of the published studies, if necessary, to request additional data.

Two independent authors used the Cochrane risk-of-bias (ROB) tool to assess the quality of eligible studies. Seven domains were assessed in each included trial: 1) random sequence generation; 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessors (detection bias),; 5) incomplete outcome data (attrition bias),; 6) selective outcome reporting (reporting bias); 7) other sources of bias. Assessor's judgments for each domain were estimated as "low risk," "high risk," or "unclear risk" of bias. Any disagreements were resolved by discussion, and further information was sought from the study authors if needed.

Statistical analysis

The mean ± standard deviation (SD) for the duration of labor and cervical dilatation, number and percentage (%) for modes of delivery were collected. The results were given as mean difference (MD) with a 95% confidence interval

(CI) to estimate effect sizes for the duration of labor and odds ratios (OR) with a 95% CI for delivery modes. For assessment of heterogeneity, a chi-square test and the (I2) statistic were used, and values of ≥ 50% were indicative of high heterogeneity. In case of significant heterogeneity, a random-effect model was used for meta-analysis. Otherwise, the fixed effect model was used. Publication bias was assessed visually using a funnel plot. Subgroup analysis was performed according to gravidity, either primigravida, multigravida, or both, and a forest plot was conducted for each group. *P-value* <0.05 was considered statistically significant. All analyses were performed using Review Manager 5.0 (The Cochrane Collaboration, 2011).

RESULTS

Search results

The Electronic database search identified 316 records, and we obtained seven articles from the manual search. After exclusion of irrelevant studies and removal of Duplicates using EndNote software (version, X8), 72 full-text articles were reviewed and screened for eligibility criteria. Fourteen articles with a total number of 2287 Patients were included in our systematic review and meta-analysis. The PRISMA flow diagram of study selection and screening process is illustrated in (Figure 1).

Fig. 1: PRISMA flow diagram of article selection process

Study characteristics

The baseline characteristics of the participants and interventions are summarized in Table 1. All eligible studies were double-blinded RCTs. All women who participated in these studies were either primigravida or multigravida and admitted with spontaneous and active labor (3cm or more cervical dilation) at term; 37 or more gestational weeks, with vertex presentation and intact membrane or spontaneous rupture of membranes and had no chronic illnesses or contraindications to vaginal delivery except Gupta *et al*., included high-risk women with various medical disorders or with low obstetric history[20]. The intervention was HBB given intravenous, intramuscular, oral, or suppository in a dose of 20 mg or 40 mg (Table 1).

Table 1: Summary of included studies baseline characteristics

Reference	Year	Study location	Sample size (N)	Intervention	Parity	Gestational age (Mean weeks ± SD)	
						HBB	control
Imaralu *et al*.[28]	2017	Nigeria	166	Two groups of patients. The first group: received 1 ml (20 mg) of HBB. The second group received 1 ml of 0.9% normal saline as a placebo. Interventions administered intravenously as a single dose	primigravida and multigravida	38.60 ± 1.23	38.81 ± 1.38
Maged *et al*.[24]	2017	Egypt	120	Three groups. Group I received 20 mg hyoscine butylbromide (1 ml HBB +1 ml saline) intravenously. Group II received 40 mg hyoscine butylbromide intravenously. Group III received 2 ml of normal saline intravenously as a placebo.	primigravid	38.95 ± 1.02 & 38.95 ± 1.02	39.12 ± 1.05
Bashir *et al*.[27]	2016	Pakistan	108	Two groups. Group "A": 1ml of HBB (20mg) given as a single intravenous dose. Group "B": 1ml normal saline given as a single intravenous dose syringe.	primi and multigravid	38.67±1.06	38.33±1.09
Jamilian *et al*.[23]	2016	Iran	216	The hyoscine group received 20 mg of IM hyoscine in a single dose, and the control group only received IM injection of 1cc distilled water in a single dose	primigravid	38.9±1.06	39.5±3.10
Srivastava *et al*.[30]	2015	India	60	Two groups. Group I, control group: no intervention. Group II: 1 IM ampoule hyoscine butyl bromide injected.	-	(Range: 37-41)	(Range: 7-41)
Kirim *et al*.[31]	2015	Turkey	382	Two groups. Group I: 1 mL (20 mg) of HBB received as a single IV dose. Group II: 1 mL of normal saline solution (placebo) received as a single IV dose.	primi and multigravid	38.99±1.05	38.94±0.99
Edessy *et al*.[22]	2015	Egypt	200	Two groups. Group I: single IV dose of 20mg Hyoscine-n-butylbromide. Group II: 1mL IV dose of normal saline as control.	primigravid	39.0±0.77	39.4±0.60
Nagi *et al*.[25]	2013	Egypt	100	Two groups. Group I: 1ml (20 mg) spasmocin intravenously. Group II: 1ml of normal saline (placebo) intravenously.	primigravid	38.8±1.1	38.8±1.1
Sekhavat *et al*.[26]	2012	Iran	188	Two groups. In hyoscine butylbromide group, 1 milliliter (20mg) of hyoscine butylbromide and in the control group, 1 milliliter of normal saline as placebo was injected intravenously.	multigravid	38.4±1.9	38.8±1.5
Al Qahtani *et al*.[10]	2011	Saudi Arabia	97	Two groups. Each group received either 2 mL HBB (40 mg) or 2 mL normal saline, given as a single IM dose.	primigravid	39.4±0.98	39.4±1.11
Makvandi *et al*.[20]	2011	Iran	130	Two groups. First group: Suppositories containing 20 mg HBB. Second group: placebo suppositories. Interventions were given at the beginning of the active phase of labor.	primigravid	(Range:37-42)	(Range:37-42)
Aldahhan *et al*.[32]	2011	Iraq	200	Two groups. Group A: I.V 20mg Buscopan in 2 ml syringe. Group B: 2 ml of a solution (placebo) and acted as a control.	primi and multigravid	-	-
Gupta *et al*.[21]	2007	India	150	Two groups. Group 1: 20 mg (1 mL) of intravenous hyoscine N-butylbromide every 30 min for a maximum of 3 doses. Group 2: not given any medication (control group).	primi and multigravid	38.58±1.22	38.67±1.1
Samuels *et al*.[29]	2007	West Indies	129	Two groups. Each group received either 1 ml of hyoscine butylbromide (20 mg) or 1 ml of normal saline. Interventions were given as a single IV dose.	primi and multigravid	(Range:37-41)	(Range:37-41)
Imaralu *et al*.[28]	2017	Nigeria	166	Two groups of patients. The first group: received 1 ml (20 mg) of HBB. The second group received 1 ml of 0.9% normal saline as a placebo. Interventions administered intravenously as a single dose	primi and multigravid	38.60 ± 1.23	38.81 ± 1.38

The studies were divided into three subgroups based on participant group I: primigravida (six studies;[10,19,21-24]); group II: multigravida (one study;[25]); group III: both primigravida and multigravida (seven studies;[20, 26-31]).

Quality assessment

None of the included trials had a low risk of bias in all domains. However, all included studies were at low risk of attrition bias except for one study, which was at high risk[10]. Only one study,[22] was at high risk of random sequence generation and allocation concealment, and two studies failed to adequately blind the participants and personnel (performance bias)[29,25]. Four studies had an unclear risk of random sequence generation[19,20,24,31], while eight studies were rated as unclear in reporting allocation concealment[19,20,23,26,29,31]. Four studies were rated as unclear in blinding of outcome assessors[23,24,29,31], and one study was rated as high risk[29]. All included studies were at low risk of reporting bias except three studies, which were at high risk[19,21,25]; (Figure 2).

Results of meta-analysis

Duration of the first stage of labor

Regarding the overall duration of the first stage: HBB decreased the duration of the first stage of labor by 60.86 minutes compared with the control group (MD = - 60.86 minutes, 95% CI [- 82.89 to -38.84]; p<0.00001). Pooled studies were significantly heterogeneous (I2= 94%) (Figure 3). In Subgroup analysis, the MD of the duration of the first stage of labor in primigravida favored HBB over placebo (MD= -82.94 minutes, 95% CI [-117.50 to -48.37], p<0.00001). Pooled studies were heterogeneous (I2= 96%) (figure 3). The MD of the duration of the first stage of labor in multigravida favored HBB over placebo (MD= -56.28 minutes, 95% CI [-68.71 to -43.85], p<0.00001). Pooled studies were homogeneous (p= 0.30, I2= 9%; Figure 3). The MD of the duration of the first stage of labor in the studies, which included primigravida and multigravida together in their analyses, was not statistically significant (MD= -31.48 minutes, 95% CI [-73.37 to 10.77], p= 0.14). There was significant heterogeneity between the pooled studies (I2= 90%; Figure 3).

Duration of the second stage of labor

The overall second stage of labor was shorter in the HBB group than in the control group (MD= -3.18 minute, 95%CI [-5.12 to -1.24]; p= 0.001). Pooled studies were heterogeneous (I2= 75%; figure 4). In Subgroup analysis; The MD of the duration of the second stage of labor in primigravida favored HBB over placebo (MD= -4.69 minutes, 95% CI [-8.43 to -0.96], p= 0.01). Pooled studies were heterogeneous (p=0.02, I2= 61%; Figure 4). Also, MD of the duration of the second stage of labor in the studies, which included primigravida and multigravida together in their analyses, was not significant (MD= -1.86 minutes, 95% CI [-4.37 to 0.64], p = 0.15). There was a significant heterogeneity between the studies (p= 0.0008, I2= 76%; Figure 4).

Duration of the third stage of labor

The MD of the overall duration of the third stage of labor favored HBB over placebo (MD= -0.84 minute, 95% CI [-1.19 to -0.50], p< 0.00001). Pooled studies were homogeneous (p= 0.28, I2= 19%; Figure 5). The MD of the third stage of labor in the studies, which included primigravida and multigravida together in their analyses, favored HBB over placebo (MD= -1.06 minutes, 95% CI [-1.06 to 0.52], p= 0.0001). Pooled studies were homogeneous (p= 018, I2= 34%) (Figure 5).

Rate of cervical dilatation

The MD of the overall rate of cervical dilatation favored HBB over placebo (MD= 0.65 minute, 95% CI [0.51 to 0.80]; p= 0.23). Pooled studies were heterogeneous (I2= 92%; Figure 6). The MD of cervical dilatation in the studies which included primigravida and multigravida together in their analyses was not significant (MD= -0.27 minute, 95% CI [-0.61 to 0.06]; p= 0.15). Pooled studies were homogeneous (p= 0.50, I2= 0%; Figure 6).

Effect of HBB on the mode of delivery

Studies with reported vaginal delivery rate outcome

The meta-analysis of ORs showed that there was no significant difference in the overall rate of vaginal delivery (OR= 1.06, 95% CI [0.73, 1.56]; p= 0.75). Pooled studies were homogeneous (p= 0.27, I2= 19%; Figure7). Subgroup analyses by parity showed no significant difference in vaginal delivery rate between HBB and the control group in primigravid women (OR= 1.05, 95% CI [0.58, 1.89]; p= 0.88). Pooled studies were homogeneous (p= 0.72, I2= 0%; figure 7). In addition, the OR of vaginal delivery in the studies which included primigravida and multigravida together in their analyses was non-significant (OR= 0.86, 95% CI [0.44, 1.66], p= 0.65). Pooled studies were heterogeneous (p= 0.05, I2= 61%; Figure 7).

Studies with reported instrumental delivery rate outcome

The overall rate of instrumental delivery was not different in HBB group and the control group (OR= 0.68, 95% CI [0.28, 1.67]; p= 0.40). The Pooled studies were statistically homogeneous (p= 0.86, I2= 0%). The subgroup analysis denoted no significant difference between HBB and placebo in instrumental delivery rate in primigravid women (OR= 0.72, 95% CI [0.23, 2.23]; p= 0.57). There was no heterogeneity between the pooled studies (p= 0.60, I2= 0%). In addition, the OR of instrumental delivery in the studies which included primigravida and multigravida together in their analyses was not statistically different (OR= 0.61, 95% CI [0.14, 2.72]; p= 0.52; Figure 8).

Studies with reported cesarean delivery rate outcome

The overall OR of cesarean delivery was not statistically different between placebo and HBB groups (OR= 1.02,

95% CI [0.70, 1.50]; p= 0.92). Pooled studies were homogeneous (p= 0.26, I2= 20%). In subgroup analysis; the OR of CD in primigravida was non-significant (OR= 1.06, 95% CI [0.61, 1.85]; p= 0.83). Pooled studies were homogeneous (p= 0.76, I2= 0%). However, the OR of CD in the studies which included primigravida and multigravida together in their analyses was non-significant (OR= 1.38, 95% CI [0.65, 2.92]; p= 0.40). Pooled studies were heterogeneous (p= 0.04, I2= 70%; Figure 9).

Publication bias

We assessed publication bias using the funnel plot. However, the assessment of publication bias is not reliable for less than ten included studies. The funnel plot of duration of the first stage of labor showed that there might be publication bias as it was asymmetrical (Figure 10), but the funnel plots of vaginal and cesarean deliveries showed that there was no publication bias (Figures 11, 12).

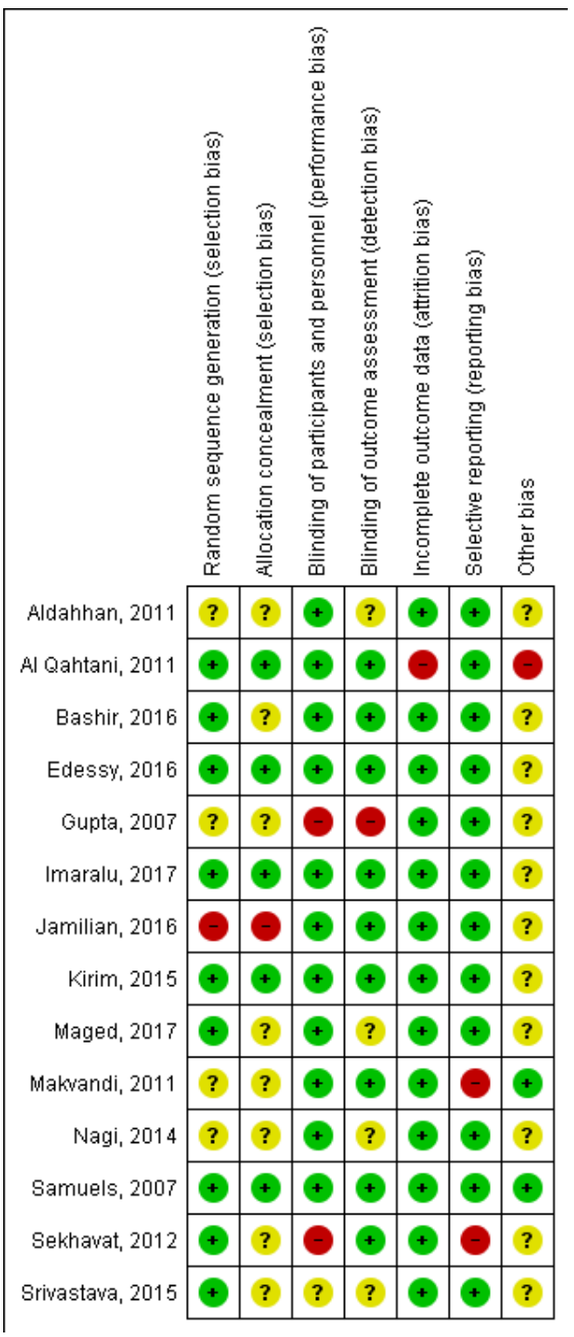

Fig. 2: Risk of bias summary according to the Cochrane risk of bias tool

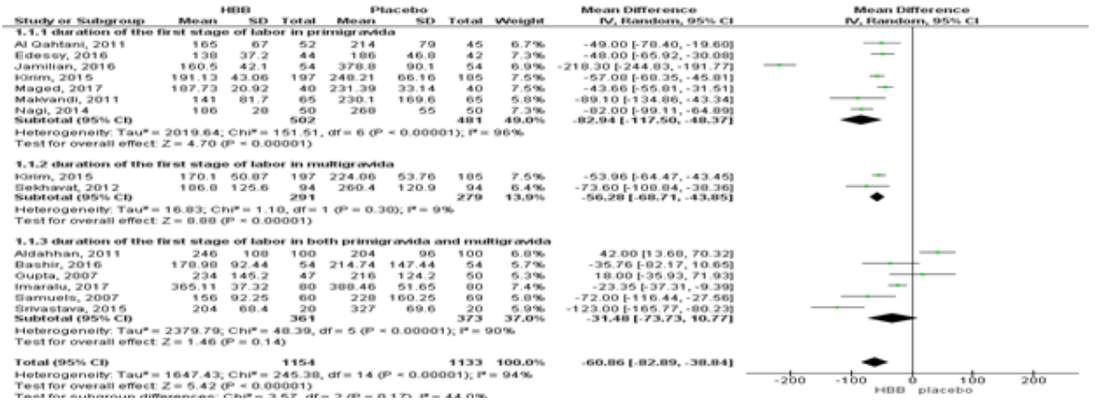

Fig. 3: Forest plot of the mean difference of the duration of the first stage of labor

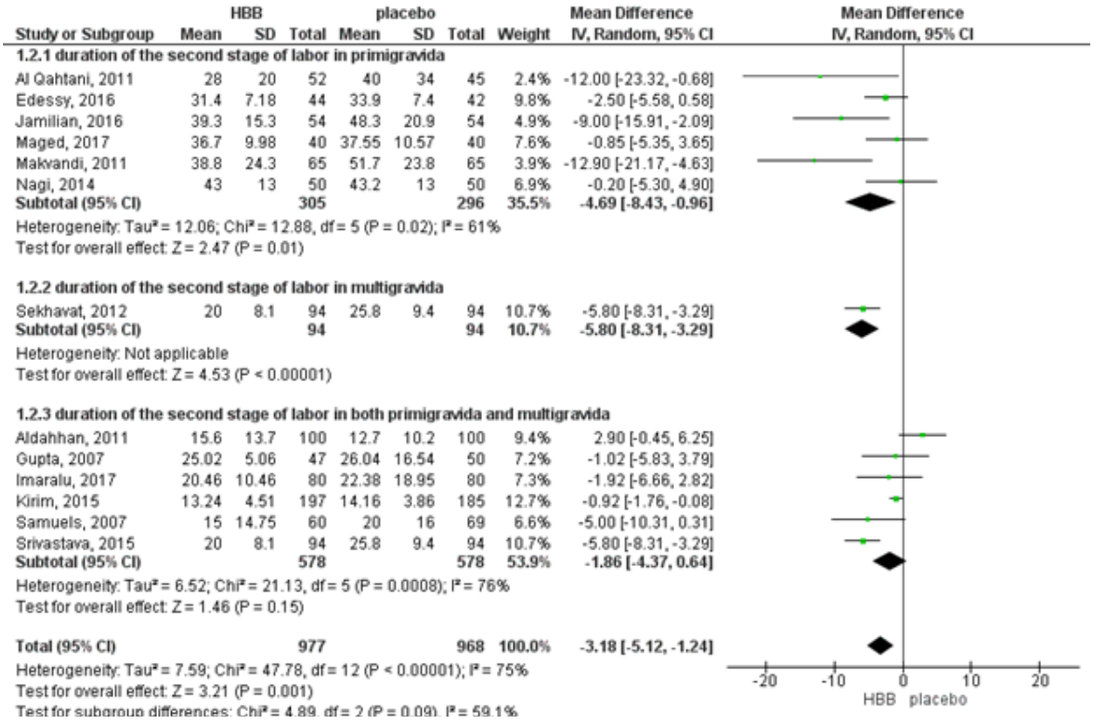

Fig. 4: Forest plot of the meandifference of the duration of the second stage of labor

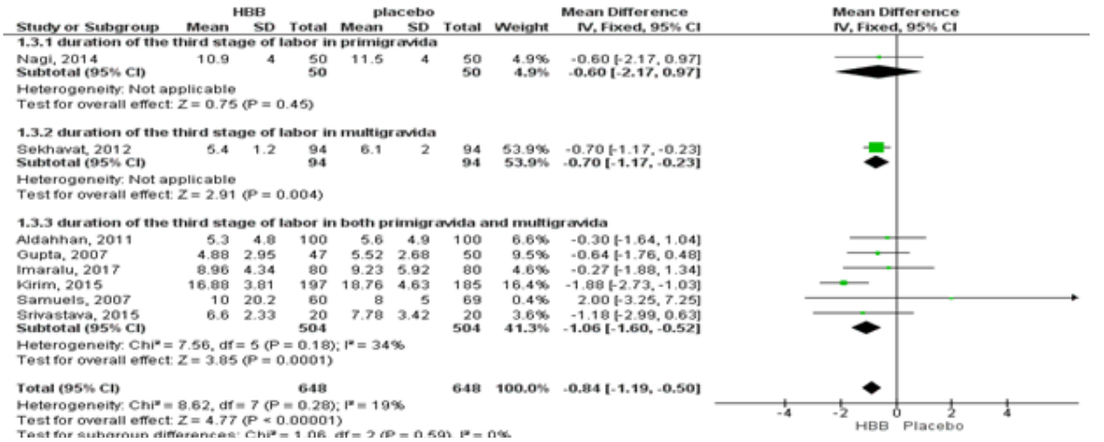

Fig. 5: Forest plot of the mean difference of the duration of the third stage of labor

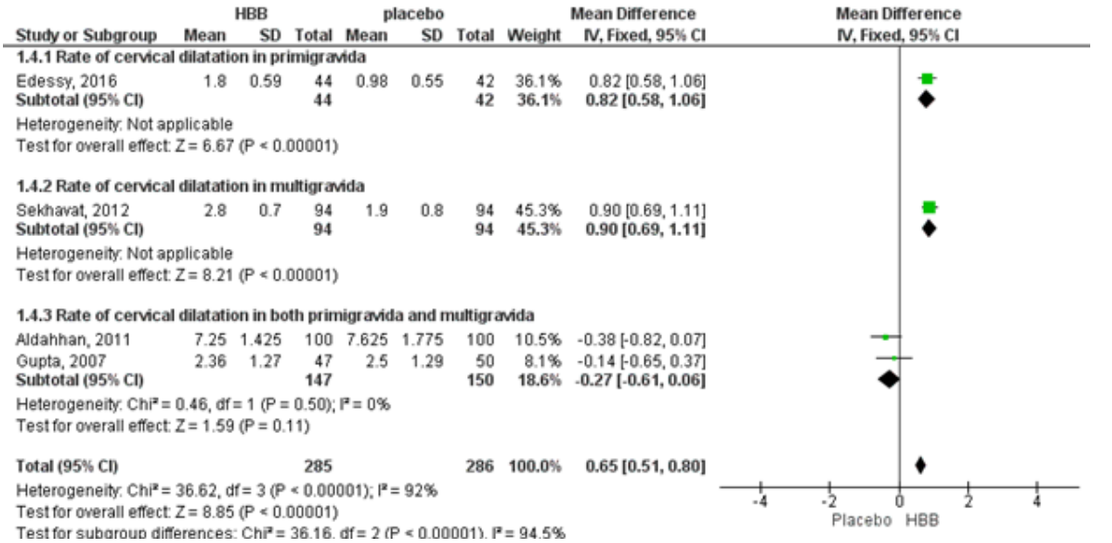

Fig. 6: Forest plot of mean difference in rate of cervical dilatation

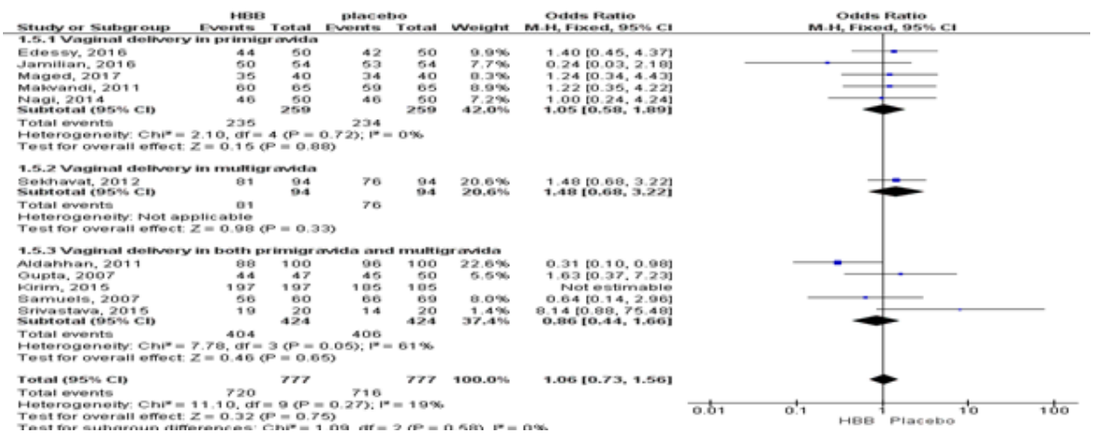

Fig. 7: Forest plot of the odds ratio of vaginal delivery

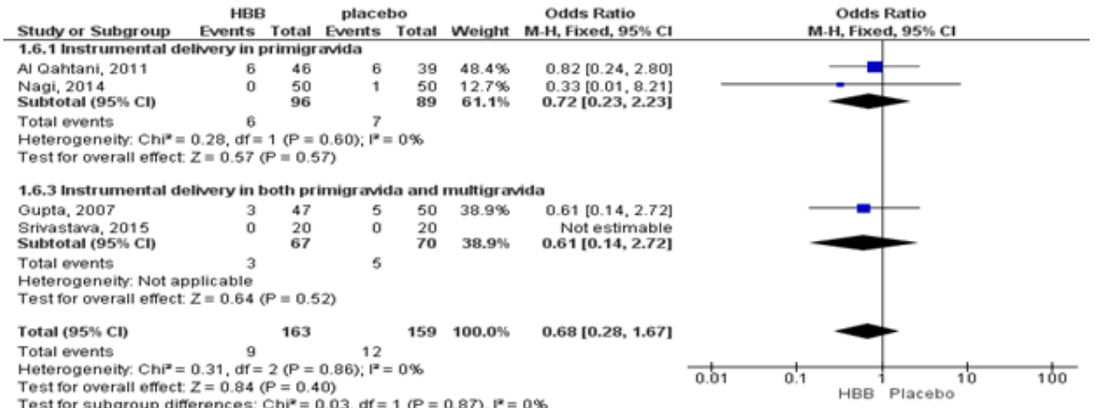

Fig. 8: Forest plot of the odds ratio of instrumental delivery

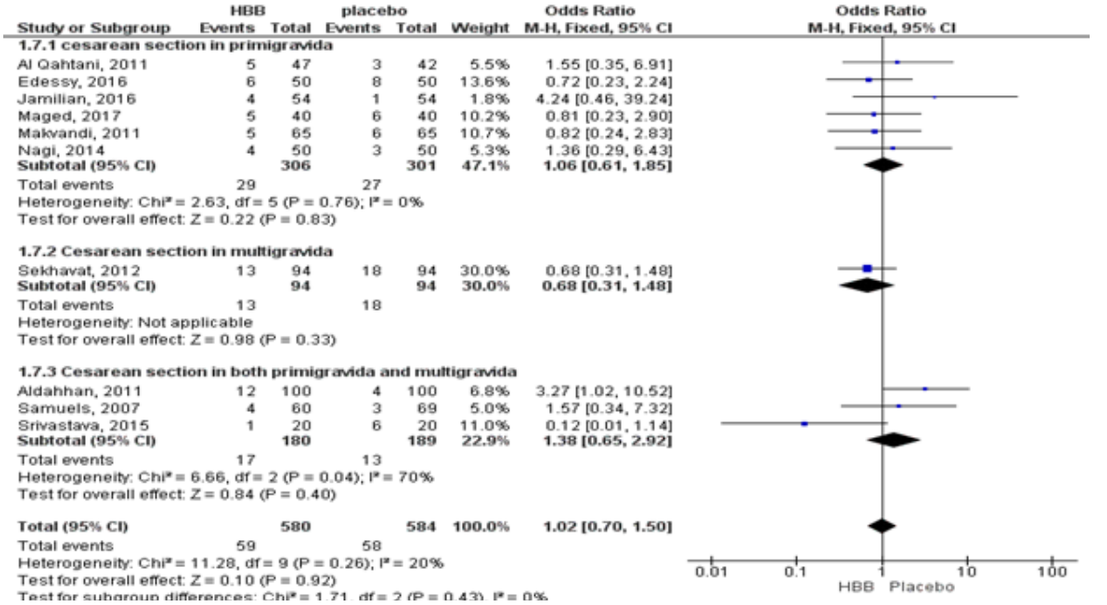

Fig. 9: Forest plot of the odds ratio of cesarean delivery

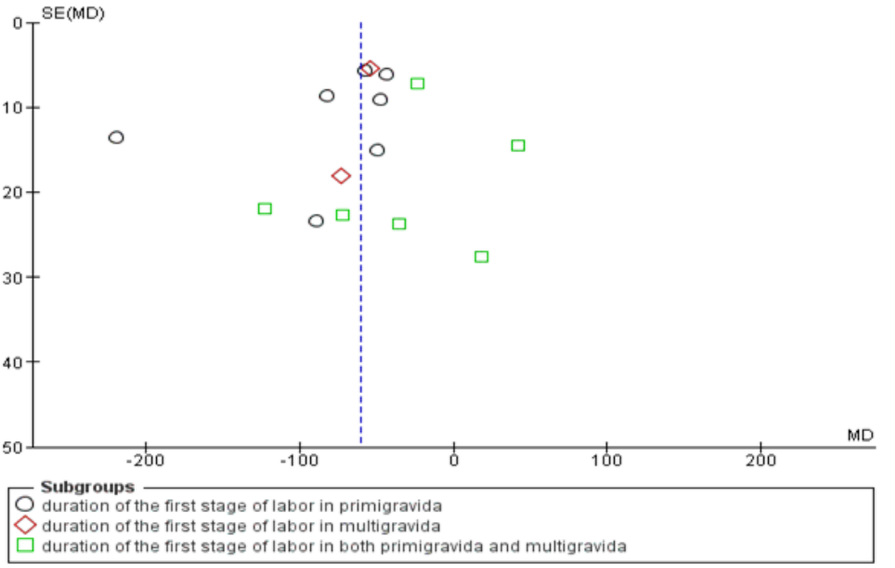

Fig. 10: Funnel plot of the first stage of labor

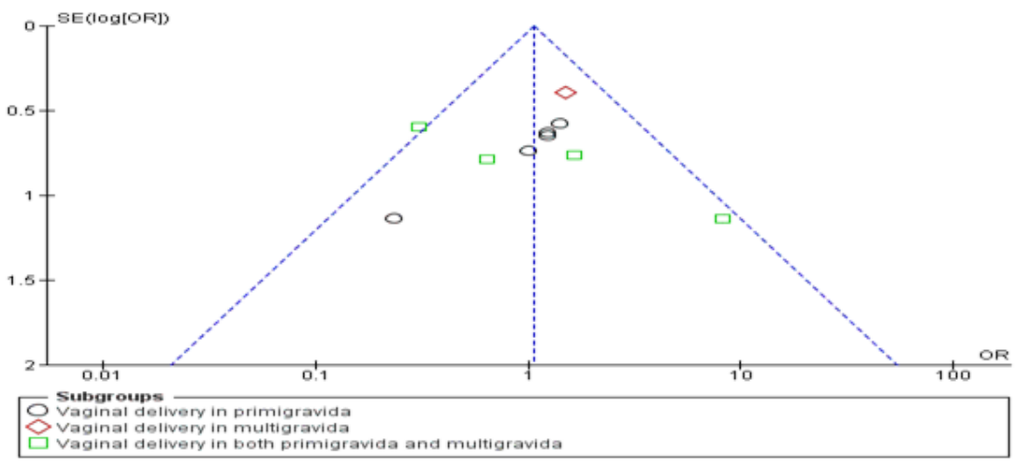

Fig. 11: Funnel plot of vaginal delivery

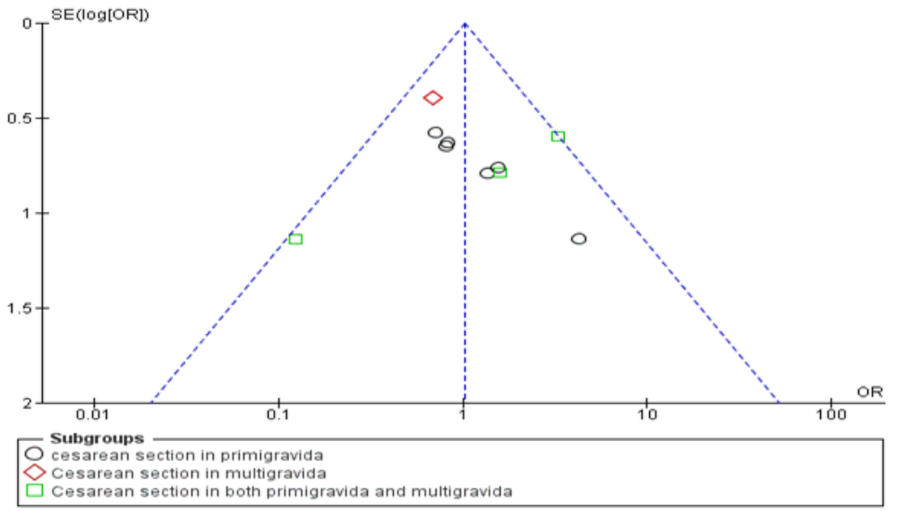

Fig. 12: Funnel plot of cesarean delivery.

DISCUSSION

Our results showed that HBB was effective in shortening the duration of labor compared to placebo in both primigravida and multigravida. The aim of the active management of labor is to shorten the duration of labor without increasing maternal or fetal morbidity and mortality[30]. Shortening the duration of labor can be enhanced by increasing the rate of cervical dilatation and through active management of labor[30]. Various forms of the anti-spasmodic agents are used to facilitate cervical dilatation and shortening duration of labor with less evident adverse effects on the mother and fetus[29]. HBB is an anti-spasmodic agent derived from atropine and acts by inhibiting cholinergic transmission[20]. In this review, HBB was superior to placebo in shortening the first, second, and third stages of labor in both primigravida and multigravida. In addition, HBB was effective than placebo in increasing the rate of cervical dilatation, but there was no difference between HBB and placebo in reducing the rate of instrumental or cesarean deliveries.

There are many well-designed, adequately powered RCTs that compared the efficacy of HBB versus placebo in reducing the duration of labor. A former Cochrane systematic review conducted in 2013 found that HBB is effective in reducing the duration of the first stage of labor and in increasing the rate of cervical dilatation but has no effect on the duration of second and third stages of labor, also on the rate of vaginal delivery[32]. Unlike the Cochrane review, we performed subgroup analysis according to the gravidity of women, whether primigravida or multigravida or both, for each outcome, and we included nine new studies, which made our results stronger and our evidence more updated.

Also, Srivastata *et al*., who compared the effect of HBB and placebo in shortening the duration of labor in both primigravida and multigravida, found that HBB was effective in significantly reducing the duration of the first stage of labor as compared to placebo[29]. Indeed, Jamilian *et al*. found the same result in primigravida[22]. On the other side, Gupta *et al*. reported that administration of HBB in both primigravida and multigravida had no effect on the active phase of labor, the third stage of labor, the rate of cervical dilatation, and the rate of instrumental delivery[20]. In contrary to our findings, Aldahhan *et al*. showed that HBB slowed down the rate of cervical dilatation and prolonged the duration of the first stage[31]. Sekhavat *et al*. demonstrated that HBB had significantly reduced the duration of the first and second stage of labor and increase the cervical dilatation rate, while Makvandi *et al*. evaluated the effect of HBB in primigravida only and had the same results regarding the first and second stages of labor[19,25].

Al Qahtani *et al*. and Maged *et al*.[10,23] assessed the effect of HBB in primigravida, while Imaralu et al., Samules *et al.*, Kirim *et al*. and Bashir *et al*.,[27,28,30] assessed the effect of HBB in both primigravida and multigravida and they all found that HBB significantly shortened the time of the first stage of labor; however, their results showed no significant difference in the duration of the second and third stages of labor as compared to placebo.

In this review, we found that HBB is more effective than a placebo in reducing the duration of the first stage of labor in primigravida and multigravida. This can be explained by the primary action of HBB on the cervix rather than promoting uterine contractions. Prolongation of labor may be attributed to oxytocin administration, which causes spasm at the level of the cervix and the lower uterine segment. HBB is more effective in reducing the duration of labor in multigravida as they usually have problems of uterine inertia with thickened cervix and cervical spasm, which can be prevented or relieved by the administration of HBB. It is also more effective in reducing the time of the second stage of labor in multigravida than primigravida, which may be explained by the local effect of HBB on the cervical region that may induce relaxation, thus causing effective myometrial contraction. Prolongation of the second stage of labor, despite the pushing effort established by laboring women, may be related to the long duration of the first stage of labor that may cause exhaustion of the myometrium. HBB administration also leads to a reduction in the third stage of labor. HBB was effective in increasing the rate of cervical dilation, which may decrease the duration of the first stage of labor.

HBB did not affect vaginal delivery or cesarean section rates. Gupta *et al*. and Srivastava *et al*.[20,29] found that HBB does not affect the mode of delivery in both primigravida and multigravida, while Samules *et al*. [28] showed that HBB has a slight increase in the rate of the cesarean section without a significant difference. However, Aldahhan *et al*. found that HBB was associated with a marked increase in the rate of CD[31]. Sekhavat *et al*. showed that vaginal and CD rates were not affected by HBB in multigravida[25]. Similar results primigravida were reported by Makvandi *et al*., Maged *et al*., Edessy *et al*., Nagi *et al*., and Jamilian *et al*.[19,21,24]. Increased rate of CD can be related to small sample size, failure of dilatation, thick meconium, and placental abruption.

In general, HBB can be used widely in labor as it shows a significant reduction in the total time of labor. It is highly safe and has no recorded adverse effects on neonatal Apgar scores and major organ systems[27]. It is also associated with average blood loss, so it does not affect postpartum uterine contraction[28]. It also decreases the need for epidural analgesia, which is not widely available and associated with a decrease in postpartum depression[23].

Strengths and limitations of the study

This meta-analysis makes strong evidence based on large sample size; the included trials with low to high risk of bias, performing subgroup analysis to assess the effect of HBB on both types of laboring women, including HBB with different routes of administration, including trials in this meta-analysis conducted in different countries which give strong evidence. We have some limitations as we could not perform pooling analysis to compare HBB

with other analgesics, could not use a combination of HBB with other drugs. We could not assess the different adverse effects of HBB and the effect of HBB on neonatal outcomes. Subgroup analysis shows high heterogeneity.

CONCLUSION

HBB is superior to placebo in shortening the duration of the first, second, and third stages of labor in both primigravida and multigravida. Also, it is effective in increasing the rate of cervical dilatation but has no effect on the frequency of vaginal and cesarean deliveries.

AUTHOR CONTRIBUTIONS

EMG&ASS contributed to data collection, data analysis, and manuscript writing. EMM&AMS contributed to data analysis, manuscript writing, and critical review. OMM and EMG &ASS and EMM performed the study selection and contributed to data collection, data tabulation, and manuscript writing. MR& AHH contributed to data analysis, manuscript writing, and critical review. EMG&MR&AHH was responsible for project development and contributed to data tabulation, manuscript writing, manuscript editing, and critical review. All authors (undergraduate researchers; EMG, ASS, EMM, AMS, OMM and Obgyn consultants; MR&AHH) approved the final version for publication.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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