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The effect of hyoscine butylbromide on active phase of labor progress: Systematic Review and metanalysis

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Ευχαριστίες

“Nanos gigantum humeris insidentes…’’ John of Salisbury, 1159 μ.Χ.

Θα ήθελα να ευχαριστήσω όλους όσους με βοήθησαν σε αυτό το εγχείρημα.

Ιδιαίτερα θα ήθελα να ευχαριστήσω τον κ. Νικόλαο Βλάχο, επιβλέποντα της διπλωματικής μου εργασίας, ο οποίος με καθοδήγησε αποτελεσματικά κατά τη διάρκεια της ανάπτυξης της διπλωματικής, έλυσε τις απορίες μου και διόρθωσε με ευγένεια τα όποια λάθη ή παραλείψεις εμφανίστηκαν. Αν και η επικοινωνία μας δεν πραγματοποιήθηκε δια ζώσης, ήταν θερμός και υποστηρικτικός και μοιράστηκε τις σκέψεις του μαζί μου, όπως αρμόζει σε έναν καθηγητή απέναντι στον μαθητή του.

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Τέλος θα ήθελα να ευχαριστήσω την οικογένεια μου, η οποία με εμπιστεύτηκε στην επιτεύξη του στόχου μου και με βοηθάει ανιδιοτελώς σε όλες τις δύσκολίες που προκύπτουν.

Contents

Ευχαριστίες....ii
Περίληψη.... 1
Abstract 2
Aims-objectives 3
Introduction.... 4
Materials and Methods 8
Identification of studies and eligibility criteria.... 8
Eligibility criteria 8
Study selection 9
Data extraction.... 9
Outcome of interest 9
Risk of bias assessment 10
Data Analysis 10
Results 11
Characteristics of included studies and quality assessment (risk of bias).... 11
Identification 12
Eligibility 12
Included.... 12
Screening 12
Primary and secondary outcomes.... 18
Subgroup analysis.... 21
Primary outcome: Duration of first stage of labor 21
Secondary outcome: Duration of second stage of labor.... 23
Secondary outcome: Total duration of labor 25
Secondary outcome: Duration of first and second stage of labor 26
Secondary outcome: Duration of first and second stage of labor 28
Discussion.... 30
Principal findings 30
Strengths and limitations 30
Implications for clinical practice and research.... 31
Compliance with ethical standards 31
Conflict of interest.... 31

References 32
Appendix A: Characteristics of the studies and Risk of Bias assessment 38
Al Qahtani et al, 2011 38
Al-Khishali et al, 2012 40
Alani et al, 2013 41
Ashraf, 2018 42
Barau et al, 2018 43
Gupta et al, 2008 45
Imaralu et al, 2017 47
Makvandi et al, 2011 49
Kirim et al, 2014 51
Mukaindo et al, 2010 53
Samuels et al, 2007 55
Sekhavat et al, 2012 56
Sheth et al, 2018 57
Shirazi et al, 2016 59
Shobha et al, 2006 61
Singh et al, 2015 62
Trevino-Salinas et al, 2015 63

Περίληψη

Σκοπός: Η μελέτη της αποτελεσματικότητας της χορήγησης βουτυλοσκοπολαμίνης (HBB) σε μονήρεις τελειόμηνες κυήσεις με κεφαλική προβολή σε ενεργή φάση του πρώτου σταδίου του τοκετού για μείωση της διάρκειας της καθώς και η μελέτη της επίδρασης που έχει το φάρμακο στο δεύτερο στάδιο του τοκετού, τη συνολική διάρκεια του τοκετού, τη συνολική διάρκεια πρώτου και δευτέρου σταδίου καθώς και στο ρυθμό διαστολής του τραχήλου κατά τον τοκετό.

Μέθοδος: Η παρούσα μελέτη είναι συστηματική ανασκόπηση της βιβλιογραφίας και μετανάλυση τυχαιοποιημένων κλινικών δοκιμών που συγκρίνουν τη χορήγηση του φαρμακού με ομάδες ελέγχου που έλαβαν εικονικό φάρμακο ή καμία θεραπεία σε τελειόμηνες μονήρεις κυήσεις με κεφαλική προβολή κατά τη διάρκεια της ενεργούς φάσης του πρώτου σταδίου του τοκετού. Ψηφιακές βιβλιοθήκες, αναρτημένες ανακοινώσεις σε συνέδρια καθώς και η βιβλιογραφία των διαθέσιμων άρθρων εξετάστηκαν μέχρι τις 31 Μαρτίου 2019 προς εξεύρεση μελετών που ικανοποιούσαν τις προϋποθέσεις που τέθηκαν. Αφού προηγήθηκε κριτική ανάγνωση των μελετών προς εκτίμηση των πιθανών συστηματικών σφαλαμάτων, πραγματοποιήθκε συγκέντρωση των διαθέσιμων δεδομένων και υπολογίστηκε η διαφορά των μέσων όρων (Mean Difference) με τα συνοδά διαστήματα εμπιστοσύνης 95% μεταξύ των δύο ομάδων όσον αφορά τη διάρκεια του πρώτου σταδίου του τοκετού, τη διάρκεια του δευτέρου σταδίου, τη συνολική διάρκεια τοκετού, τη διάρκεια του πρώτου και δευτέρου σταδίου αθροιστικά και το ρυθμό διαστολής του τραχήλου κατά τον τοκετό.

Αποτελέσματα: Δεκαεπτά μελέτες που αφορούσαν 2761 ασθενείς συμπεριλήφθηκαν στην ανασκόπηση. Η μετανάλυση που προέκυψε για αυτά τα δεδομένα απέδειξε πως η χορηγήση βουτυλοσκοπολαμίνης κατά τη διάρκεια της ενεργής φάσης του πρώτου σταδίου τοκετού μειώνει σημαντικά τη διαρκειά του (MD -61.46 minutes, 95% CI -85.83, -37.1, p<0.001, I^2=95%), όπως και τη διάρκεια του δευτέρου σταδίου (MD -2.49 minutes, 95%CI -3.99 to -0.98, p=0.001, I^2=76%), τη συνολική διάρκεια τοκετού (MD -96.45 minutes, 95%CI -192.14 to -0.77, p=0.05, I^2=93%), τη διάρκεια πρώτου και δευτέρου σταδίου αθροιστικά (MD -57.11 minutes, 95%CI -94.99 to -19.22, p=0.003, I^2=73%) καθώς αυξάνει και το ρυθμό διαστολής του τραχήλου κατά τον τοκετό (MD 0.57 cm/hour, 95%CI 0.15 to 1.00, p=0.008, ^{2}=89%). Δεν παρατηρήθηκαν σημαντικές επιπλοκές από τη χορήγηση του φαρμάκου.

Σύνοψη: Η χορηγηση βουτυλοσκοπολαμίνης κατά τη διάρκεια της ενεργής φάσης του πρώτου σταδιου του τοκετού σε γυναίκες με τελειόμηνη μονηρή κύηση σε κεφαλική προβολή φαίνεται να είναι αποτελεσματική για την μείωση της διάρκειας του πρώτου στάδιου και ασφαλής τόσο για την μητέρα όσο και για το έμβρυο.

Abstract

Objective: To evaluate the effectiveness of the administration of Hyoscine Butylbromide (HBB) for shortening the active phase of first stage of labor and study the effect of the drug on the second stage of labor, the total duration of labor, first and second stage of labor and the cervical dilatation rate.

Methods: This is a systematic review and meta-analysis of randomized controlled trials comparing the administration of HBB at the active phase of first stage of labor to placebo/no treatment in women with single cephalic term pregnancies in labor. Digital libraries, congresses abstracts and references of articles searched from their inception until 31st March 2019. The primary outcome was the duration of the first stage of labor. After critical assessment of the studies for risk of bias, data extracted from studies and Mean Differences (95% CI) were calculated.

Results: Seventeen studies involving 2761 patients were included. A meta-analysis including data for these studies showed that the administration of HBB during the active phase of first stage of labor significantly reduced the duration of first stage of labor (MD -61.46 minutes, 95% CI -85.83, -37.1, $p<0.001$, $I^2=95\%$). Furthermore the administration of HBB was associated with a significant reduction in the duration of the second stage of labor (MD -2.49 minutes, 95%CI -3.99 to -0.98, $p=0.001$, $I^2=76\%$), the total duration of labor (MD -96.45 minutes, 95%CI -192.14 to -0.77, $p=0.05$, $I^2=93\%$), the time from the administration of the drug until the delivery of the fetus (MD -57.11 minutes, 95%CI -94.99 to -19.22, $p=0.003$, $I^2=73\%$) and a significant increase of the cervical dilatation rate (MD 0.57 cm/hour, 95%CI 0.15 to 1.00, $p=0.008$, $I^2=89\%$). No significant adverse effects noted.

Conclusion: It seems that the administration of HBB is effective in shortening the duration of the first stage of labor in single term vertex cephalic pregnancies and safe for both fetus and mother.

Aims-objectives

The systematic review and metanalysis aims at studying the effectiveness of administration of HBB on the active phase of labor in order to shorten its duration.
The objectives of this study include a literature review of all recent, relevant published studies that evaluate the use of this spasmolytic drug at the active phase of labor.
The metanalysis evaluate the differences of duration of first and second stages of labor, total duration of labor and dilatation rate between the control and intervention groups at nulliparous and multiparous women at term.

Introduction

Active management of labor is a concept introduced since 1970s for the reduction of total duration of labor without increasing fetal and maternal adverse outcomes [1]. The efficacy and safety of active management of labor has been also proved through multiple studies as well as the association with decreased trend in Cesarean Sections (CS) [2–5].

Worldwide one of the main indications for CS is dystocia, an umbrella term which includes failure to progress, prolonged labor, protraction disorders, arrest disorders of labor, fetopelvic or cephalopelvic disproportion, prolonged active phase, secondary arrest of dilatation, arrest of descent, malposition. All these definitions include the reasons that lead to the same result in labor progress, the inability of adequate progression of cervical dilatation and effacement and fetal descent in order to achieve normal vaginal delivery [6–8].

It is estimated that dystocia affects 8-37% of pregnancies and affects mainly nulliparous women at the first stage of labor [9–12]. Some risk factors for this condition include increased maternal age, increased BMI, increased fetal weight, increased fetal head circumference, shorter maternal height, increased interpregnancy interval as well as the involvement of genetic factors [8,9,12–17].

According to the obesity epidemics, increased maternal age as well as the macrosomia (>4000g) incidence worldwide (8-20%) it can be deducted that dystocia will remain a common problem the next decades and efforts for reducing cesarean sections should take that in count [14,15,18–23].

It is well described by many researchers that prolonged labor can lead to hazardous consequences for both the mother and the fetus. Women with a prolonged labor have a negative perspective to normal vaginal delivery compared to women with a normal labor, increased risk for operative vaginal delivery or CS, third / fourth degree perineal laceration, postpartum hemorrhage, chorioamnionitis and uterine atony [8,12,24–27] . The fetus that will deal with that stress is at increased risk for Neonatal Intensive Care Unit (NICU) admission and five minutes APGAR score < 7 [24,27].

It is for those reasons, among others, that there is a continuous need to reevaluate current techniques for shortening the duration of first stage of labor, without increasing fetal and maternal complications.

The two major factors that determine duration of labor are uterine contractility and rate of cervical dilation and ideally a drug that can accelerate dilatation without inhibiting uterine contractility would be a perfect choice for shortening the duration of labor.

Spasmolytics have been used in obstetrics in order to help cervical effacement and dilatation and thus reduce the time of the first stage of labor. Current data is controversial and more good quality studies are needed at the field.

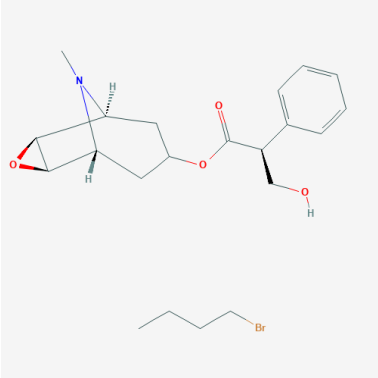


Figure 1: Scopolamine N-butyl bromide, hyoscine butyl bromide C21H30Br NO4
[7(s) – (1,2,4,5,7)] -- (hydroxy – methyl) benzene acetic acid 9-butyl 9-methyl, 3-oxa-9-azatricycleonon –7-yl ester, bromide salt (HBB); Source: PubChem

Hyoscine-N-butylbromide (HBB) is an antispasmodic drug widely used worldwide since 1950s to treat many types of abdominal pain. It exists as a semisynthetic quaternary alkaloid derivative of scopolamine and is a competitive antagonist of acetylcholine at muscarinic receptors. The drug is a competitive antagonist of acetylcholine at postganglionic parasympathetic nerve endings, so it has a selective blocking action on the intramural parasympathetic ganglia. By that mechanism it inhibits cholinergic transmission in the abdominal and pelvic parasympathetic ganglia, thus relieving spasm in the smooth muscles of gastrointestinal, biliary, urinary tract and female genital organs, especially the cervico-uterine plexus and thus aiding cervical dilatation [28,29]. Although it was believed that HBB has no effect nicotinic receptors, more recent studies suggest that HBB can block them too [30,31].

Unlike atropine it does not cross the blood brain barrier, so it does not act centrally and hence has no side effects from the central nervous system. Its effects limit on the abdominal organs which have autonomic innervation, like gastrointestinal tract and urogenital organs.

Its influence on eye, salivary glands and heart is extremely weak.
The drug is commercially distributed worldwide as a tablet, suppository or vial for parenteral use (intravenous, intramuscular or subcutaneous).

After intravenous administration HBB is rapidly distributed (t1/2 = 29 minutes) into the tissues. The volume of distribution is 128L (corresponding to approximately 1.7L/Kg) and plasma protein binding is low (4.4%) [32].

HBB is contraindicated in myasthenia gravis, mechanical gastrointestinal stenosis or obstruction, ileus, megacolon and in patients who have demonstrated prior hypersensitivity to hyoscine butylbromide or any other component of the products. In addition, it should not be administered parenterally in the following disorders: untreated narrow angle glaucoma, tachycardia and hypertrophy of the prostate with urinary retention. Intramuscular use is contraindicated in patients being treated with anticoagulant drugs since intramuscular hematoma may occur.

The drug's safety intrapartum have been tested in a satisfactory number of trials without showing severe adverse effects [33–42], although two cases of eclamptic seizures after the administration oh HBB with severe preeclampsia complicated by HELLP syndrome have been reported [43].

HBB has also a proved effect in reducing pain during labor [38,44]

Labor stages:

The interpretation of the labor progress has proposed a division in three distinct stages (first, second and third) in order to explain the dynamic mechanical changes that occur in order to achieve delivery. Evaluation and management depend on the stage and phase.

First stage: The time from the onset of labor until full dilatation of the cervix. This can be further subdivided in two phases (latent and active).

Latent phase of first stage of labor: Though it is impossible to document when the dilatation of the cervix has started as changes may occur for weeks before labor, this phase is usually documented by asking the woman when she believes that contractions' frequency was more than 8-10 in an hour period with relative same inter-contraction interval and it is characterized by slow progress

Active phase of first stage of labor: This phase is characterized by rapid changes of the cervix and increased cervical dilatation rate. It starts after the latent phase of first stage and ends by the full dilatation of the cervix as documented with vaginal examination.

Second stage: The time from complete cervical dilation to fetal expulsion.

Third stage of labor: The time between fetal expulsion and placental expulsion.

Labor progress and criteria for normal progress of labor

The traditional definition used to set the onset of labor at the time where there are at least three contractions lasting minimum 30 seconds in a ten-minute period and the cervical dilatation is at least 3 cm.

According to the traditional criteria for normal progress of labor, originally proposed by Emanuel Friedman in 1950s, the transition from the latent phase to active phase appeared to occur at 3 to 4 cm cervical dilation [45,46]. It has been recently suggested though by Jun Zhang, that the true labor progress is slower than what calculated by Friedman (dilatation rate 1.2 cm/hour for nulliparous women and 1.5 cm/hour for multiparous women) and that the active phase of first stage of labor characterized by accelerating dilatation can be observed when the dilation reaches 6cm regardless of parity, while differences at the rate of cervical dilatation exist among subgroups according to parity [47,48]. A recent multicenter randomized control trial (RCT) evaluating the progress of labor and active management of labor among two groups using partographs based on traditional Friedman criteria and the recent Zhang criteria showed no statistical differences among the two groups intrapartum CS rates. However both study groups demonstrate a significant decrease in intrapartum CS rate during that period compared with the period before the trial [49].

Identification of studies and eligibility criteria

We searched MEDLINE, EMBASE, Google Scholar, Cochrane Library, Cochrane Central Register of Controlled Trials and ScienceDirect using a combination of the words “labor”, “labour”, “cervix”, “dilatation”, “dilation”, “ripening”, “augmentation”, “buscopan”, “hyoscine”, “scopolamine” to collect all RCTs conducted among human participants up to March 31st, 2019.

The language was limited only to English. We also performed a complete manual search from the bibliographies of each peer reviewed paper selected. Furthermore, there was no limitation regarding publication form.

Eligibility criteria

Inclusion criteria

1. Term pregnancies >36 weeks of pregnancy
2. Spontaneous or induced onset of labor
3. Amniotomy or not
4. Single pregnancies
5. Parenteral administration of HBB
6. Full text available in English language
7. HBB versus placebo
8. HBB administrated at the first stage of labor
9. Vertex cephalic presentation of the fetus
10. Ranadomised clinical trials

Exclusion criteria

1. Preterm labor
2. Previous uterine scar
3. Prelabor rupture of fetal membranes >12 hours
4. Language other than English
5. Full text not available
6. Studies that didn’t report clinical outcomes

Study selection

The titles and abstracts of identified publications were screened by 2 independent reviewers, with those deemed relevant by at least one reviewer carried forward for full-text review, where disagreements were resolved by consensus.
Included studies were RCTs that investigated the effectiveness of administration of HBB on the active phase of labor in term pregnancies who were randomly allocated to receive HBB or no treatment / placebo. Trials were included if the primary aim of the study was the shortening of active phase of labor.
The definition used to describe the onset of active phase labor was the one used by the researchers of each group.

Data extraction

Extracted data included (i) general characteristics such as authors, year, location, (ii) study design characteristics such as randomization generation, blinding after assignment to interventions, allocation concealment, primary and secondary outcomes, (iii) population characteristics such as age, parity, number of participants, (iv) the type of intervention (route of administration, dose, interval of repeated doses if any) (v) the definition of onset of active phase as used, (vi) additional interventions such as use of oxytocin, amniotomy, anesthesia, mechanical detachment of membranes (sweeping), active management according to partographs interpretation, (vii) the duration of active phase of first stage of labor, the duration of second stage of labor, the duration of first and second stage of labor, total duration of labor and cervical dilatation rate among different groups, (viii) adverse effects

Outcome of interest

The primary outcome was the Mean Difference of duration of the active phase of first stage labor between the intervention and control arms.
Secondary outcomes were the Mean Differences in the duration of Second stage of labor, first and second stage of labor, total duration of labor and cervical dilatation rate between the two groups.

Risk of bias assessment

Assessments of risk of bias for included trials were done independently by two investigators according to the seven domains outlined in the Cochrane Handbook for Systematic Reviews of Interventions (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). This tool categorizes studies by low, unclear, or high risk of bias in each domain[50]. We resolved any disagreement regarding the risk of bias assessment by consensus.

Data Analysis

Statistical analysis performed in order to compare the mean difference in duration of the active phase of first stage of labor, duration of second stage of labor, duration of first and second stage of labor, total duration of labor and cervical dilatation rate between the intervention and control groups. Because of differences among the studies design, population and intervention, it considered reasonable to perform a random effects meta-analysis. All results calculated Mean Differences with CI 95% and a p value <0.05 was considered as the level of statistical significance.

All data extracted from the studies converted to minutes for interpretation.

Further subgroup analysis according to the parity, route of administration of the drug, single or repeated dosage and active management of labor at any time (augmentation with oxytocin, amniotomy) was also done for the primary and secondary comparisons.

Statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics was also assessed.

The statistical analysis performed using the Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Characteristics of included studies and quality assessment (risk of bias)

Literature searches identified 30 RCTs that met the eligibility criteria and full texts assessed. Of these 13 studies were excluded due to lack of randomization [29,33,38,42,51,52], because there was no placebo-control group [23,53–55], one because the full text article was not in English language [56], one because it was a retrospective study [44] and one because it was case control study [40]. Thus the remaining 17 studies included for qualitative synthesis gave 21 eligible groups for evaluation and a total of 2761 patients (1379 at the intervention group and 1381 at the control group) that compared HBB vs. placebo or no treatment in singleton term cephalic pregnancies at the active phase of the first stage of labor with the aim of studying the effect of HBB at the duration of active phase of labor obtained for the analysis (Figure 2).
All included studies were one center randomized clinical trials, in both low-, middle- and high-income countries (India – 5 studies, Iran – 3 studies, Iraq – 2 studies, Nigeria – 2 studies, Jamaica, Kenya, Saudi Arabia, Mexico, Turkey). All studies included single term vertex cephalic pregnancies >17 years old. Some included only nulliparous [57–61], some only multiparous [36,62] and some both nulliparous and multiparous women [35,37,41,63–67]. Ten studies used intravenous HBB [34–36,41,61,62,64–67], three studies intramuscular administration [57,63,68] and four per rectum suppositories [58–60,69]. Different dosing regimens used among studies, of which the main characteristics regarding the intervention and basic characteristics of the population (gravidity, spontaneous or induced onset of labor and low or high risk population) are summarized in Table 2. Full characteristics of included studies are available in Appendix 1.

Figures 3 and 4 show the risk of bias for each study.

Figure 2: Summary of evidence search and selections

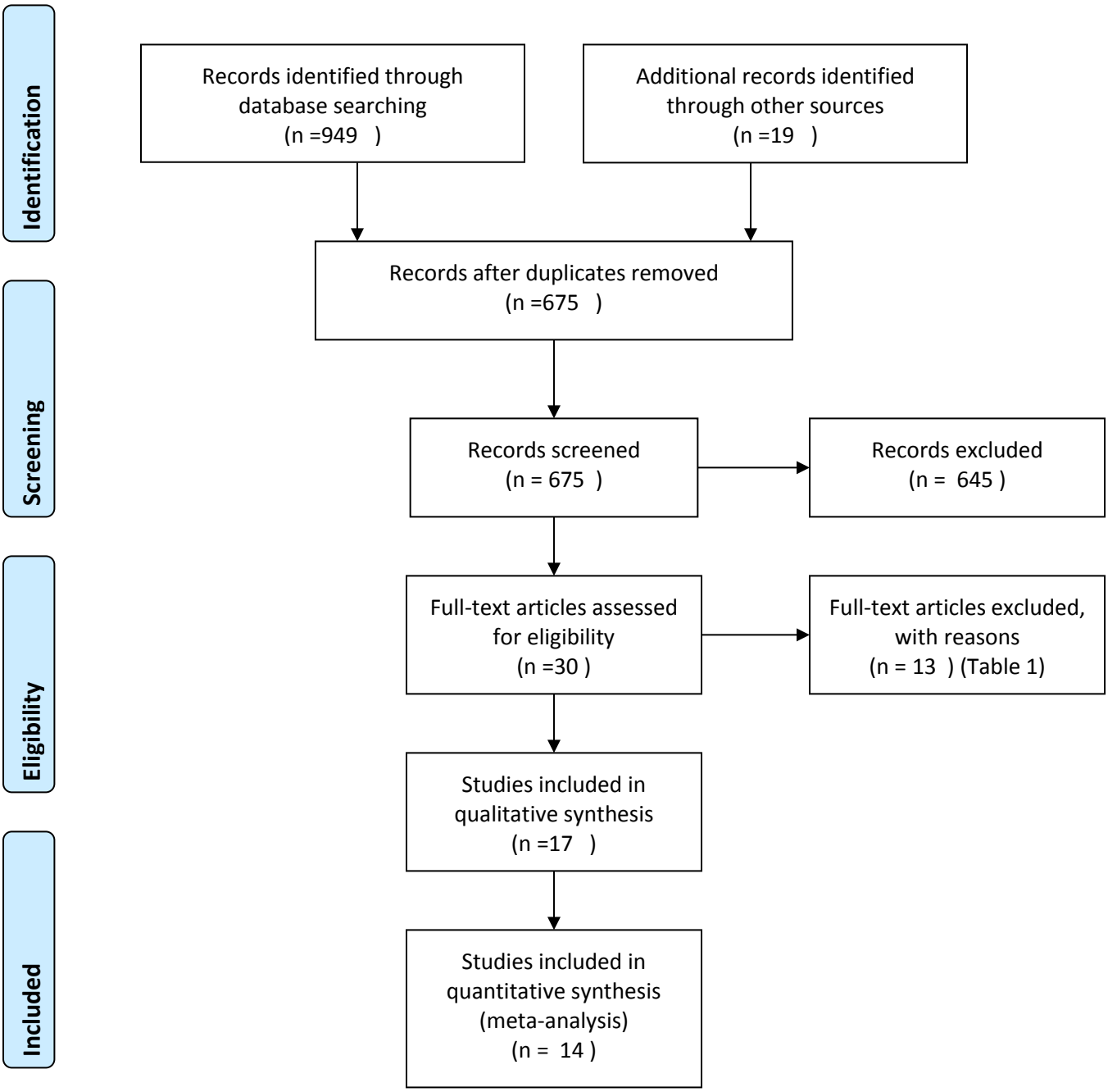


Table 1: Studies excluded and reason of exclusion

Guerresi et al, 1981 [53]	No control group
Baracho et al, 1982 [29]	Study does not indicate randomization
Bhattacharaya et al, 1984 [51]	No randomization
Sirohiwal et al, 2005 [33]	No randomization
Aggarwal et al, 2008 [38]	Consecutive randomization process, thus no truly randomization took place
Manpreet et al, 2008 [54]	No placebo group
Akleh et al, 2010 [52]	No randomization
Zagami et al, 2012 [56]	Full text available in Persian language
Sreelatha et al, 2015 [42]	No randomization
Fardiazar et al, 2013 [23]	No placebo group
Zubor et al, 2016 [44]	Retrospective study
Mukhopadhyay et al, 2018 [55]	No placebo group
Maged et al, 2018 [70]	Case control study

Table 2: Summary of the population characteristics and interventions from each study included

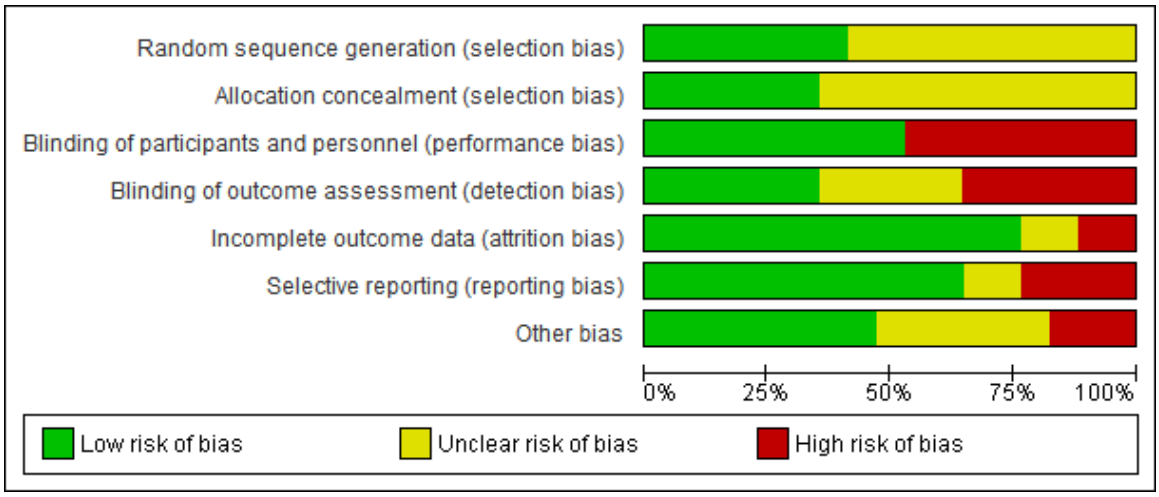
Study	Trial Enrollment	Population	Participants	Intervention (n)	Placebo (n)	Intervention (HBB)	Additional care
Shobha et al, 2006[60]	India	Nulliparous, spontaneous and induced	200	100	100	10 mg pr, repeat every 60 minutes, maximum of 3 doses at cervical dilatation equal to 3-5 cm	Oxytocin augmentation according to partograph
Samuels et al, 2007[34]	Jamaica	Nulliparous and multiparous, spontaneous, low risk	129	60	69	20 mg iv, at 4-5 cm	Oxytocin augmentation according to partograph, amniotomy at 3 cm and opioid analgesia after amniotomy
Gupta et al, 2008[35]	India	Nulliparous and multiparous, low and high risks	97	47	50	20 mg iv, repeat every 30 minutes, maximum of 3 doses at 3cm	Active management (oxytocin augmentation and amniotomy) according to partograph
Mukaindo et al, 2010[61]	Kenya	Nulliparous, spontaneous, low risk	79	37	42	40 mg iv, at 3-6cm, repeat once after 240 min	
Makvandi et al, 2011[58]	Iran	Nulliparous, spontaneous, low risk	130	65	65	20 mg pr, at 3-4 cm	Amniotomy at the time when the presenting fetus was fixed
Al Qahtani et al, 2011 [57]	Saudi Arabia	Nulliparous, spontaneous, low risk	97	52	45	40 mg im, at 3-4 cm	Oxytocin augmentation according to partograph, amniotomy at 4 cm and opioid analgesia after amniotomy

Sekhavat et al, 2012 [36]	Iran	Multiparous, spontaneous, low risk	188	94	94	20 mg iv, at 3-4 cm	Oxytocin augmentation if the uterine contractions are not efficient, amniotomy at 4cm
Al-Khishali et al, 2012 [67]	Iraq	Nulliparous and multiparous, spontaneous, low risk	200	100	100	20 mg iv, at 3-4 cm and full effacement of the cervix	Oxytocin augmentation according to partograph, amniotomy at 4 cm
Alani et al, 2013 [62]	Iraq, Kurdistan	Multiparous, spontaneous, unclear if high risk women included	260	130	130	40 mg iv, at 4 cm	
Singh et al, 2015[68]	India	Nulliparous, spontaneous	220	110	110	40 mg im, at the active phase	
Trevino-Salinas et al, 2015 [66]	Mexico	Nulliparous and multiparous	86	43	43	20 mg iv, at 4cm and the presence of 3-4 contractions / 10 min	
Kirim et al, 2014 [41]	Turkey	Nulliparous and multiparous, low risk	382	197	185	20 mg iv, at 4cm and >50% effacement	Amniotomy at 8 cm
Shirazi et al, 2016 [65]	Iran	Nulliparous and multiparous, spontaneous, low risk	60	30	30	40 mg iv, repeat every 240-360 minutes, maximum of 2 doses at the presence of at least 3 contractions lasting >40s / 10min	
Imaralu et al, 2017 [64]	Nigeria	Nulliparous and multiparous, spontaneous, low risk	160	80	80	20 mg iv, at 4 cm	Oxytocin augmentation if the uterine contractions were not adequate (<3 contractions lasting <40s / 10 minutes)

Barau et al, 2018 [63]	Nigeria	Multiparous, spontaneous, low risk	123	59	64	20 mg im, at 4-5 cm	Oxytocin augmentation (no more information reported)
Sheth et al, 2018 [59]	India	Nulliparous, spontaneous, low risk	50	25	25	10 mg pr, at 3 cm and / >50% effacement	Amniotomy at 3 cm
Ashraf, 2018 [37]	India	Nulliparous and multiparous, spontaneous, low risk	300	150	150	10 mg pr, repeat every 60 minutes, maximum of 3 doses, at 3-4 cm	

iv: intravenous administration
im: intramuscular administration
pr: per rectum administration
cm: centimeters

Figure 3: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



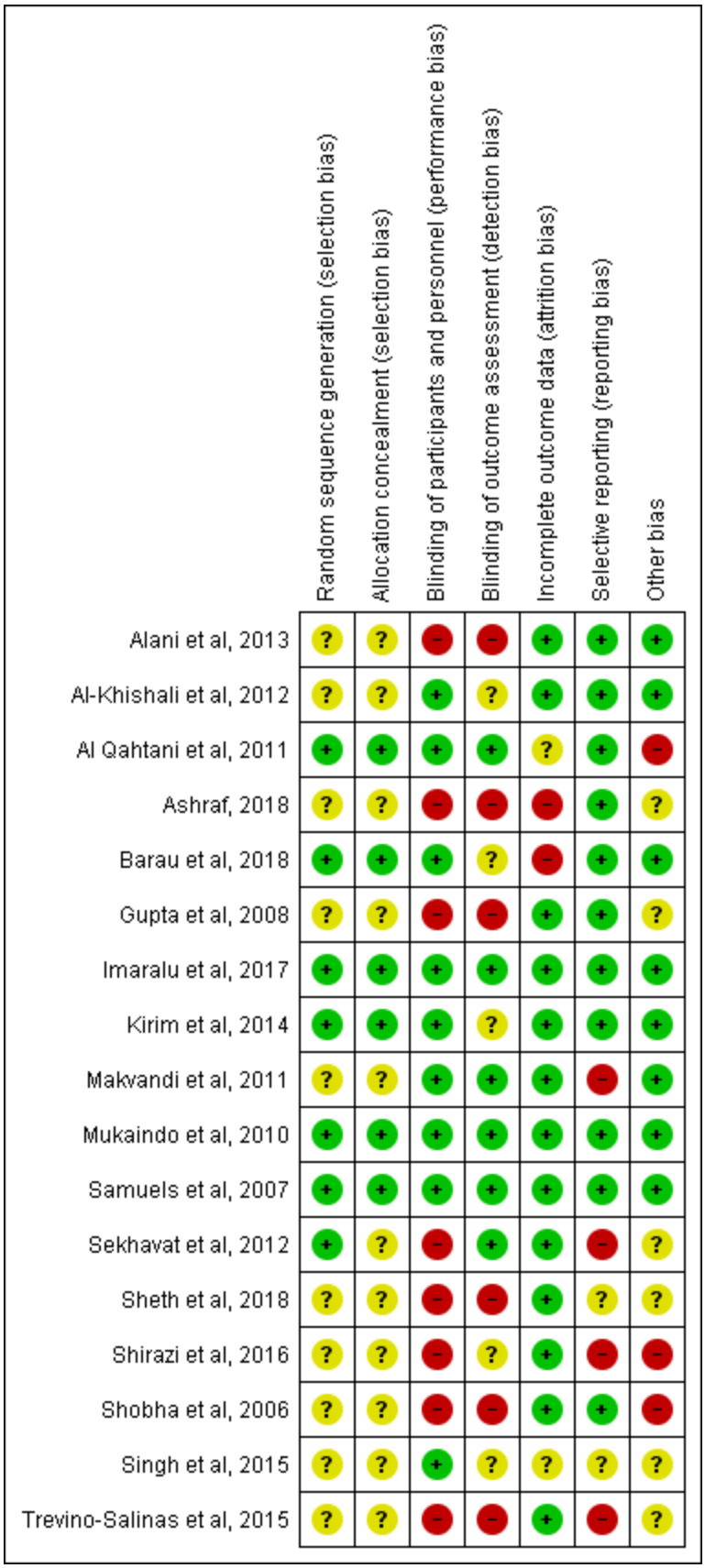


Figure 4: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Primary and secondary outcomes

The administration of HBB reduced significantly the duration of the active phase of first stage of labor (MD -61.46 minutes, 95% CI -85.83, -37.1, p<0.001, I^2=95%) (Figure 5). Furthermore the administration of HBB was associated with a significant reduction in the duration of the second stage of labor (MD -2.49 minutes, 95%CI -3.99 to -0.98, p=0.001, I^2=76%) (Figure 6), the total duration of labor (MD -96.45 minutes, 95%CI -192.14 to -0.77, p=0.05, I^2=93%) (Figure 7), the time from the administration of the drug until the delivery of the fetus (MD -57.11 minutes, 95%CI -94.99 to -19.22, p=0.003, I^2=73%)(Figure 8) and a significant increase of the cervical dilatation rate (MD 0.57 cm/hour, 95%CI 0.15 to 1.00, p=0.008, I^2=89%) compared to the control group (Figure 9).

Figure 5: Duration of the first stage of labor comparing the administration of HBB to control

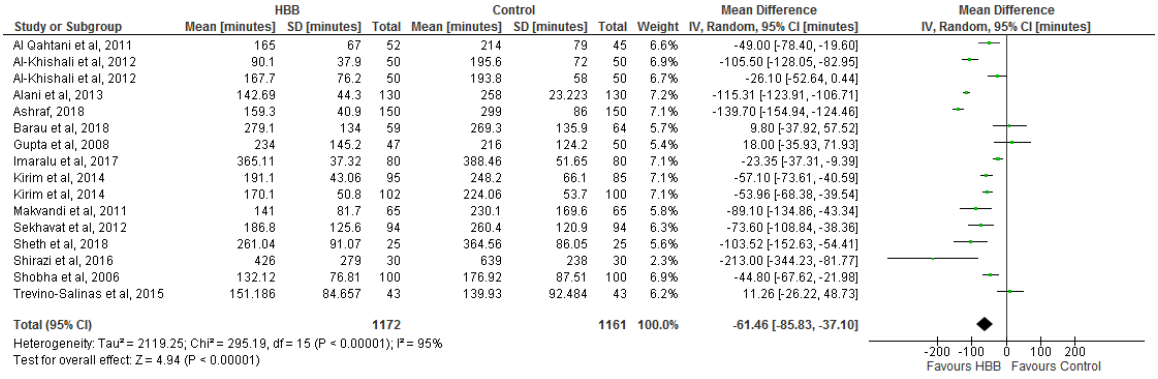


Figure 6: Duration of the second stage of labor comparing the administration of HBB to control

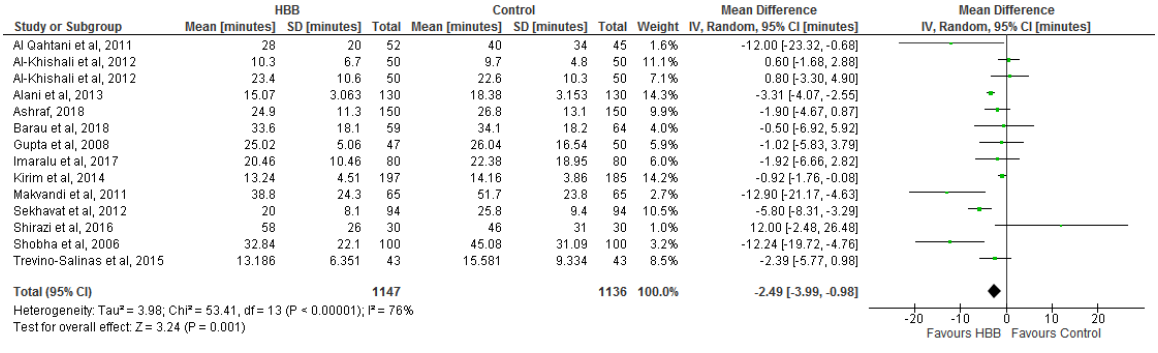


Figure 7: Total duration of labor comparing the administration of HBB to control

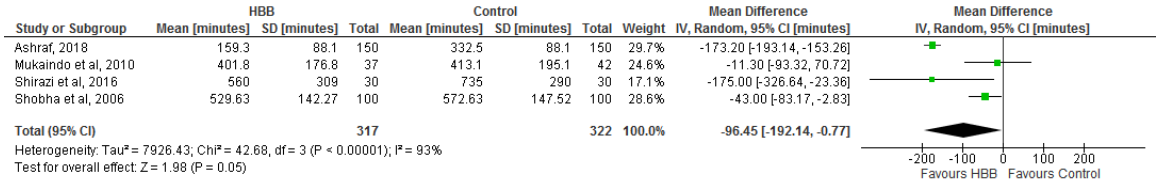


Figure 8: Duration of first and second stage of labor comparing the administration of HBB to control

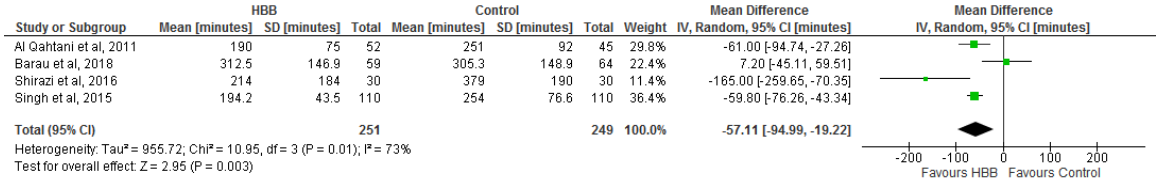
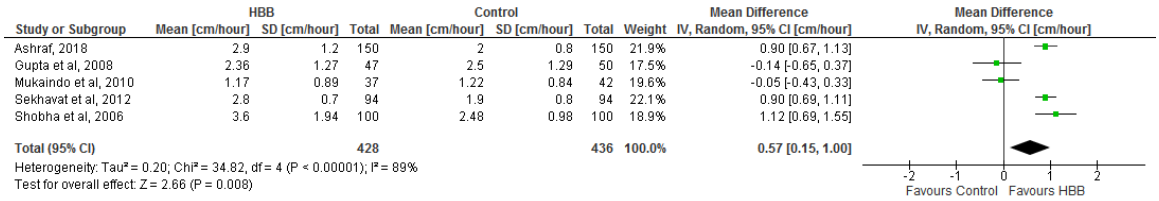


Figure 9: Dilatation rate comparing the administration of HBB to control



No significant maternal or fetal adverse effects reported overall. One study reported statistical significant difference among the groups for fetal and maternal heart rate immediately after the administration of the drug contributing to transient tachycardia that was resolved after two hours [65] and another reported that the incidence of nausea and vomiting was 24% for the intervention group without reporting on the control group [35]. No differences for fetal outcome addressed to any of the included studies. A summary for the reported adverse effects can be found in Table 3.

Table 3: Summary of the reported maternal and fetal adverse effects

Shobha et al, 2006	Transient tachycardia 8% Vomiting 1% No dryness of mouth, flushing of face, blurring of vision or headache were observed
Samuels et al, 2007	Blood loss 150 ml; no different from the control group
Gupta et al, 2008	Nausea and vomiting 24% Tachycardia 5/47 patients The incidence of PPH was similar among groups
Mukaindo et al, 2010	Transient palpitations 1/37 patients PPH 5.2% (Placebo group 7.3%)
Makvandi et al, 2011	Mean heart rate:83.34 beats/min, SD:10.56; Mean systolic BP: 108.78 mmHg, SD: 12.34 Placebo group: Mean heart rate:86.65 beats/min, SD:12.87; Mean systolic BP: 110.09 mmHg, SD:13.67
Al Qahtani et al, 2011	PPH: 0/52; Tear: 2/50
Sekhavat et al, 2012	No adverse effects
Al-Khishali et al, 2012	No significant differences among groups: Dry mouth, headache, nausea, vomiting, tachycardia, urinary urgency, hypotension, blurred vision
Alani et al, 2013	PPH 1/130 patients
Singh et al, 2015	No adverse effects
Trevino-Salinas et al, 2015	NR
Kirim et al, 2014	No adverse effects
Shirazi et al, 2016	Statistical important differences: maternal heart rate immediately after the drug administration 97.6±10.37 compared to 86.2±7.69 (placebo group) and one hour later 91.83±8.18 compared to 86.2±7.69 (placebo group), and fetal heart rate immediately after the drug administration 147.67±10.83 compared to 137.27±13.53. No significant difference for length of hospitalization, maternal or fetal heart rate two hours after taking the drug and blood loss
Imaralu et al, 2017	No ocular, urologic or neurologic side effects reported. No significant differences among groups for dry mouth and tachycardia

Barau et al, 2018	No significant differences among groups for blood loss, episiotomy, perineal tear
Sheth et al, 2018	The only adverse effects presented were nausea, vomiting and urinary retention, with no statistical differences among groups
Ashraf, 2018	No significant differences among groups for maternal tachycardia, fetal tachycardia, mouth dryness, nausea/vomiting, flushing, fetal distress, birth asphyxia, vaginal tear

PPH: Postpartum hemorrhage
NR: Not reported

Subgroup analysis

Primary outcome: Duration of first stage of labor

Fourteen studies involving 2333 patients were included in this random effect meta-analysis. The subgroup analysis did not show significant heterogeneity between subgroups for route of administration of HBB (intravenous, intramuscular, per rectum), parity, single or multiple dose regimens I^2=35.9%, I^2=29.4%, I^2=0% , respectively, but only showed statistical significant differences when active management of labor applied (use of oxytocin or amniotomy) compared to those studies that active management was not reported, I^2=70% / p=0.07 (Figures 10-13)

Figure 10: Duration of first stage of labor: Administration route

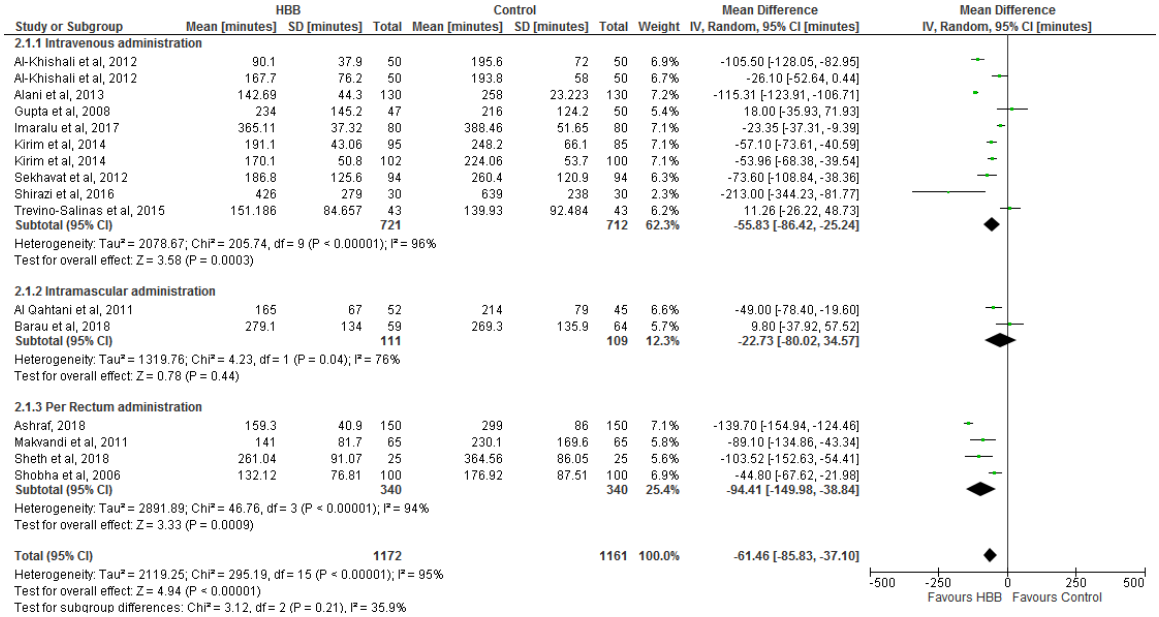


Figure 11: Duration of first stage of labor: Nulliparous – Multiparous

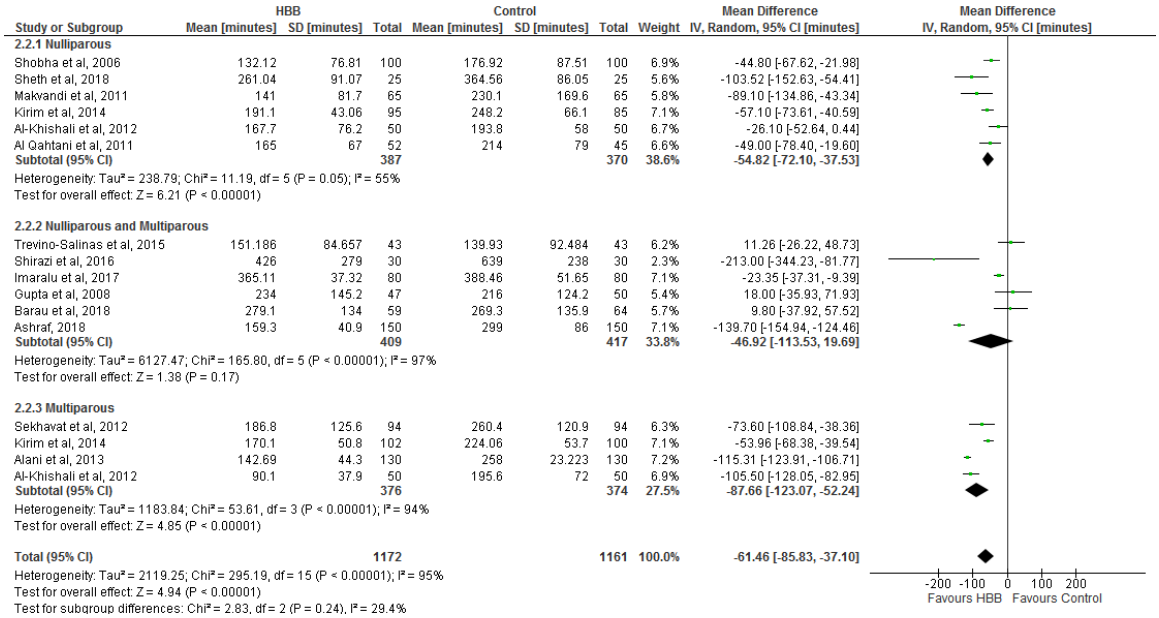


Figure 12: Duration of first stage of labor: Single dose – Multiple doses

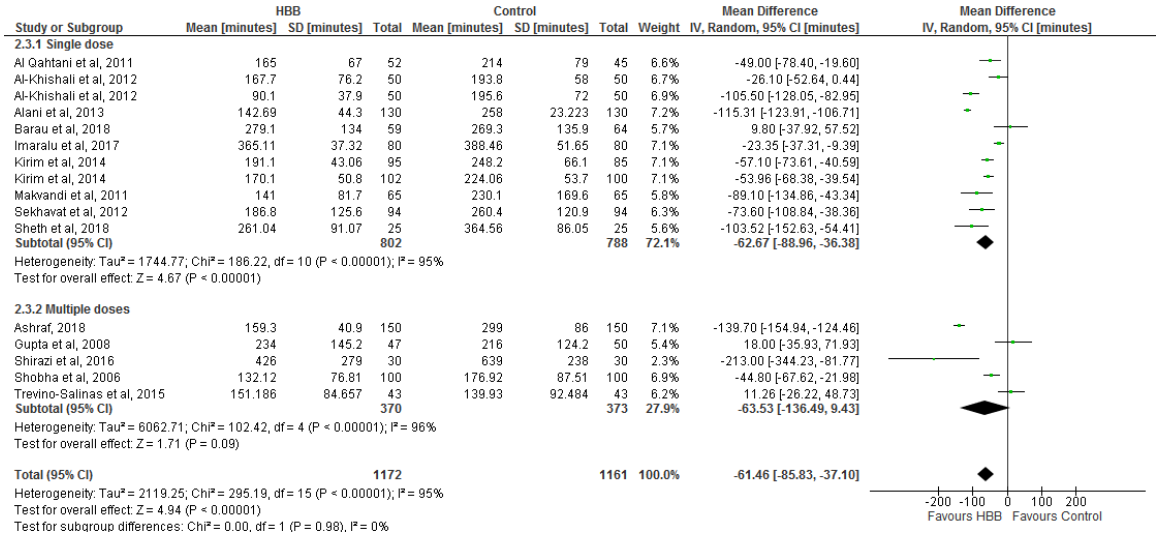
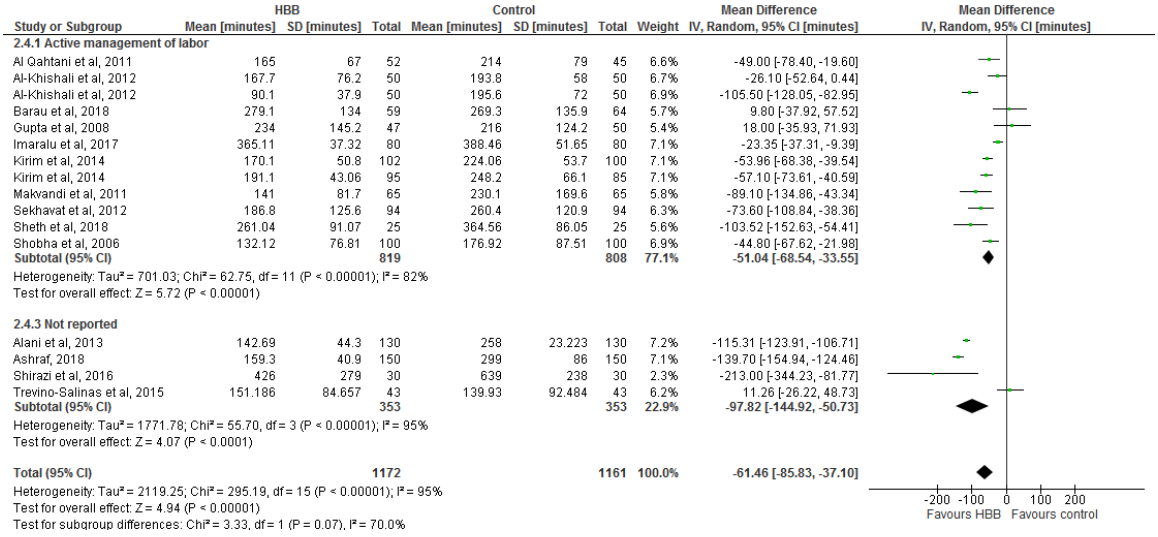


Figure 13: Duration of first stage of labor: Active management of labor



Secondary outcome: Duration of second stage of labor

Thirteen studies involving 2283 patients were included in this random effect meta-analysis. The subgroup analysis did not show significant differences between subgroups for route of administration of HBB (intravenous, intramuscular, per rectum), single or multiple dose regimens, active management of labor or nulliparous vs multiparous women I^2=24.2% / p=0.27, I^2=0% / p=0.24, I^2=0% / p=0.98% , I^2=52.6% / p=0.07 respectively (Figures 14-17).

Figure 14: Duration of second stage of labor: Administration route

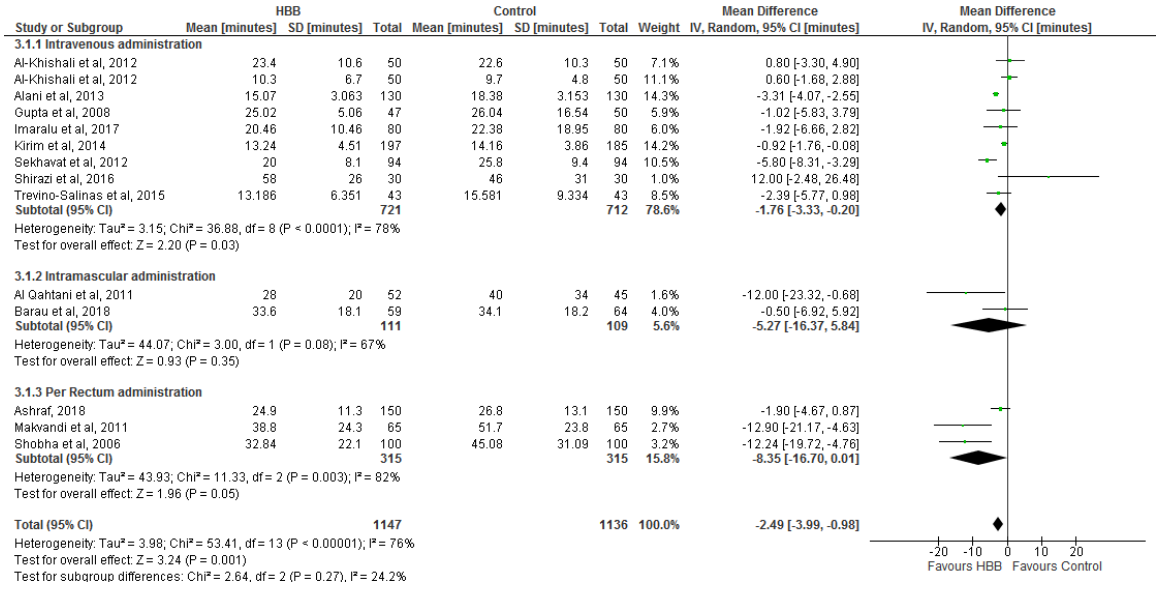


Figure 15: Duration of second stage of labor: Nulliparous – Multiparous

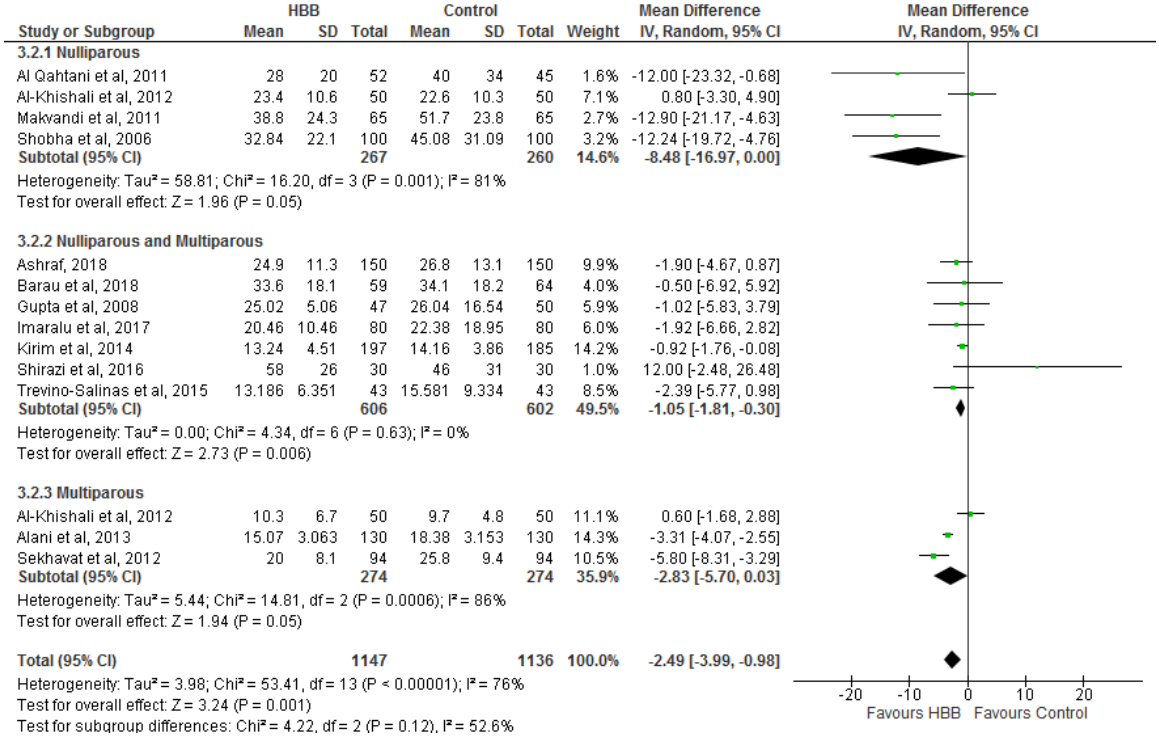


Figure 16: Duration of second stage of labor: Single dose – Multiple doses

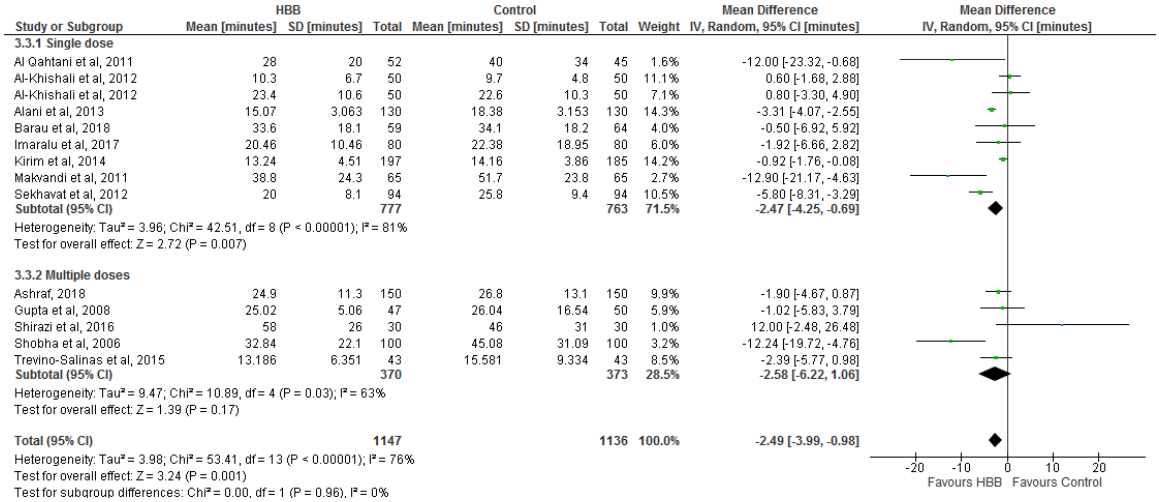
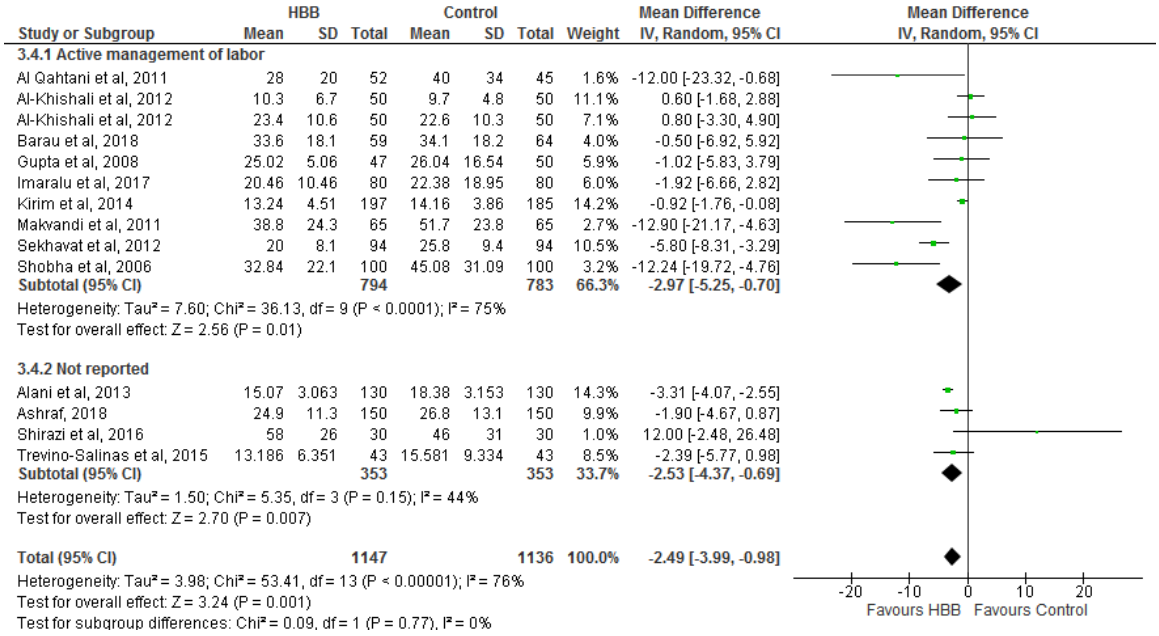


Figure 17: Duration of second stage of labor: Active management of labor



Secondary outcome: Total duration of labor

Four studies involving 639 patients were included in this random effect meta-analysis. The subgroup analysis did not show significant differences between subgroups for route of administration of HBB (intravenous, per rectum), single or multiple dose regimens and active management of labor I^2=0% / p=0.78, I^2=27.8% / p=0.24, I^2=62.7% / p=0.1 respectively. It showed significant differences only for nulliparous and multiparous women (I^2=97.6% / p<0.001) (Figures 18-21).

Figure 18: Total duration of labor: Route of administration

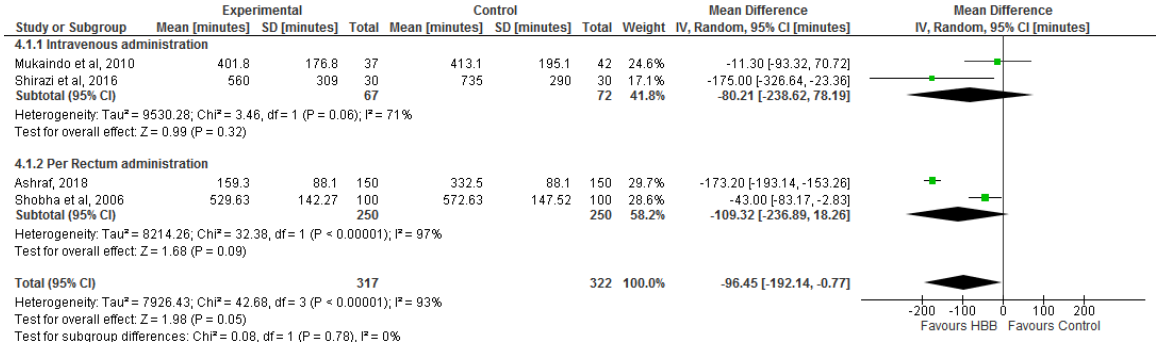


Figure 19: Total duration of labor: Nulliparous – multiparous

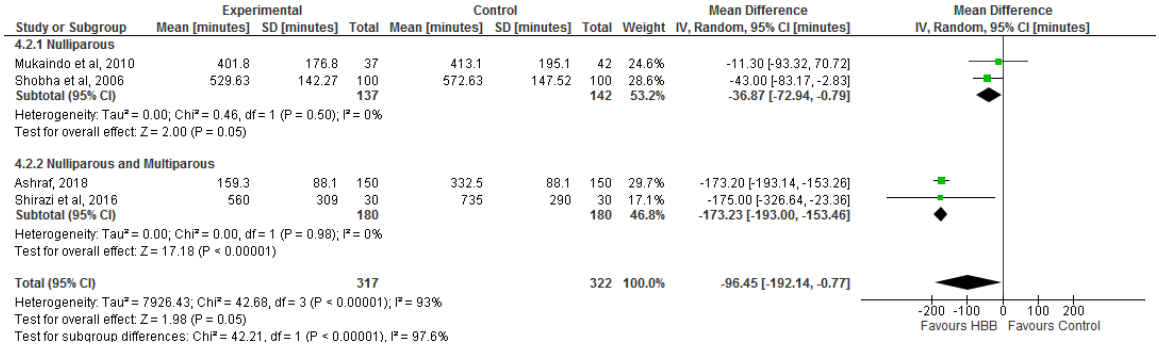


Figure 20: Total duration of labor: Single dose – multiple doses

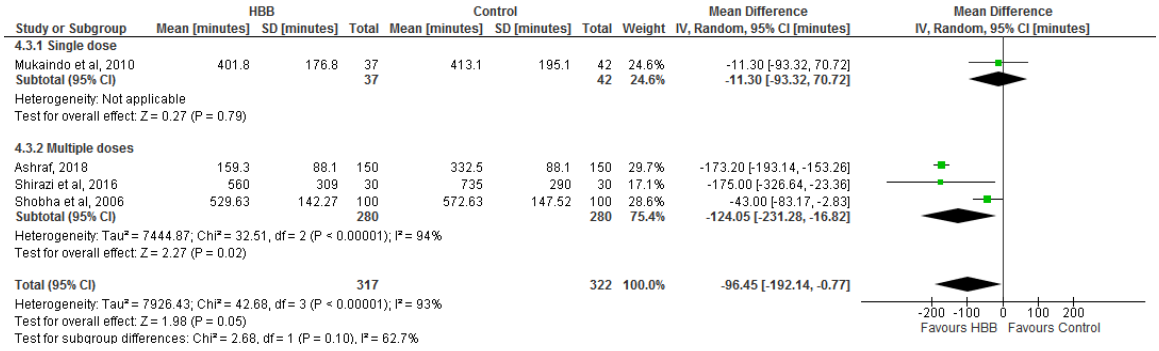
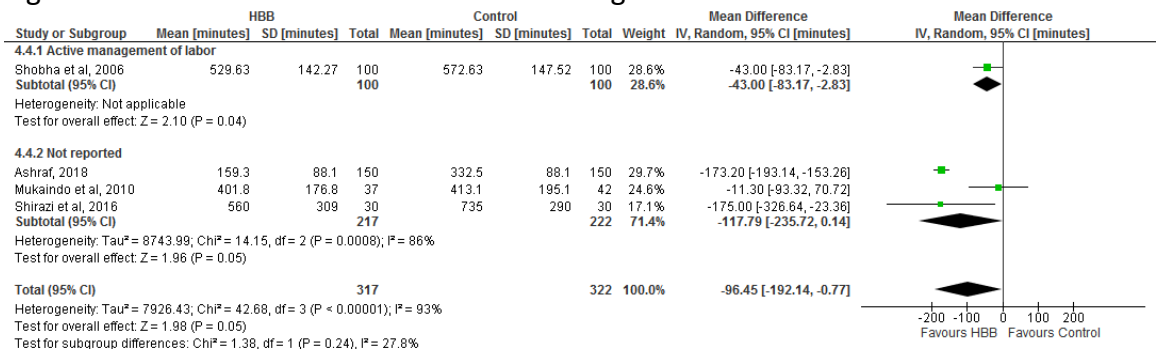


Figure 21: Total duration of labor: Active management of labor



Secondary outcome: Duration of first and second stage of labor

Four studies including 500 patients were included in this random effects meta-analysis. The subgroup analysis did not reveal significant differences between subgroups for active management of labor and parity, I^2=0%/ p=0.46, I^2=0% / p=0.32, respectively. It showed significant differences for the route of administration of HBB (intravenous, intramuscular) (I^2=81.8%, p=0.02) and single or multiple dose regimens, (I^2=78.2%, p=0.03). (Figures 22-25).

Figure 22: Duration of the first and second stage of labor: Route of administration

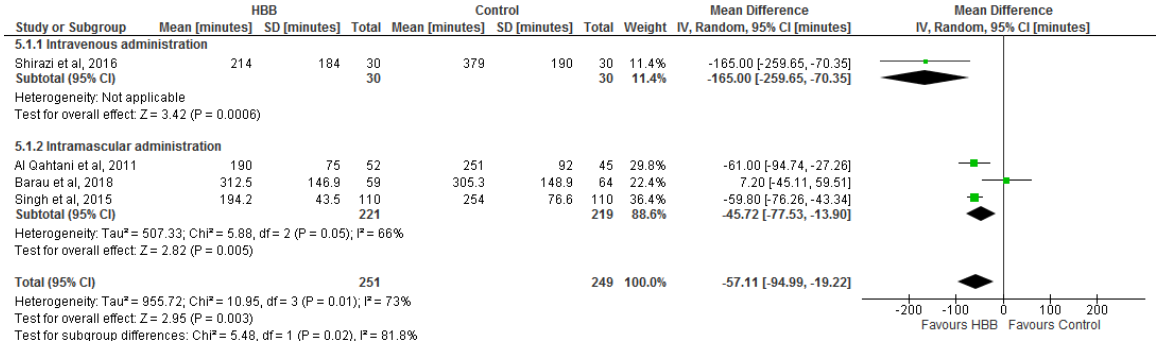


Figure 23: Duration of the first and second stage of labor: Nulliparous -Multiparous

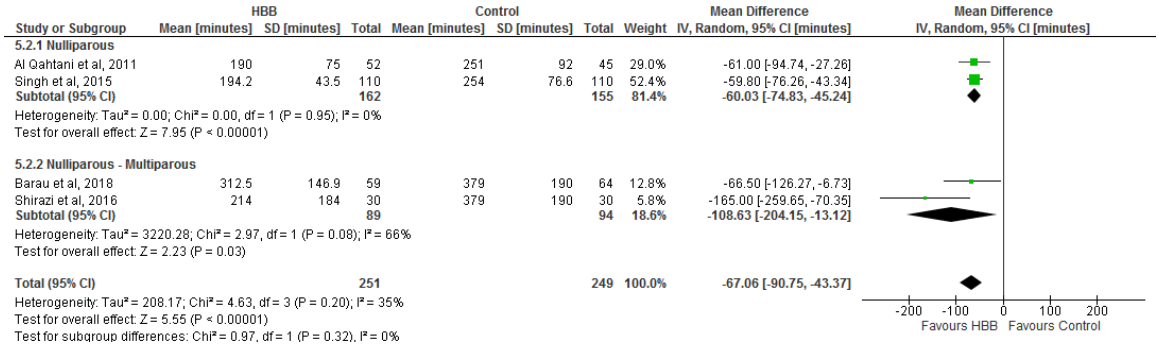


Figure 24: Duration of the first and second stage of labor: Single dose – Multiple doses

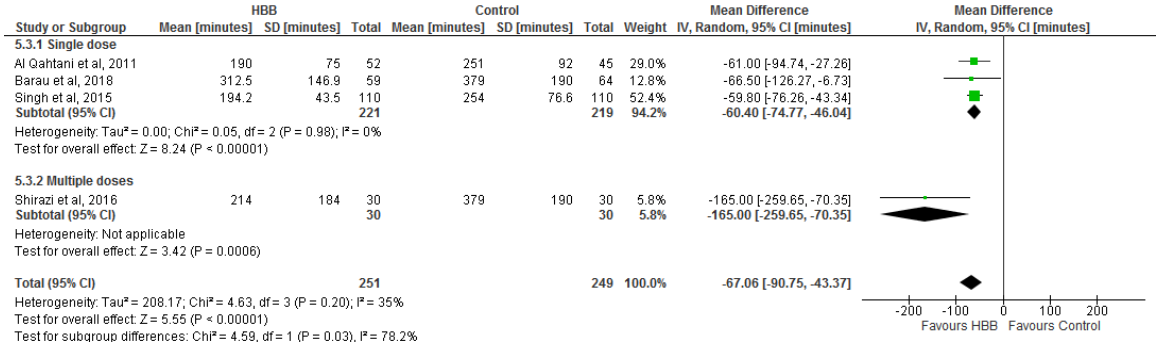
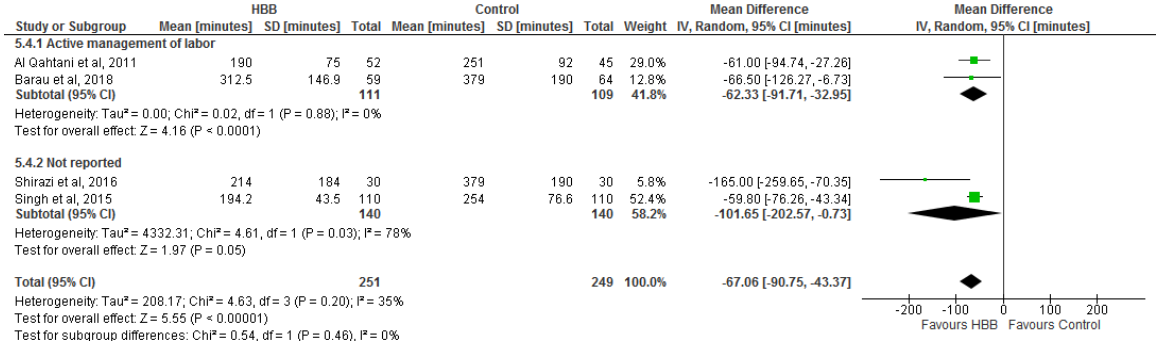


Figure 25: Duration of the first and second stage of labor: Active management of labor



Secondary outcome: Dilatation Rate

Five studies including 864 patients were included in this random effects meta-analysis. The subgroup analysis did not show significant differences between subgroups for parity, single or multiple doses of the drug, active management of labor or route of administration I^2=0%/p=0.55, I^2=0%/p=0.77, I^2=0%/p=0.7, I^2=67.1%/p=0.08 respectively (Figures 26-29).

Figure 26: Dilatation rate: Route of administration

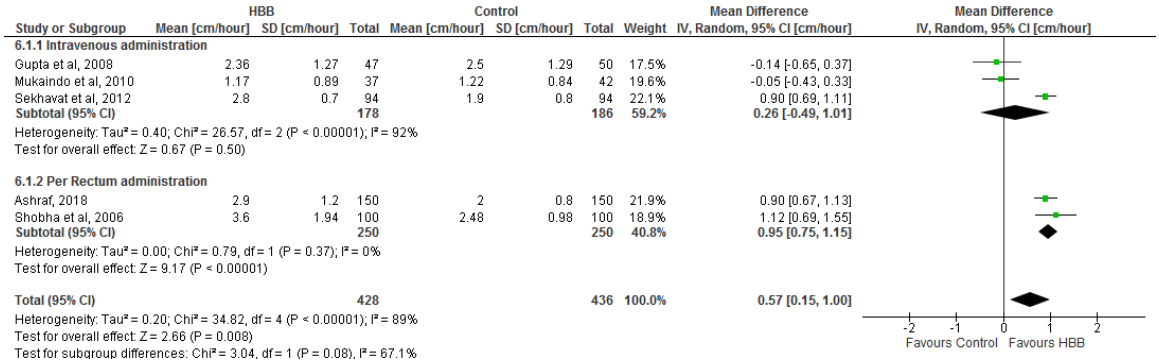


Figure 27: Dilatation rate: Nulliparous – Multiparous

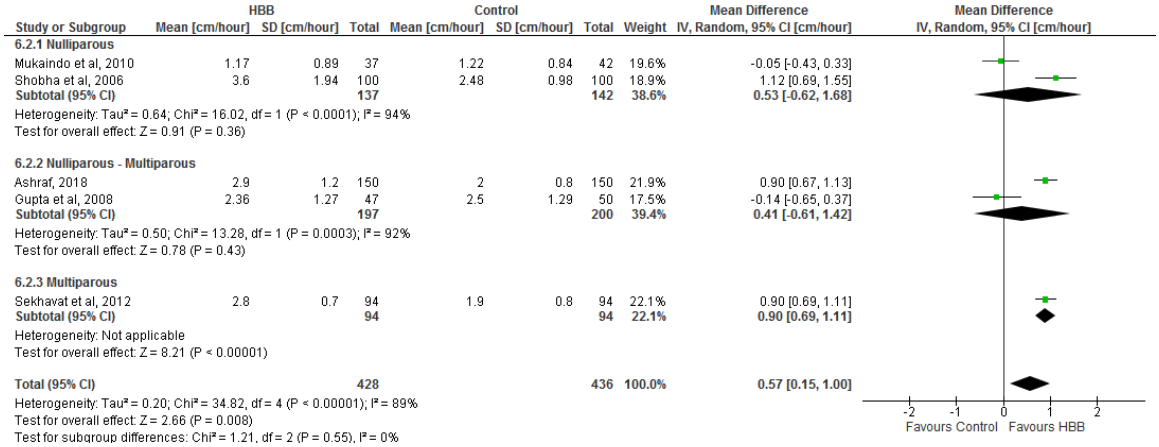


Figure 28: Dilatation rate: Single dose – Repeated doses

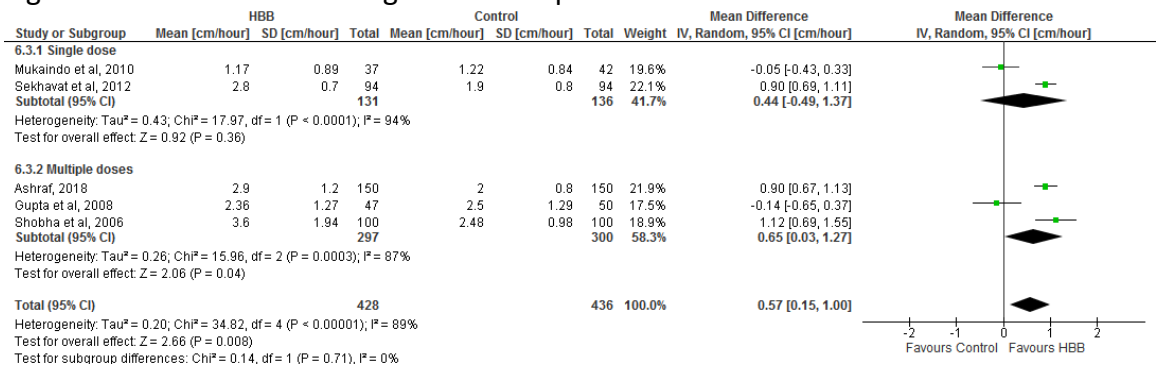
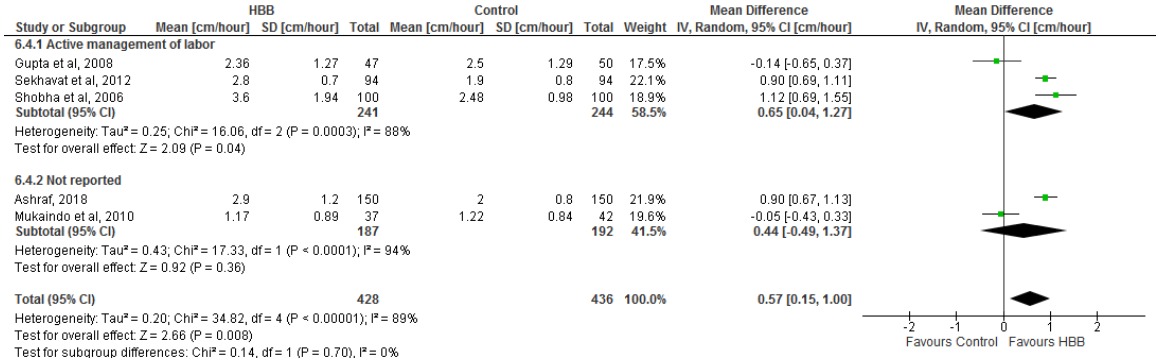


Figure 29: Dilatation rate: Active management of labor



Principal findings

This systematic review and random effects meta-analysis included data from seventeen studies who randomized 2761 patients into intervention and control groups to assess the effectiveness of HBB as a factor that can shorten the duration of active phase of first stage of labor.
It shows that it can shortens the duration of that stage of labor by a mean of 61.46 minutes, with some subgroups present even greater effect. Per rectum administration presented a mean reduction of 94.41 minutes, while multiparous women seem to benefit more than nulliparous (mean reduction of 87.66 minutes). An interesting finding is that studies that did not report active management of labor showed a significant reduction of mean duration of first stage by 97.82 minutes, although significant heterogeneity was reported among that subgroup, compared to those that have active management in which the mean reduction was 51.04 minutes. This seems logical since women in which treated by active management intrapartum experience a reduction of the duration of this stage
Duration of the second stage of labor was also significantly shorter by 2.49 minutes but this is probably of no significant clinical value.
Accordingly, total duration of labor was also significantly reduced by 96.45 minutes, with the greater benefit to those intervention groups that used multiple doses regimens during the first stage of labor (MD -124.05).
As expected, dilatation was significantly accelerated among the intervention groups by a mean additional rate of 0.57 cm/hour compared to the control groups. Again, among the subgroup that was administered per rectum suppositories, the cervical dilatation rate was higher than the general population (MD 0.95 cm/hour), but this was not statistical signifficant.
Moreover, no significant adverse outcomes reported for the mothers or the fetuses in any of the studies, fact which proves the safety of the drug.

Strengths and limitations

The findings of this study are supported by: 1. The quantitative way of summarizing the evidence; 2. The extensive research of databases to include all relevant RCTs up to date, published and unpublished; 3. Inclusion of studies from different countries with different economic status and level of provided medical care; 4. A rigorous methodology on performing the systematic review and metanalysis was adopted throughout the process;

Limitations of the study: 1. Limited data were available for secondary outcomes compared to the primary; 2. Limited data for high risk pregnancies; 3. Limited data for induced labor; 4. Not reporting about the rate of normal vaginal delivery, vaginal assisted delivery and CS among the two arms; 5. Limited data were available about the painkillers or type of anesthesia used intrapartum; 6. Limited data for the status of fetal membranes as this is a factor that can alter the progression of labor; 7. High levels of heterogeneity noticed: This can be explained by population baseline differences, intervention differences, as well as methodology differences among studies.; 8. Unclear or high risk of bias for the majority of the studies.

Implications for clinical practice and research

Hyoscine butylbromide is an agent that can alter the progress of normal labor in many ways. First, there is evidence that can safely shorten the duration of first stage of labor and act as analgesic for women intrapartum. It is a cheap and easy to administer drug, thus it can be used worldwide to help women in labor.
More RCTs are needed to be conducted in order to study the effects on different populations, low and high risk pregnancies, nulliparous and multiparous women, spontaneous and induced labor as well as an alternative and a synergic factor to already established active management of labor protocols. Furthermore, the most effective route of administration and dose regimen should be studied in order to increase its impacts.
Moreover, fields of physiology on normal labor progress that remain grey zone for scientists should be further explored. The relationship between normal labor and local acidosis, the role of AMP/K+ channels, differences in membrane polarization and the interaction of local secretary mechanisms before, during and after labor should be studied extensively, in order to better understand the progress and find possible pharmaceutic targets.

Compliance with ethical standards

Conflict of interest

No conflict of interest declared.
No funding received for this study.

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Appendix A: Characteristics of the studies and Risk of Bias assessment

Al Qahtani et al, 2011		
Methods	Study design: Randomized controlled trial. Allocation generation: Cards with either "HBB" or "placebo" written on them placed in sealed envelopes. Envelopes were placed in a box, mixed and drawn by the nurse in charge. Allocation concealment: Opaque sealed envelopes containing cards with either "HBB" or "placebo" written on them mixed in a box and drawn by the nurse in charge when the patient consented for participation in the study. Blinding: Patients, nurses and physicians unaware of contents of syringe. Nurse in charge prepared syringe according to card in envelope. HBB and saline are both colorless and the contents of the syringes could thus not be established. Loss to follow up: Intervention: 10%. Control: 13%.	
Participants	Total number of participants randomized: 110. Inclusion criteria: 1. singleton pregnancy 2. vertex presentation at term 3. no chronic or pregnancy-induced illnesses 4. no contraindications to vaginal delivery 5. established, spontaneous labor with either intact or spontaneous rupture of membranes for less than 12 hours. Exclusion criteria: 1. previous uterine scarring 2. malpresentation 3. antepartum hemorrhage 3. multiparity 4. twin pregnancy 5. induced delivery 6. any medical disease 7. oxytocin induction 8. prolonged premature rupture of membranes (more than 12 hours) 9. epidural analgesia.	
Intervention	Intervention: Hyoscine Butylbromide 40 mg (2 mL) im; n = 58 (randomized); n = 52 (analyzed). Control: Placebo (normal saline) 2 mL im; n = 52 (randomized); n = 45 (analyzed). Timing of intervention: 3-4 cm cervical dilatation, full effacement	
Outcomes	Primary outcomes: 1. Duration of first stage of labor (from 4 cm cervical dilatation to full dilatation). 2. Duration of first and second stage of labor (from 4 cm cervical dilatation to delivery of baby). 3. Duration of second and third stage of labor. Secondary outcomes: 1. Postpartum hemorrhage. 2. Rate of caesarean sections. 3. Apgar score.	
Notes	Ethics: informed consent signed by participants before randomization, study approved by Ethical committee of the University of Dammam. Location: Saudi Arabia. Other: Some data obtained from Cochrane Review ''Antispasmodics for labor''	
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low Risk	Drawing envelopes containing cards either placebo or HBB written on them from a box
Allocation concealment (selection bias	Low Risk	Sequentially numbered, opaque, sealed envelopes – mixed in box and drawn by nurse in charge once patient had signed consent.
Blinding of participants and personnel (performance bias)	Low Risk	Nurse in charge prepared syringes containing either placebo or HBB, which are both colorless fluids. She then attached the card from the envelope to the participants file after delivery. Participants, physicians and attending nurses were thus blinded.
Blinding of outcome assessment (detection bias)	Low Risk	Principal investigator collected the raw data sheets from the labor rooms and was also blinded
Incomplete outcome data (attrition bias)	Unclear Risk	Unclear in study report whether 13 participants not included in the analysis were randomized to a group before being excluded. Author confirmed that seven of these received placebo and six received HBB and were excluded from analysis due to augmentation with oxytocin which indicates that there was attrition of 10% in the intervention group and 13% in the placebo group. data obtained from Cochrane Review "Antispasmodics for labor"
Selective reporting (reporting bias)	Low Risk	No protocol of the study found, but all outcomes prespecified in methods section addressed.
Other bias	High Risk	Yes – 44% (23/52) participants in HBB group had spontaneous ROM at baseline, compared with 22% (10/42) in the placebo group – this is a statistically significant difference (P = 0.0039) which can influence the duration of labor

Al-Khishali et al, 2012		
Methods	Study design: Randomized controlled trial. Allocation generation: Not described Allocation concealment: Not described Blinding: Double blinded - No further information given Loss to follow-up: Intervention: 0%. Control: 0%.	
Participants	Total number of participants randomized: 200 Inclusion criteria: 1. 18 years age and older 2. singleton pregnancy 3. from completed 37 weeks to completed 42 weeks 4. vertex presentation 5. established spontaneous labor 6. reassured fetal heart rate. Exclusion criteria: 1. women with previous uterine scar 2. fetal malpresentation 3. cephalopelvic disproportion 4. antepartum hemorrhage 5. chronic or pregnancy induced illnesses.	
Intervention	Intervention: 20mg HBB iv; n=100 Control: 1.0 ml of normal saline; n=100 Timing of administration: cervix was fully effaced and was dilated to 3-4 cm.	
Outcomes	1. Duration of the active phase of the first stage 2. Duration of the second stage 3. Duration of the third stage 4. Rate of caesarean sections 5. APGAR score (1 and 5 mins) 6. Neonatal admission to neonatal intensive care unit 7. Incidence of adverse effects	
Notes	Location: Iraq Ethics: The study protocol was approved by the Obstetrics and Gynecology Committee of the Iraqi Board for Medical Specialization and the Local Hospital Ethics Committee; full informed consent was obtained from all participants.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Simple randomization, method not explicitly described
Allocation concealment (selection bias	Unclear Risk	No allocation concealment described
Blinding of participants and personnel (performance bias)	Low Risk	Double blinded - No further information given
Blinding of outcome assessment (detection bias)	Unclear Risk	Not reported
Incomplete outcome data (attrition bias)	Low Risk	All participants accounted for, no missing data.
Selective reporting (reporting bias)	Low Risk	All outcomes prespecified in the methods section reported on.
Other bias	Low Risk	Unlikely that other bias is present No funding received from any pharmaceutical company.

Alani et al, 2013		
Methods	Study design: Randomized controlled trial. Allocation generation: Simple randomization, not explicitly described Allocation concealment: Not described Blinding: No blinding Loss to follow-up: Intervention: 0.8% Control: 1.5% because of the need for CS	
Participants	Total number of participants randomized: 260 Inclusion criteria: 1. multigravida (Para 1-4) 2. term pregnancy (completed 37 - 42 weeks) 3. viable singleton pregnancy 4. vertex presentation 5. spontaneously established labor Exclusion criteria: women who do not fit the inclusion criteria	
Intervention	Intervention: 40 mg Hyoscine N-butyl bromide iv; n=130 randomized; n=129 analyzed Control: 2 ml NaCl 0.9%; n=130 randomized; n=128 analyzed	
Outcomes	1. Active phase duration by measuring time interval from drug administration till delivery 2. Mode of delivery their 3. Indication of CS if performed 4. Maternal side effects. 5. Neonatal APGAR score (1st and 5th minute)	
Notes	Location: Iraq Ethics: Verbal informed consent obtained, ethical approval not reported	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Simple randomization, method not explicitly described.
Allocation concealment (selection bias	Unclear Risk	No allocation concealment described
Blinding of participants and personnel (performance bias)	High Risk	No blinding
Blinding of outcome assessment (detection bias)	High Risk	No blinding
Incomplete outcome data (attrition bias)	Low Risk	1/130 patients in intervention arm and 2/130 in control arm were excluded from the analysis because of the need for CS, no missing data.
Selective reporting (reporting bias)	Low Risk	All outcomes prespecified in the methods section reported on.
Other bias	Low Risk	No other sources of potential bias detected. Drug company sponsorship: No

Ashraf, 2018		
Methods	Study design: Randomized control trial Allocation generation: Simple randomization Allocation concealment: Not reported Blinding: No blinding Loss to follow-up: Intervention: 0% Control: 0%	
Participants	Total number of participants randomized: 300 Inclusion criteria: 1. Primigravida and multigravida 2. age between 18-30 year 3. intact fetal membranes 4. vertex presentation 5. regular established uterine contraction at the rate of at least 2/10 minutes, each contraction lasting for at least 20 seconds 6. cervical dilatation of 3-4 cm 7. no evidence of maternal or fetal distress. Exclusion criteria: 1. Malpresentation 2. twin pregnancy 3. cervical surgery in the past 4. history of cervical injury 5. induced labor 6. maternal systolic pressure below 100mm Hg or above 150 mm Hg 7. patients on antihypertensive therapy 8. if any other spasmolytic agent had been used within 48 hours.	
Intervention	Intervention: 10 mg HBB suppository pr. The drug was repeated every hour up to a maximum three doses; n=150 Control: No drug; n=150 Time of administration: established labor i.e. at 3 or 4 cm cervical dilatation with regular uterine contractions of >2 per 10 mins each lasting 20 seconds.	
Outcomes	1. Duration of first, second and third stages of labor. 2. Rate of cervical dilatation 3. Mode of delivery 4. Neonatal condition at birth 5. Maternal complications 6.Side effects	
Notes	Location: India Ethics: ethical approval not reported, informed consent obtained.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Simple randomization - No further information
Allocation concealment (selection bias	Unclear Risk	No allocation concealment described
Blinding of participants and personnel (performance bias)	High Risk	No blinding
Blinding of outcome assessment (detection bias)	High Risk	No blinding
Incomplete outcome data (attrition bias)	High Risk	5/150 (3.3%) patients in intervention arm and 8/150 (5.3%) in the control arm delivered with CS because of fetal distress or arrest of labor with no more information reported for each group separately. Those patients included for analysis
Selective reporting (reporting bias)	Low Risk	All outcomes prespecified in the methods section reported on.
Other bias	Unclear Risk	The control group received no drug Drug company sponsorship: No

Barau et al, 2018		
Methods	Study design: Randomized clinical trial Allocation generation: Computer-generated list by means of sequentially numbered, opaque, sealed envelopes indicating their medication Allocation concealment: Sequentially numbered Opaque, sealed envelopes indicating their medication Blinding: Both the patient and attending Nurse or Doctor were blinded to whether its HBB or Normal saline that was served as they both appear colorless in the syringe Loss to follow-up: Intervention:7/66 (10.61%) Control:2/66 (3.03%)	
Participants	Total number of participants randomized: 132 Inclusion criteria: 1. multigravida 2. spontaneous onset of labor 3. singleton cephalic presenting pregnancy at term 4. no contraindication for vaginal delivery. Exclusion criteria: 1. Patients who refused consent to participate 2. any chronic medical or pregnancy induced illness 3. parturient who were administered antispasmodic medication before presentation in labor ward 4. rupture of membranes (more than 12 hours) 5. history of drug allergy.	
Intervention	Intervention: Hyoscine butyl bromide 20 mg (2 ml) im; n=66 (randomized); n=59 (analyzed) Control: Normal saline 2 ml im; n=66 (randomized); n=64 (analyzed) Timing of administration: Active phase labor with a cervical dilation of 4 - 5 cm.	
Outcomes	1. The duration of 1st stage of labor from administration of the drug to full cervical dilatation. 2. The 2nd stage from full cervical dilatation to delivery of the fetus 3. The 3rd stage of labor from delivery of the fetus to the delivery of the placenta. 4. Maternal complications 5. APGAR, score at 1 min and 5min	
Notes	Location: Nigeria Ethics: ethical approval obtained from Ethical Committee of the Hospital, informed consent obtained.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Computer-generated list by means of sequentially numbered, opaque, sealed envelopes indicating their medication
Allocation concealment (selection bias	Low Risk	Sequentially numbered, opaque, sealed envelopes indicating their medication
Blinding of participants and personnel (performance bias)	Low Risk	Both the patient and attending Nurse or Doctor were blinded to whether its HBB or Normal saline that was served as they both appear colorless in the syringe
Blinding of outcome assessment (detection bias)	Unclear Risk	Not reported
Incomplete outcome data (attrition bias)	High Risk	Of these, two patients (2/66 3.03%) from placebo and seven (7/66 10.61%) from hyoscine group were excluded because it became necessary for them to have abdominal birth or instrumental vaginal deliveries. No further information given

		for the characteristics of excluded patients for the two groups.
Selective reporting (reporting bias)	Low Risk	All prespecified outcomes were reported on
Other bias	Low Risk	Unlikely that other bias is present No funding received from any pharmaceutical company

Gupta et al, 2008		
Methods	Study design: Randomized controlled trial. Allocation generation: Participants randomized by simple randomization - No further information reported Allocation concealment: Not described. Blinding: No blinding. Loss to follow-up: Intervention: 4% Control: 0%.	
Participants	Total number of participants randomized: 150. Inclusion criteria: 1. primi- and multigravidas 2. term pregnancy 3. Singleton pregnancy 4. Cephalic presentation. 5. High-risk pregnancies were included: Hypertensive disorders, gestational diabetes, portal hypertension, tuberculosis, idiopathic thrombocytopenia, intra-hepatic cholestasis, anemia, IUGR and oligohydramnios. Exclusion criteria: 1. preterm gestation 2. multiple pregnancy 3. CPD 4. non-vertex presentation	
Intervention	Interventions: 1. Drotaverine hydrochloride 40 mg (2 mL) im in active labor at 3 cm dilatation, repeated every 2 h; n = 50. 2. Hyoscine Butyl bromide 20 mg, (1 mL) iv in active labor at 3 cm dilatation, repeated every 20 min; n = 50. Control: No medication; n = 50.	
Outcomes	Primary outcomes: 1. Duration of active phase of labor (3 cm to full cervical dilatation). 2. Rate of cervical dilatation (cm/h). 3. Duration of second stage of labor. Secondary outcomes: 1. Duration of third stage. 2. Mode of delivery. 3. Complications.	
Notes	Location: India. Ethics: informed consent obtained, ethical approval not mentioned.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Simple randomization, method not explicitly described.
Allocation concealment (selection bias	Unclear Risk	No allocation concealment described
Blinding of participants and personnel (performance bias)	High Risk	No blinding
Blinding of outcome assessment (detection bias)	High Risk	No blinding
Incomplete outcome data (attrition bias)	Low Risk	All participants accounted for, no missing data.
Selective reporting (reporting bias)	Low Risk	All outcomes prespecified in the methods section reported on.
Other bias	Unclear Risk	Medications were given via different routes and no placebo was used, the control group did not

		receive any medication Cervical dilatation was not the same at starting point in all the groups - although it was shown not to be statistically significant (P value: 0.5). Drug company sponsorship: not mentioned.

Imaralu et al, 2017		
Methods	Study design: Randomized controlled trial Allocation generation: The permutated block randomization method using computer generated random number sequence Allocation concealment: The intervention drugs were both colorless and were each predrawn into 2ml syringes, dispensed in sealed brown paper envelope packets, which were prepared at the hospital pharmacy Blinding: Both the investigators and the subjects were blinded as to the subject's allocation to receive HBB or placebo Loss to follow-up: Intervention: Control:	
Participants	Total number of participants randomized: 166 Inclusion criteria: 1. 18-35 years old, 2. singleton pregnancies 3. vertex presentation 4. in active phase (cervical dilatation of 4 cm) 5. spontaneous labor 6. term pregnancies (37-41 weeks gestation) 7. without chronic or pregnancy-induced illnesses. Exclusion criteria: 1. Grand multiparity (defined as parturient who have carried 5 or more pregnancies beyond 28 weeks which is the age of viability in Nigeria) 2. previous uterine scar 3. caesarean section 4. presence of any contraindication to vaginal delivery 5. cervical cerclage 6. prelabor rupture of fetal membranes 7. maternal pyrexia 8. maternal allergy to pentazocine, hyoscine or their excipients. 9. Patients with history suggestive of, or diagnosed previously to have glaucoma, myasthenia gravis, obstructive uropathy, Down's syn-drome, asthma, cardiac, liver or renal disease, persistent gastroesophageal reflux disease, severe constipation, persistent diarrhea, ulcerative colitis, seizure disorder or psychiatric illness	
Intervention	Intervention: 1 ml (20 mg) of Hyoscine butyl- bromide; n=84 (randomized); n=80 (analyzed) Control: 1 ml of 0.9% normal saline; n=82 (randomized); n= (80 analyzed) Time of administration: when cervical dilatation reached 4 cm observed by vaginal examination.	
Outcomes	Primary outcome: The duration of active phase of labor Secondary outcomes: 1. Duration of the second stage of labor 2. Duration of the third stage of labor 3. Estimated blood loss 4. Postpartum hemorrhage 5. APGAR scores at 1 and 5 minutes 6. Maternal adverse effects 7. Fetal adverse effects	
Notes	Location: Nigeria Ethics: ethical approval obtained from the research and ethics committee of the OAUTHC Ile-Ife, informed consent obtained	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Permutated block randomization method using computer generated random number sequence
Allocation concealment (selection bias	Low Risk	The intervention drugs were both colorless and were each predrawn into 2ml syringes, dispensed in sealed brown paper envelope packets, which were prepared at the hospital pharmacy

Blinding of participants and personnel (performance bias)	Low Risk	Both the investigators and the subjects were blinded as to the subject's allocation to receive HBB or placebo.
Blinding of outcome assessment (detection bias)	Low Risk	Investigators were blinded as to the subject's allocation to receive HBB or placebo.
Incomplete outcome data (attrition bias)	Low Risk	A total of 160 parturient, had their data included in the analysis (Hyoscine butyl bromide n=80, Placebo n=80). Six parturient (3 had Caesarean section and 1 had vacuum extraction in the Hyoscine butyl bromide group; 1 had Caesarean section and 1 refused trial drug in the placebo group), were replaced and their data excluded from analysis, giving a total number of recruited participants n=166. Thus, the total dropout rate was 6/166 (3.61%), while the dropout rate due to caesarean section was 4/166 (2.41%). Groups were comparable with respect to baseline obstetric data.
Selective reporting (reporting bias)	Low Risk	All outcomes prespecified in the methods section reported on.
Other bias	Low Risk	Unlikely that other bias is present No funding received from any pharmaceutical company

Makvandi et al, 2011		
Methods	Study design: Randomized controlled trial. Allocation generation: Block randomization. Allocation concealment: Suppositories were prepared by a pharmaceutical technician who was not included in the trial. No details about packaging of suppositories. Blinding: patients and medical investigator were blinded. Loss to follow-up: Intervention: 7.6% had caesarean sections; Control: 9.23% had caesarean sections	
Participants	Total number of participants randomized: 130. Inclusion criteria: 1. primigravid women 2. between 18 and 34 years of age 3. normal, singleton pregnancy 4. 37-42 weeks gestational age 5. cephalic presentation 6. spontaneous onset of labor. Exclusion criteria: 1. body mass index>25 2. maternal tachycardia 3. antepartum hemorrhage 4. prolonged rupture of membranes 5. previous uterine scar 6. cephalopelvic disproportion 7. augmentation of labor with oxytocin 8. preeclampsia 9. heart disease 10. any other serious medical conditions.	
Intervention	Intervention: Hyoscine 20 mg suppository at beginning of active phase of labor (3-4 cm cervical dilatation); n = 65. Control: Placebo suppository consisting of a suppocire AM-15 (semi-synthetic fatty acid glyceride) at beginning of active phase of labor; n = 65. Timing of intervention: at beginning of active phase of labor (3-4 cm cervical dilatation) in the presence of moderate uterine contractions (those during which the underlying fetal parts were not palpable, but fingers could still be indented in the abdominal wall)	
Outcomes	Primary outcomes: 1. Duration of active phase of labor (not defined). 2. Rate of cervical dilatation. 3. Duration of second stage of labor. Secondary outcomes: 1. Neonatal Apgar scores at 1 and 5 minutes after birth. 2. Fetal heart rate. 3. Maternal pulse rate. 4. Maternal blood pressure.	
Notes	Location: Iran Ethics: study approved by Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. Written consent obtained at antenatal visits.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Block randomization (blocks of 4) unclear what method of sequence generation was used
Allocation concealment (selection bias	Unclear Risk	Random numbers were assigned to each package. They do not mention whether the packages were identical.
Blinding of participants and personnel (performance bias)	Low Risk	Patients were unaware of the contents of the package, unclear whether personnel were blinded.
Blinding of outcome assessment (detection bias)	Low Risk	Medical investigator was unaware of the contents of the packages
Incomplete outcome data (attrition bias)	Low Risk	All participants accounted for.

Selective reporting (reporting bias)	High Risk	The primary outcome (pain relief), as specified in the protocol, was not at all addressed in the study report.
Other bias	Low Risk	Unlikely that other biases are present. Drug company sponsorship: absent. No conflict of interest.

Kirim et al, 2014		
Methods	Study design: Randomized, double-blinded, controlled trial Allocation generation: Sealed envelope system with cards Allocation concealment: A yellow card and a red card were sealed in separate envelopes. The syringes containing the drug and placebo were prepared by the investigational pharmacy staff and labeled with a yellow or red sticker. The color of the card corresponded to the sticker color on the syringe. both liquids were colorless Blinding: The participants, nurses, and physicians were all blinded to the syringe designation. Loss to follow-up: Intervention: 6.19% Control: 11.91%.	
Participants	Total number of participants randomized: 420 Inclusion criteria: 1. Primigravid and multigravid women 2. singleton pregnancy 3. vertex presentation. 4. women at term (gestational age range: 37–41 weeks) 5. no chronic or pregnancy-induced diseases. Exclusion criteria: 1. premature membrane rupture 2. preeclampsia 3. eclampsia 4. placental abruption 5. placenta previa 6. abnormal placental attachment 7. twin pregnancy 8. non-cephalic presentation 9. previous uterine surgery 10. cephalopelvic disproportion	
Intervention	Intervention: 20 mg (1ml) HBB; n=197 (analyzed); n=210 (randomized) Control: 1 ml of normal saline; n= 185 (analyzed); n= 210 (randomized) Timing of administration: cervical dilatation of 4 cm and 50% cervical effacement in the presence of regular uterine contractions (2–3 contractions every 10 min).	
Outcomes	Primary outcome: The mean duration (min) of the first stage of labor Secondary outcomes: 1. prepartum–postpartum hemoglobin values 2. Vaginal lacerations 3. Postpartum hemorrhage 4. Chorioamnionitis 5. Postpartum endometritis. 6. APGAR scores	
Notes	Location: Turkey Ethics: ethical approval obtained by the Institutional Human Ethics Committee, informed consent obtained.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Sealed enveloped system with cards
Allocation concealment (selection bias	Low Risk	A yellow card and a red card were sealed in separate envelopes. The syringes containing the drug and placebo were prepared by the investigational pharmacy staff and labeled with a yellow or red sticker. The color of the card corresponded to the sticker color on the syringe. both liquids were colorless
Blinding of participants and personnel (performance bias)	Low Risk	The participants, nurses, and physicians were all blinded to the syringe designation
Blinding of outcome assessment (detection bias)	Unclear Risk	The participants, nurses, and physicians were all blinded to the syringe designation. No reporting about the investigtors status

Incomplete outcome data (attrition bias)	Low Risk	12 patients had cesarean delivery and 1 patient had vacumm-assited vaginal delivery in intervention group (13/210 6.19%) and 23 patients had cesarean delivery and 2 patients had vacumm-assited vaginal delivery (25/210 11.91%) in control group. A flow chart showing the analysis process according to the protocol described in Methods section was reported adequately.
Selective reporting (reporting bias)	Low Risk	All outcomes prespecified in the methods section reported on.
Other bias	Low Risk	Unlikely that other bias is present No funding received from any pharmaceutical company

Mukaindo et al, 2010		
Methods	Study design: Randomized controlled trial. Allocation generation: Computer-generated random sequence of numbers. Allocation concealment: Randomization sequence was sequentially coded. The pharmacist, who was the only one with access to the code, prepared the syringes, which were only labelled with the randomization number, accordingly and handed them over to the labor ward staff. Blinding: participants, labor ward staff and investigator were blinded. Loss to follow-up: intervention: 8% were excluded from the analysis. Control: 7% were excluded from the analysis	
Participants	Total number of participants randomized: 85. Inclusion criteria: 1. nulliparas 2. above 18 years of age 3. at term 4. singleton pregnancy 5. cephalic presentation 6. spontaneous labor 7. without contraindications to hyoscine butyl bromide. Exclusion criteria: 1. multiparas, 2. induced labor 3. preterm labor 4. contraindications to vaginal delivery 5. contraindications to hyoscine butyl bromide 6. high-risk pregnancies.	
Intervention	Intervention: Hyoscine butyl bromide 40 mg (2 mL) iv; n = 40. Placebo: Sterile water, 2 mL iv; n = 45. Timing of intervention: between 3 and 6 cm cervical dilatation	
Outcomes	Primary outcome: Duration of labor (from diagnosis of active phase of labor to delivery). Secondary outcomes: 1. Rate of cervical dilatation (cm/h). 2. Maternal postpartum satisfaction scores.	
Notes	Location: Kenia. Ethics: all participants required to sign informed consent. Study was approved by the ethics committee of the Aga Khan University Hospital. Full text did not reach, and data were extracted from the Cochrane Review: Antispasmodics in labor, 2013	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Computer-generated random sequence of numbers.
Allocation concealment (selection bias	Low Risk	Randomization sequence was sequentially coded. The pharmacist, who was the only one with access to the code, prepared the syringes, which were only labelled with the randomization number, accordingly and handed them over to the labor ward staff.
Blinding of participants and personnel (performance bias)	Low Risk	Participants and labor ward staff were blinded.
Blinding of outcome assessment (detection bias)	Low Risk	Investigator was blinded until conclusion of the study.
Incomplete outcome data (attrition bias)	Low Risk	All participants accounted.
Selective reporting (reporting bias)	Low Risk	All outcomes prespecified in the methods section reported on.

Other bias	Low Risk	Unlikely that other bias is present No funding received from any pharmaceutical company

Samuels et al, 2007		
Methods	Study design: Randomized controlled trial. Allocation generation: Computer-generated random sequence of numbers. Allocation concealment: Sequentially numbered syringes only PI knew correlation, which was only shown after analysis Blinding: Participants, midwives and obstetricians were blinded. Loss to follow-up: Intervention: 0% Control: 0%	
Participants	Total number of participants randomized: 129. Inclusion criteria: 1. primi- and multigravidas 2. > 18 years old 3. at term 4. in established, spontaneous labor 5. no pregnancy induced or chronic illness. Exclusion criteria: complicated pregnancies (not further specified).	
Intervention	Intervention: Hyoscine butyl bromide 20 mg (1 mL) iv; n = 60. Control: Placebo: NaCl 1 mL iv; n = 69. Timing of intervention: between 4-5 cm dilatation	
Outcomes	Primary outcome: Duration of first stage of labor (time from intervention to full dilatation). Secondary outcomes: 1. Duration of second and third stages of labor. 2. Blood loss. 3. Rate of caesarean section. 4. Apgar scores.	
Notes	Location: Jamaica. Other: standard deviations not reported. Ethics: ethical approval obtained, informed consent obtained.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Computer-generated random sequence of numbers
Allocation concealment (selection bias	Low Risk	Sequentially numbered syringes. Content of syringes was only known to PI during the study and was revealed after completion of the study.
Blinding of participants and personnel (performance bias)	Low Risk	Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low Risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low Risk	All participants accounted.
Selective reporting (reporting bias)	Low Risk	Primary outcome: duration of first stage of labor: adequately reported. Secondary outcomes: duration of 2nd and 3rd stages of labor, blood loss at delivery, rate of caesarean section, Apgar scores: all adequately reported 95% confidence intervals present. No standard deviations reported with the means
Other bias	Low Risk	No other sources of potential bias detected. Drug company sponsorship: no.

Sekhavat et al, 2012		
Methods	Study design: Randomized controlled trial. Allocation generation: Computer-generated random number list. Allocation concealment: Not described. Blinding: Participants and caregivers/physicians not blind. Outcome assessors blind. Loss to follow-up: Intervention: 0% Control: 0%.	
Participants	Total number of participants randomized: 188. Inclusion criteria: 1. Multigravidas 2. normal, singleton pregnancy 3. gestational age 37-42 weeks 4. vertex presentation 5. normal labor (spontaneous, presence of regular uterine contractions) 6. active phase of labor (3-4 cm cervical dilatation) 7. intact membranes. Exclusion criteria: 1. Chronic or pregnancy-induced illnesses 2. contraindication to vaginal delivery 3. antepartum hemorrhage 4. multiple pregnancy 5. previous caesarean section 6. parity > 4.	
Intervention	Intervention: Hyoscine butyl bromide 20 mg (1 mL) iv; n = 94. Control: Placebo: NaCl 1 mL iv; n = 94. Timing of administration: after admission to labor ward (at 3-4 cm cervical dilatation)	
Outcomes	Primary outcomes: 1. Duration of first stage of labor. 2. Duration of second stage of labor. 3. Duration of third stage of labor. 4. Cervical dilatation rate. Secondary outcomes: 1. Delivery route. 2. Clinical side effects. 3. Neonatal Apgar score at one and five minutes.	
Notes	Location: Iran. Other: Authors did not address conflict of interest. Ethics: Ethical approval obtained by the ethics committee of Shadid Sadoughi University of Medical Sciences, Yazd, Iran, informed consent obtained from participants.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Computer-generated random number list.
Allocation concealment (selection bias	Unclear Risk	Not described.
Blinding of participants and personnel (performance bias)	High Risk	Both participants and physicians were unblinded.
Blinding of outcome assessment (detection bias)	Low Risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low Risk	All participants accounted.
Selective reporting (reporting bias)	High Risk	Authors did not report on maternal adverse effects (prespecified in methods section)
Other bias	Unclear Risk	Not clear what outcome authors used to calculate sample size. Study only included multiparous women.

Sheth et al, 2018		
Methods	Study design: Randomized controlled trial Allocation generation: Simple random method. Allocation concealment: Not reported Blinding: No blinding Loss to follow-up: Intervention: Control:	
Participants	Total number of participants randomized: Inclusion criteria: 1. Primipara. 2. Spontaneous labor at term, 38 to 42 weeks (266 to 294 days). 3. Singleton pregnancy. 4. Vertex presentation, station |-2| or below at onset of active stage of labor. 5. Cervical effacement ≥ 50% at onset of active stage of labor. 6. Normal admission CTG. 7. Post amniotomy – clear liquor and normal CTG. Exclusion criteria: 1. Age of mother less than 20 years or more than 30 years. 2. Previous abortion, spontaneous or induced. 3. Previous preterm delivery. 4. Birth weight of first child less than 2.5 kg. 5. Presentations other than vertex. 6. Non-engaged head. 7. CPD. 8. Women with high risk factors, in previous or present pregnancy like preeclampsia, antepartum hemorrhage, Gestational diabetes, Anemia, Heart disease, any medical or surgical disorder. 9. History of procedure involving dilatation of cervix other than previous normal delivery. 10. History of cervical/perineal tear in previous delivery. 11. Previous uterine scar. 12. Contraindications to vaginal delivery. 13. Meconium. 14. Any contraindication for Buscopan usage.	
Intervention	Intervention: Buscopan suppository 10 mg; n=25 Control: No drug; n=25 Time of administration: Suppository was given per rectally at 3 cm cervical dilatation, post amniotomy	
Outcomes	Primary outcome: Active phase of 1st stage and 2nd stage of labor Secondary outcomes: 1. Maternal adverse effects 2. Fetal adverse effects 3. APGAR scores at 1st and 5th minute	
Notes	Location: Ethics: ethical approval obtained, informed consent obtained. Other:	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Simple randomization - No further information reported
Allocation concealment (selection bias	Unclear Risk	Not reported
Blinding of participants and personnel (performance bias)	High Risk	No blinding
Blinding of outcome assessment (detection bias)	High Risk	No blinding
Incomplete outcome data (attrition bias)	Unclear Risk	All participants accounted for, no missing data. It is suspicious that APGAR>8 reported for all neonates and no CS needed
Selective reporting (reporting bias)	Low Risk	All prespecified outcomes were reported on

Other bias	Unclear Risk	The control group received no drug; Drug company sponsorship: No

Shirazi et al, 2016		
Methods	Study design: Randomized clinical trial Allocation generation: Patients randomly divided into 2 groups - No further information reported Allocation concealment: Not reported Blinding: Double-blind controlled clinical trial Loss to follow-up: Intervention:0% Control:0%	
Participants	Total number of participants randomized: 60 Inclusion criteria: 1. term pregnancies 2. 37 - 42 weeks gestation3. age>18 years old 3. 3 spontaneous contractions (40 seconds) in 10minutes 4. amniotic sac rupture in the last 6 hours with spontaneously contractions Exclusion criteria: 1. abnormal fetal heart rate 2. vaginal bleeding 3. placenta previa 4. placental abruption 5. multigestational pregnancy 6. advanced medical conditions such as a mother's heart disease 7. non-cephalic presentation 8. fetal macrosomia 9. history of infertility or fetal abnormalities or death 10. grand multiparity (gravida greater than or equal to 5) 11. rupturing of the amniotic sac 11. intrauterine growth restriction 12. fetal weight higher than 4000 grams 13. history of uterine surgery 14. history of maternal medical disease (especially heart disease) 15. maternal tachycardia 16. history of preeclampsia 17. prescription of narcotic drugs and analgesics 18. oxytocin infusion in the first and second stages of labor 19. contraindications to prescribe HBB such as glaucoma and paralytic ileus	
Intervention	Intervention: 40 mg or 2 mL of HBB, in the absence of dilatation another dose of HBB administrated; n=30 Control: 2 ml serum; n=30 Timing of intervention: active phase of labor with at least 3 spontaneous contractions (40 seconds) in 10 minutes	
Outcomes	1. Duration of taking the drug till the full dilatation 2. Duration of labor 3. Duration of the first stage of labor 4. Duration of the second stage of labor 5. Maternal and fetal heart rate evaluation before and after the administration of the drug 6. Maternal adverse effects	
Notes	Location: Iran Ethics: ethical approval not reported, informed consent obtained.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Patients randomly divided into 2 groups - No further information reported
Allocation concealment (selection bias	Unclear Risk	Not reported
Blinding of participants and personnel (performance bias)	High Risk	Double blind trial - No further information reported. In the absence of dilatation another dose of HBB administrated 4-6 hours later. Authors do not report the same about the control group which raises concerns about the blinding of the process

Blinding of outcome assessment (detection bias)	Unclear Risk	Not reported
Incomplete outcome data (attrition bias)	Low Risk	All participants accounted for, no missing data.
Selective reporting (reporting bias)	High Risk	APGAR score although evaluated is not reported. Mode of delivery is not reported even though the all patients' data imported for analysis
Other bias	High Risk	Exclusion criteria: rupturing of the amniotic sac Inclusion criteria: amniotic sac rupture in the last 6 hours with spontaneously contractions participated in this study It seems that the study has design limitations

Shobha et al, 2006		
Methods	Study design: Randomized controlled trial Allocation generation: Simple randomization (no details present). Allocation concealment: Not described. Blinding: No blinding Loss to follow-up: Intervention: 0% Control: 0%	
Participants	Total number of participants randomised:300 Inclusion criteria: 1. Primigravidae 2. full term gestation 3. vertex presentation with – a) Cervical dilatation of 3 – 5 cm b) Cervical effacement of ≥ 50% c) Membranes intact / ruptured d) Spontaneous and induced labor Exclusion criteria: 1. Preterm labor. 2. Abnormal presentation 3. Antepartum hemorrhage 4. Cephalopelvic disproportion 5. Multifoetal gestation	
Intervention	Interventions 1.Drotaverine 8mg iv, interval of 2 hours up to a maximum of 3 injections; n=100 2. Hyoscine butylbromide 10mg suppository pr, interval of 1-hour up to a maximum of 3 doses; n=100 Control: No medication; n=100	
Outcomes	1. Duration of first stage of labor. 2. Duration of active phase of labor 3. Rate of cervical dilatation 4. Mode of delivery 5. First dose to delivery interval. 6. Neonatal condition at birth. 7. Maternal adverse effects	
Notes	Location: India Ethics: ethical approval not reported, informed consent obtained.	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Participants were "chosen by simple randomization" - No further information given
Allocation concealment (selection bias	Unclear Risk	Not described
Blinding of participants and personnel (performance bias)	High Risk	No blinding
Blinding of outcome assessment (detection bias)	High Risk	No blinding
Incomplete outcome data (attrition bias)	Low Risk	1% from each group had CS and included in analysis
Selective reporting (reporting bias)	Low Risk	All prespecified outcomes were reported on
Other bias	High Risk	The study does not report about the status of fetal membranes which is a factor that can influence the progression of labor Drug company sponsorship: no.

Singh et al, 2015		
Methods	Study design: Randomized controlled trial Allocation generation: Not described Allocation concealment: Not described Blinding: Patients and research personnel were blinded Loss to follow-up: Intervention: Control:	
Participants	Total number of participants randomized: 220 Inclusion criteria: Not reported Exclusion criteria: Not reported	
Intervention	Intervention: 40mg (2ml) Hyoscine butyl bromide im; n= 110 Control: 2 ml placebo im; n=110	
Outcomes	Primary outcomes: 1. the injection delivery interval 2. percentage of change in pain. Secondary outcomes: 1. blood loss at delivery 2. mode of delivery 3. APGAR scores for the neonates	
Notes	Article published only as an abstract Ethics: ethical approval obtained, informed consent not mentioned	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Method not explicitly described
Allocation concealment (selection bias	Unclear Risk	No allocation concealment described.
Blinding of participants and personnel (performance bias)	Low Risk	Patients and research personnel were blinded
Blinding of outcome assessment (detection bias)	Unclear Risk	Not described
Incomplete outcome data (attrition bias)	Unclear Risk	"The neonatal outcome and mode of delivery was comparable in two groups. No adverse maternal effects were observed" with no more information reported
Selective reporting (reporting bias)	Unclear Risk	Article published as an abstract
Other bias	Unclear Risk	Article published as an abstract

Trevino-Salinas et al, 2015		
Methods	Study design: Randomized controlled study Allocation generation: " Patients were chosen randomly and distributed into one of the two groups" - No more information reported Allocation concealment: Not described Blinding: Not reported Loss to follow-up: Intervention: 2/45 (4.44%) Control: 2/45 (4.44%)	
Participants	Total number of participants randomized: 90 Inclusion criteria: 1. patients older than 18 years 2. term pregnancy (37-42 weeks) 3. independent from the parity 4. cephalic presentation 5. clinically adequate pelvis for labor 6. no evidence of macrosomia (estimated fetal weight over 4000 g) 7. active phase of the first stage of labor (dilatation of 4 cm or more) with regular uterine activity (3-4 contractions in 10 min). Exclusion criteria: All patients who needed to complete childbirth abdominally due to different causes.	
Intervention	Intervention: 20 mg of BBH (diluted in 9 ml of saline solution) iv on two occasions with an interval of 1 h; n=43 (analyzed); n=45 (randomized) Control: 10 ml of saline solution iv at a similar dosage and interval; n=43 (analyzed); n=45 (randomized) Timing of intervention: active phase of labor (dilatation of 4 cm or more) with regular uterine activity (3-4 contractions in 10 min)	
Outcomes	1. Duration of the first stage of labor 2. Duration of the second stage of labor 3. Duration of the third stage of labor 4. Fetal neonatal status (weight, size, APGAR at 1st and 5th minutes)	
Notes	Location: Mexico Ethics: informed consent obtained, ethical approval not reported	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	" Patients were chosen randomly and distributed into one of the two groups" - No more information reported
Allocation concealment (selection bias	Unclear Risk	" Patients were chosen randomly and distributed into one of the two groups" - No more information reported
Blinding of participants and personnel (performance bias)	High Risk	No blinding reported
Blinding of outcome assessment (detection bias)	High Risk	No blinding reported
Incomplete outcome data (attrition bias)	Low Risk	2 patients from each group discarded because of the need to deliver abdominally. All remaining participants accounted for
Selective reporting (reporting bias)	High Risk	No maternal adverse effects reported.
Other bias	Unclear Risk	No other sources of potential bias detected. Drug company sponsorship: no.