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Review Article

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Efficacy of hyoscine butylbromide and promethazine on the labor's active phase duration: a systematic review and meta-analysis of randomized controlled trials

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Abstract

***Background & Aims*:** There are different types of drugs to shorten prolonged labor. Spasmolytic drugs are used frequently in the delivery section to overcome cervical spasms and reduce the duration of labor. The study's objective was to evaluate the therapeutic efficacy of hyoscine N-butyl bromide (HBB) and Promethazine on the duration of the active phase of labor.

***Materials & Methods*:** We searched the Science Direct, PubMed Scopus, Google Scholar, MEDLINE, Web of Science, Cochrane Library, PsycINFO, and ProQuest databases, and reviewed the literature and reference lists of retrieved articles. We included reports of quantitative studies published in all Persian and English articles from 2000 to 2021 that focused on Promethazine or Hyoscine during. Two authors independently screened titles and abstracts and assessed articles in full text against the inclusion criteria. These criteria included vertex presentation, no previous uterine surgery, intact membranes, and spontaneous labor, with mothers having no contraindications for normal vaginal delivery.

***Results*:** Out of a total of 170 records initially screened, we included 44 articles in our review, and other studies were excluded. The results showed that 10, 20, 40 mg of HBB decreased the first stage of labor duration by 147.02 min, 58.95 min, and 71.60 min, respectively. Additionally, HBB decreased the first stage of labor duration by 100.61 min in multiparous women and 66.04 min in primipara women. To evaluate the Promethazine effect on labor duration, the results showed that the combined MD was not significant ($p=0.67$, 0.85, and 0.44 in the first, second, and third stages, respectively).

***Conclusion*:** HBB is more effective in multiparous women compared to primiparous women. On the other hand, Promethazine has no effect on reducing total labor duration and any stages of labor, so its use is not recommended.

***Keywords*:** Hyoscine N-Butyl Bromide, Labor Duration, Pregnancy, Promethazine

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Introduction

Labor is one of the most important events in women's lives; therefore, negative labor experiences can be emotionally and psychologically challenging for mothers and their families (1-3). According to the results of a study, 210 million women get pregnant every year, and of those, 20 million will suffer from pregnancy-related illnesses, and 500,000 will die of complications during pregnancy and childbirth (4). The duration of the active phase of labor is a significant factor associated with maternal and fetal complications (5), so prolonged labor is a common risk factor that influences pregnancy outcomes (6, 7). Additionally, more prolonged labor has many adverse effects on both infants like low Apgar scores, neonatal trauma, sepsis, umbilical artery acidosis, birth asphyxia-related complications, and neonatal intensive care units, and mothers, including chorioamnionitis, early and late postpartum hemorrhage, perineal trauma, episiotomy usage, operative delivery, uterine rupture (8-11). Approximately 3-8% of labors are prolonged, three times higher in nulliparous women than multiparous women (12).

There are different types of drugs to shorten prolonged labor (13, 14). Spasmolytic drugs are frequently used in the delivery section to overcome cervical spasms and reduce the duration of labor (15, 16). Hyoscine butyl bromide (HBB) is a parasympatholytic drug, a muscarinic antagonist acting as an anticholinergic drug. The primary mechanism of action of HBB is to block neural impulses in the intramural parasympathetic ganglia of abdominal organs, exerting a spasmolytic action on the smooth muscle of the gastrointestinal, biliary, urinary, and female genital organs, especially the cervix and lower uterine segment that may cause cervical dilatation and effacement (17-19). After intravenous injection, it is rapidly released into the tissue, and final removal takes about 5 hours; its full clearance is 1.2 liters per minute (20).

Promethazine is a Histamine H1 receptor antagonist (HA1RA) derived from phenothiazine, exhibiting sedation, anesthesia, neuroprotection, and antiemetic effects associated with its antimuscarinic properties (21, 22). Promethazine also has anticholinergic effects and central nervous system depression. Therefore, it is prescribed to increase a woman's ability to endure labor pain. Due to its effect on the smooth muscles of the uterus and its ability to reduce anxiety and fear during pregnancy, its use seems to affect the duration of labor (23). On the other hand, some researchers believed that the injection of Hyoscine and Promethazine might prolong the first stage of labor due to the antispasmodic effects of these drugs (3, 19, 20, 24-26). But some studies showed that Hyoscine and Promethazine reduce the duration of the first stage of labor (3, 20, 27).

Several studies have been conducted to evaluate the use of Hyoscine and Promethazine in shortening the phases of labor, with different settings and results. However, no quantitative analysis has been conducted to validate these findings. Thus, the purpose of the present study was to conduct a systematic review of randomized controlled trials assessing Hyoscine-Promethazine's effectiveness in reducing labor phases, ultimately reducing healthcare costs and drug waste.

Materials & Methods

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this systematic review was conducted in 2021. This present study is a systematic review and meta-analysis of the current research literature on the effectiveness of Hyoscine and Promethazine on the duration of labor. The protocol of this study was accepted in PROSPERO [PROSPERO 2021 CRD42021272783], Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021272783.

Search Strategies:

We conducted an in-depth search in electronic databases included, Science Direct, PubMed Scopus, Google Scholar, MEDLINE, Web of Science, Cochrane Library, PsycINFO, and ProQuest. We also checked Iranian databases consisting of the Scientific Information Database (SID), Magiran, and IranDoc. We

searched for terms and keywords including the following: ["Hyoscine" OR "Hyoscine N-Buthyl Bromide," OR "Buscopan"] AND ["Promethazine"] OR " ["labor" OR "duration of labor, "OR "active phase, "OR "shortening of the active phase," OR "reduction of active phase"] AND ["randomized controlled trials" OR "randomized placebo-controlled trials" OR "randomized double-blind controlled trials OR "interventional studies" OR "pilot randomized trials"]. This Study included all Persian and English articles from 2000 to 2021, regardless of their geographical location, journal of published article authors' name, and other bibliographic information of the journals. Notably, the latest search process was performed between July and September 2021 separately by two researchers and then checked by both of them.

Eligibility Criteria and Data Collection:

Following the inclusion and exclusion criteria in relevant studies, we screened the title and abstract of relevant studies separately and obtained the full text. Women who received Promethazine or Hyoscine during labor had singleton pregnancies, vertex presentation, without previous uterine surgery, intact membranes, and spontaneous labor, and mothers with no contraindication for normal vaginal delivery were included in the Study. Exclusion criteria included: Placenta abruption or rupture, placenta previa, women with a history of caesarian delivery, and also studies published in other languages except English and Persian were also excluded from this systematic review.

Type of outcome measure:

The primary outcome measured in this study was a systematic assessment of the interventions regarding the effectiveness of Hyoscine-Promethazine on labor phase duration.

Data Extraction and analysis:

A descriptive table was prepared after carefully reading each article and extracting the information required by FH and MJ, which MA cross-checked. During group discussions, the third author resolved disagreements between the authors. The extracted data included authors' names, publication year, country, age of participants, number of participants in each group, gestational age, duration of labor, intervention, control drug dosage, and gravity of participants.

The means and SDs of outcomes after the intervention were used for the meta-analysis. The summary measures were reported as summary mean difference (MD) with a 95 % confidence interval (CI) using the random-effects model of Der Simonian and Laird. All P-values were considered significant at the level of < 0.05. Results were summarized in a forest plot. Cochran's Q test and I^2 were used to assess between-study heterogeneity. We considered between-study heterogeneity as I^2 values of 50% or more. Also, we used a funnel plot to check studies' publication bias (due to the large volume of the article, figures were not reported). In addition, we applied subgroup analysis based on random-effects models to find probable sources of heterogeneity for some variables, including drug dosage and the gravidity of participants in the first stage of labor duration. The data analysis was carried out using Review Manager 5.4.1 Build Date: 21/09/20 19:16 (The Nordic Cochrane Centre 2014, Copenhagen, Denmark).

Assessing the Quality of Selected Articles:

Methodological quality of the clinical trials was assessed using the Jadad score calculation. Jadad's scale consists of two sets of questions: three direct questions and eight indirect questions (28). Three direct questions were asked regarding the Study: whether it appeared to be randomized, whether it was double blinded and whether there were any descriptions of withdrawals or dropouts. As a response to the first direct question, one point was given if the randomization method was described, as well as an additional point if the randomization process was described. Studies in which the randomization method was inappropriate did not receive an additional point. For the second direct question, one point was awarded if blinding was mentioned in the study, and an additional point was awarded if the appropriate method of blinding was

described. If the withdrawals or dropouts are described, a point is awarded for the third direct question. According to the first set of questions, the average score ranged from 0 to 5, with higher scores indicating high quality research. Scores ≥3 were considered to be acceptable and appropriate quality studies, while studies scoring <3 were considered to be of weak in quality. There are eight indirect questions in the second section of the Jaded scale regarding the study objectives, obvious outcomes, an explanation of the inclusion and exclusion criteria, an explanation of sample size, a description of the interventions, a description of at least one control group, an explanation of how adverse effects were assessed, and a description of the statistical analysis techniques. The articles selected for this review study were evaluated only in accordance with the three direct questions outlined above (29-31).

Results

After searching, 170 studies were selected for initial screening. After reading the title and abstract of searched studies, 105 studies were excluded because they did not meet inclusion criteria or were irrelevant to the study objectives. Among the remaining studies, we excluded nonrandomized studies (n=10), compared HBB or Promethazine with another drug without a control group (n=3), compared different concentrations of drugs without a control group (n=2), took the medication orally for some time before labor (n=1), and use the combination of HBB or Promethazine with another drug (n=5). Finally, we selected 44 studies that met all the criteria for analyzing their data (Figure 1).

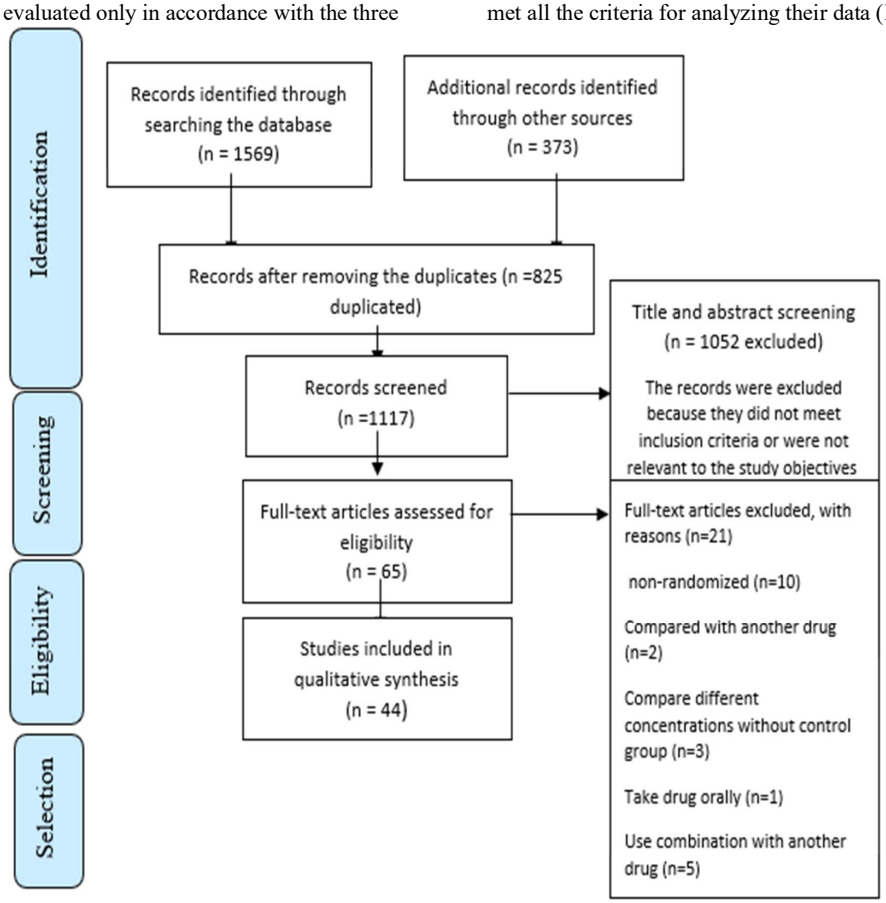

Fig. 1. PRISMA flow diagram

The total samples in intervention and control groups were 3083 and 3084, respectively. The mean age in intervention and control groups were 25.50 ± 4.30 and 25.67 ± 4.12, respectively. All studies had equal or almost equal sample sizes in two groups, and the mean age of participants in both groups was the same. Thirty-nine studies only used HBB in intervention groups (16, 19, 20, 27, 32-66), two studies only used Promethazine (26, 67), and three studies used both to compare their effectiveness (3, 68, 69).

A Summary of the Included Studies is Presented in the Supplementary:

The studies' publication dates ranged from 2001(26) to 2021 (57). Studies were conducted in several countries, fifteen studies in Iran (3, 26, 32, 45, 48, 51, 58-60, 62, 64, 65, 67-69), eight studies in India (20, 33, 34, 36, 44, 46, 54, 61), six studies in Nigeria (27, 43, 47, 49, 55, 57), six studies in Egypt (16, 38, 39, 50, 52, 63), two studies in Iraq (35, 37), one study in Bahrain(66), one study in Kenya (41), one study in Mexico (42), one study in Saudi Arabia (19), one study in Spain (53), one study in Tanzania (56), and one study in Turkey (40). In total, 6167 women participated in these studies (3083 women intervention groups, 3086 women control groups). Three studies that have used both HBB and Promethazine intervention groups use one control group, so we use this control group for both interventions (3, 68, 69). In one study, 8 mg of dexamethasone was administrated six hours before induction, then 40 mg HBB was injected at the active phase for the intervention group (50). Participants in intervention groups get HBB in 10, 20, or 40 mg doses by injection (IM or IV) or suppository. Promethazine intervention groups get 1, 25, or 50 mg doses by injection. Control group's participants get a placebo or have no intervention.

HBB:

In total, 42 RCT studies' data were included in this meta-analysis to determine HBB efficacy in reducing labor duration (3, 16, 19, 20, 27, 32-66, 68, 69). The sample size of the included trials varied from 40 to 382 in both the intervention and the control groups. In total, 5907 women with a gestational age of 37–42 weeks enrolled in the studies, 2953 women in the intervention, and 2954 women in the control or placebo group. The timeframe of publication was between 2004 and 2021.

Stages of Labor:

All studies that represent labor duration as the primary outcome were included in the meta-analysis. All 42 studies represented the first stage of labor duration (3, 16, 19, 20, 27, 32-66, 68, 69), 31 reported first and second stage duration (16, 19, 20, 27, 34, 35, 37-39, 41-45, 48-50, 52, 53, 55-62, 64, 65, 68, 69), and 21 represented first, second, and third stage duration (16, 20, 27, 35, 37-39, 41, 44, 48, 50, 55-57, 59-61, 64, 65, 68, 69). We analyze these subgroups to determine the HBB administration effect on each stage separately.

HBB in the First Stage: Dilation and Fetal Descent:

A total of 42 studies report the first stage duration average for the intervention, and control groups were included in the analysis (3, 16, 19, 32-66, 68, 69). These studies observed MD ranging from -171.60 min to 78.47 min, with most estimates being negative (87.8 %). The accurate outcomes appear to be heterogeneous (I^2 = 95%, $p < 0.0001$) so to find sources of heterogeneity, we performed group analysis based on HBB dosage and the parity of participants and used the random effect model. Based on the random-effects model, the estimated combined MD was -66.75 (95% CI: -80.22 to -53.28) ($Z = 9.71$ $P < 0.001$) HBB in any given dose (10, 20, or 40 mg) decreased the first stage duration by 66.75 min. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Figure 2. The forest plot indicated the combined MD (Figure 2).

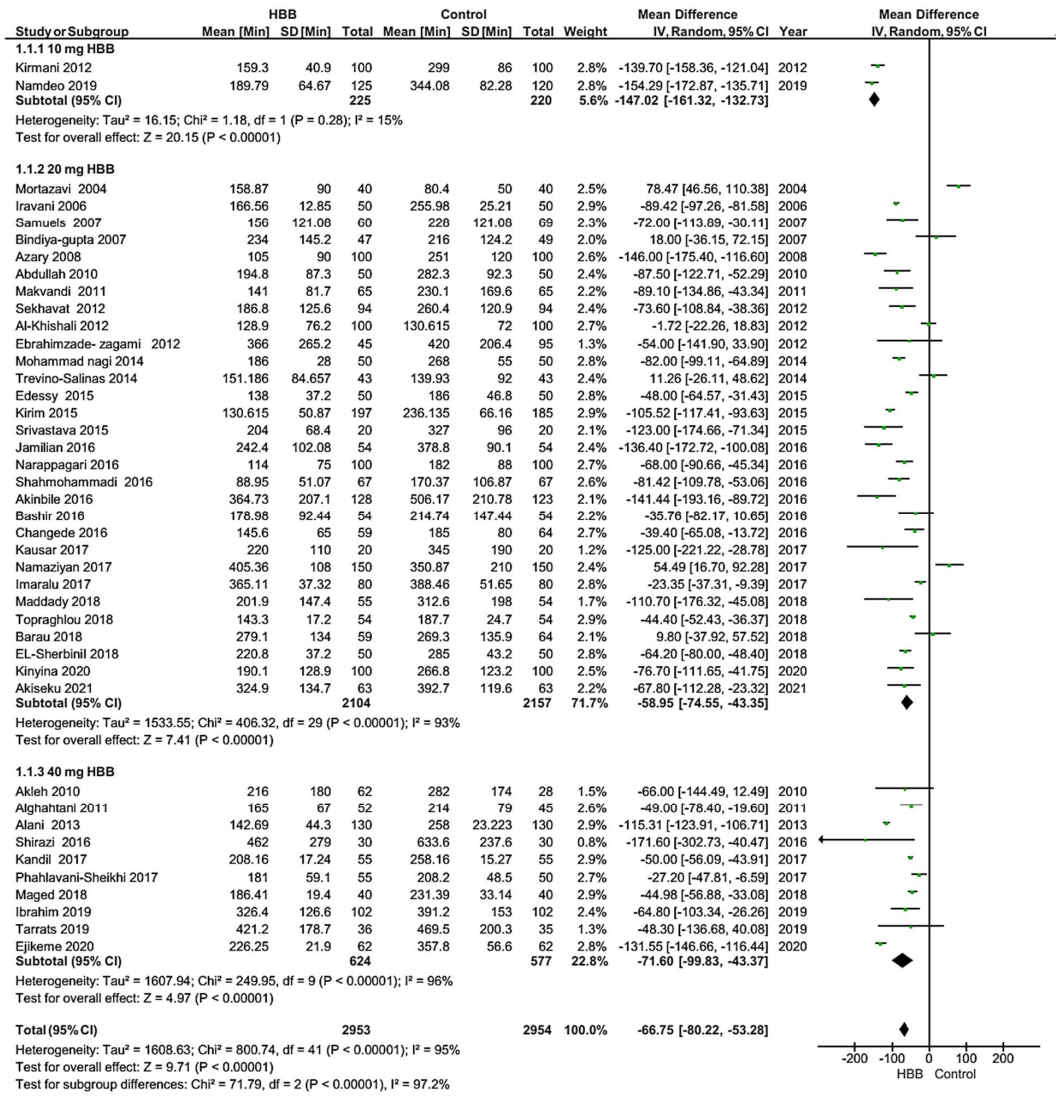

Fig. 2. Forest plot showing the observed outcomes and the estimate of the random-effects model for the duration of the first stage of labor in 10, 20, and 40 mg HBB RCTs

To explore potential sources of heterogeneity, a sensitivity analysis was conducted by removing studies. By eliminating 20 studies(16, 20, 35-37, 39, 40, 42, 43, 45, 47-49, 52, 54, 55, 58-60, 68) (including the entire 10 mg subgroup), A significant statistical difference was still found regarding the effect of HBB on the first stage of labor despite a reduction in heterogeneity to 42% ($p = 0.02$) (Z=15.78, $p = 0.001$). We couldn't find any common feature between the eliminated studies. A funnel plot of the estimated Study's bias is shown in Figure 3.

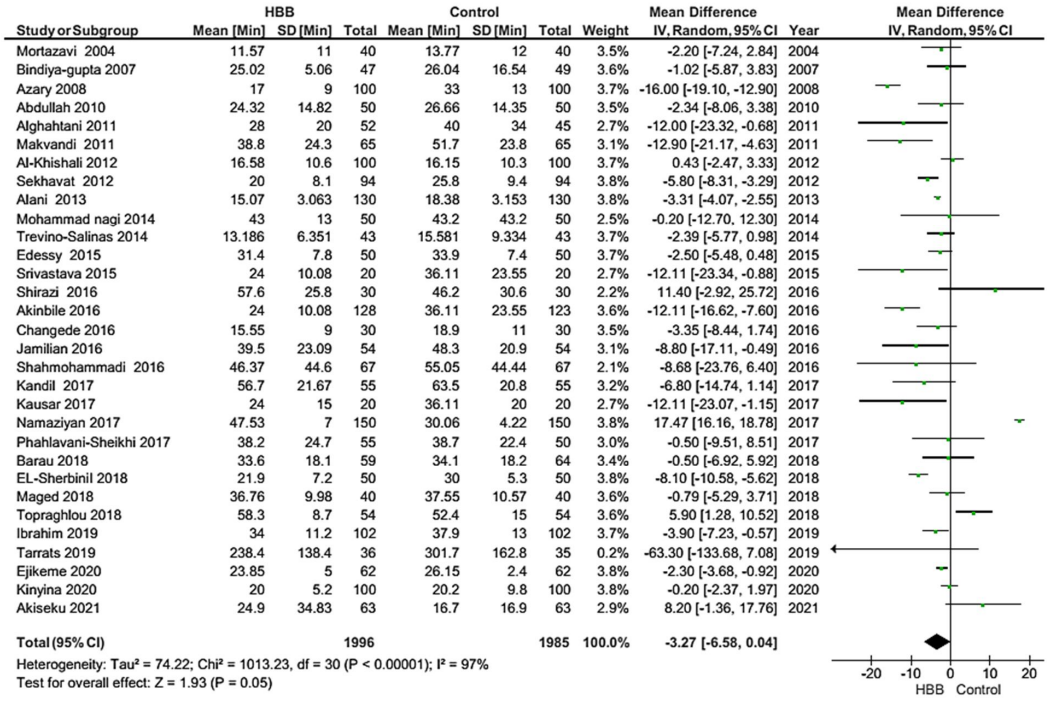

Fig. 3. Forest plot showing the observed outcomes and the estimate of the random-effects model for the duration of the second stage of labor in HBB RCTs

HBB in the Second Stage: Delivery of the Infant:

Among the selected studies, 31 of them represent both first and second stages duration data (16, 19, 20, 27, 34, 35, 37-39, 41-45, 48-50, 52, 53, 55-62, 64, 65, 68, 69). Those studies were included in the analysis to determine the HBB effect on the second stage of labor. The observed MD of these studies ranged from -63.30 min to 17 min, with most estimates being negative (87%). The true outcomes appear heterogeneous (I^2 = 97%, $p < 0.001$). Based on the random-effects model, the estimated MD was -3.27 min (95% CI -6.58 to 0.04), (Z= 1.93, $p = 0.05$) and HBB in any given concentration (10, 20, or 40 mg) did not affect the second stage of labor duration. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Figure 3.

HBB in the Third Stage: Delivery of the Placenta:

We include 21 studies that report all three stages of labor duration in the analysis for this section (16, 20, 27, 35, 37-39, 41, 44, 48, 50, 55-57, 59-61, 64, 65, 68, 69). We use the third-stage duration data to observe the HBB effect on this stage of labor. The observed MD of analyzed studies ranged from -3.60 min to 2.40 min, with most estimates being negative (62%). Based on the random-effects model, the estimated combined MD was -0.60 min (95% CI: -1.13 to -0.08) and (Z = 2.27, $p = 0.02$). So HBB in any given dose (10, 20, or 40 mg) did not affect the third stage of labor duration. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Figure 4. The true outcomes appear to be heterogeneous (I^2 = 86%); Chi^2 = 141.74, df = 20 ($p < 0.001$).

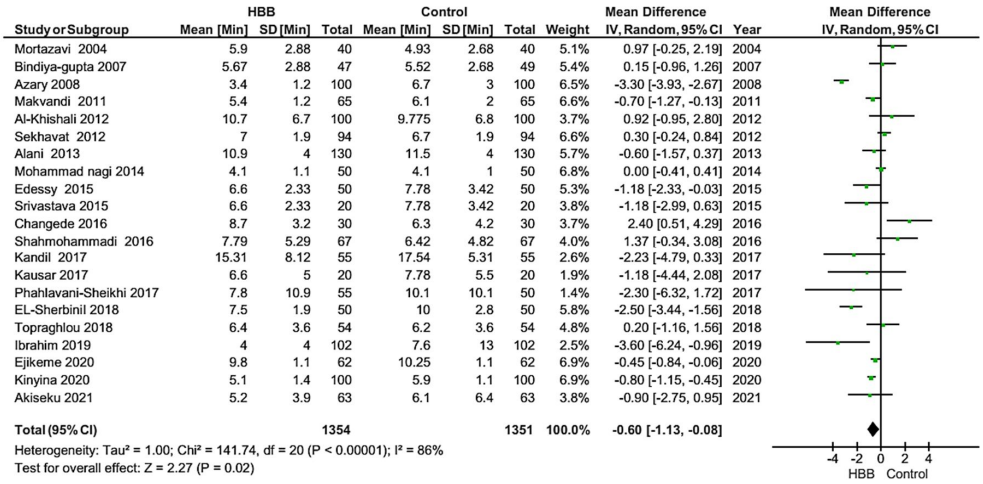

Fig. 4. Forest plot showing the observed outcomes and the estimate of the random effects model for the duration of the third stage of labor in HBB RCTs

HBB Concentration:

Different concentrations of HBB have been administrated in reviewed studies. In 2 studies, women in the intervention group get 10 mg (36, 54), 30 studies get 20 mg(3, 20, 32-35, 38-47, 49-51, 56-61, 63-65, 68, 69), and 10 studies get 40 mg(16, 19, 27, 37, 48, 52, 53, 55, 62, 66) HBB by injection (39 studies) or rectal suppository (3 studies)(36, 54, 64). Since HBB only reduces the first stage of labor duration significantly, we use these subgroups' data to investigate whether the HBB effect on the first stage duration is concentration-dependent or not. The result indicated that there is a hetroginty between studies so we used the random effects model; I^2 = 95%; Chi^2 800.74, df = 41 ($p < 0.00001$).

10-mg HBB:

In 2 studies researchers used 10 mg of HBB in the intervention group (36, 54); these two studies were included in the analysis. These studies' observed MD ranged from -154.29 min to -139.70 min, and all estimates have been negative (100%). The estimated standardized combined MD based on the random-effects model was -147.02 min (95% CI: -161.32 to -132.73) and (Z = 20.15, $p = 0.001$. So, 10 mg of HBB decreased the first stage of labor duration by 147.02 min. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Figure 2.

20-mg HBB:

In most studies (30 studies), the concentration of 20 mg of HBB has been administrated (3, 20, 32-35, 38-47, 49-51, 56-61, 63-65, 68, 69). These studies' observed MD ranged from -146.00 min to 78.47 min, with most of the estimates being negative (83%). Based on this model, the estimated combined MD was -58.95 min (95% CI: -74.55 to -43.35), (Z = 7.41, $p < 0.001$). So this results showed that 20 mg HBB decreased the first stage of labor duration by 58.95 min. A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Figure 2.

40-mg HBB:

The highest concentration of HBB used in reviewed studies is 40 mg; in 10 studies, this concentration was administrated (16, 19, 27, 37, 48, 52, 53, 55, 62, 66). The observed mean differences of these studies ranged from -171.60 min to -27.20 min, with all estimates being negative. The estimated combined MD based on the random-effects model was -71.60 min (95% CI: -99.83 to -43.37) (Z = 4.97, $p = 0.001$). According to this combined MD, 40 mg of HBB decreased the first stage of labor duration by 71.60 min. Moreover, these results were shown in Figure 2.

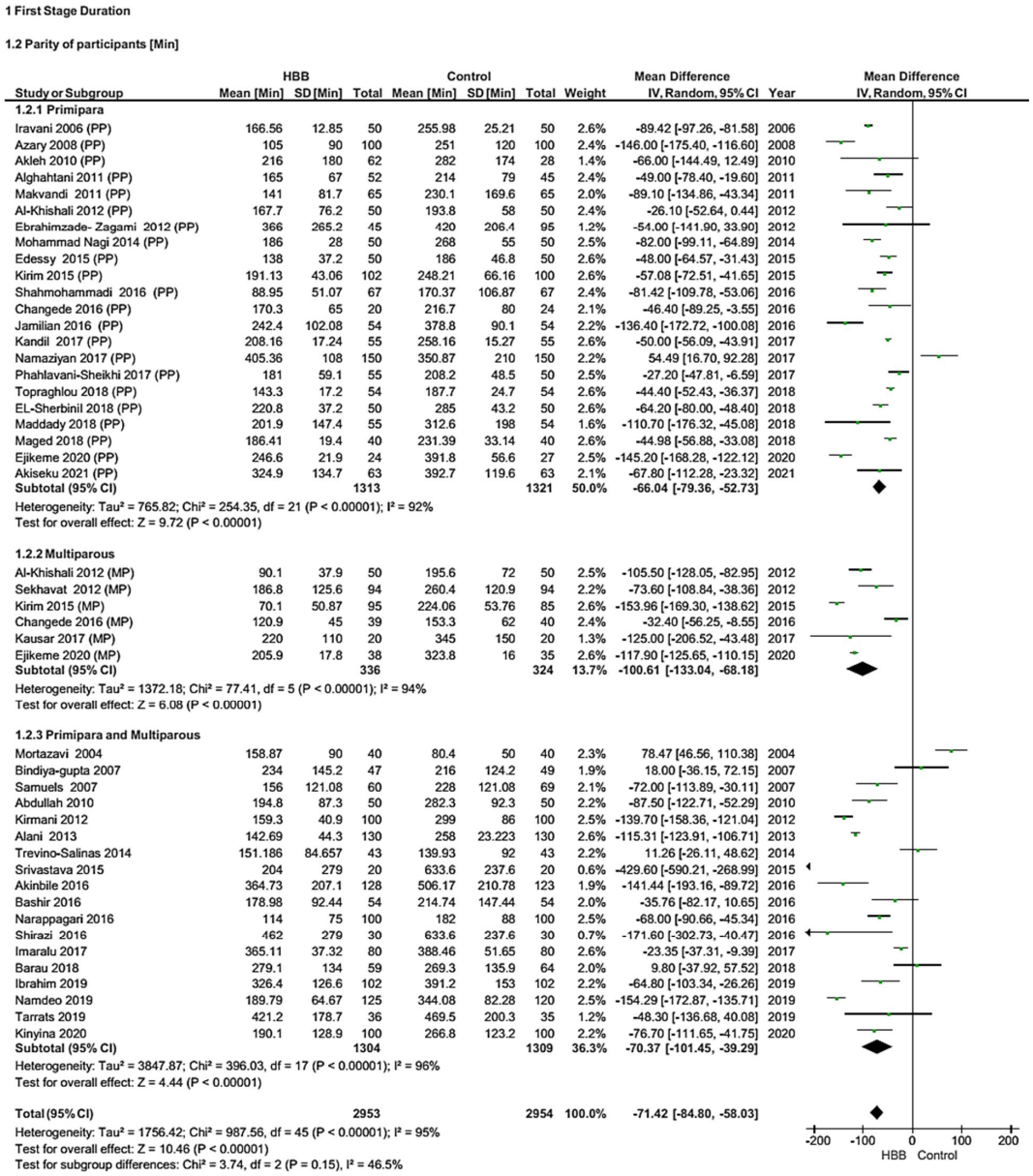

Fig. 5. Forest plot showing the observed outcomes and the estimate of the random-effects model for the duration of the first stage of labor in Primipara, Multiparous, and Primipara and Multiparous women

Gravidity of Participants:

We investigate the effects of previous pregnancy on HBB efficacy in reducing labor duration. A total of 24 studies report data for primipara women and six studies for multiparous women. Studies that didn't specify participants' status were excluded.

Primipara Women:

In 24 studies (3, 16, 19, 32, 35, 38-40, 44, 45, 48, 50-52, 55, 57-60, 64, 66, 69), data for primipara women were reported separately; these studies were included in the analysis. The observed MD of included studies

ranged from -146.00 min to 54.49 min, with most estimates being negative (96%). According to the Cochran's Q test. A hetroginty was appeared in studies ($Chi^2 = 254.35$, ($p < 0.00001$); $I^2 = 92\%$). The estimated combined MD based on this model was -66.04 min (95% CI: -79.36 to -52.73) and ($Z = 9.72$, $p < 0.001$.) According to the results were summarized in Figure 5, HBB decreased the first stage of labor duration by 66.04 min in primipara women.

Multiparous Women:

A total of 6 studies (35, 40, 44, 55, 61, 65) that reported data for multiparous women were included in the analysis. The observed MD ranged from -153.96 min to -32.40 min, with most estimates being negative (100%). The true outcomes appear to be heterogeneous ($Tau^2 = 1372.18$; $Chi^2 = 77.41$, df = 5 ($p < 0.00001$); $I^2 = 94\%$). Based on the random-effects model, the estimated combined MD was -100.61 min (95% CI: -133.04 to -68.18 and p<0.001). So, HBB decreased the first stage of labor duration by 100.61 min in multiparous women (Figure 5).

Promethazine

***Promethazine in the First Stage*:**

A total of 5 RCT studies that use Promethazine to reduce labor duration and met criteria were included in the analysis (3, 26, 67-69). These studies report the first stage duration as the primary outcome. The observed mean differences for these studies ranged from -81.42 min to 65.97 min, with most estimates being negative (60%). The true outcomes appear to be heterogeneous ($Tau^2 = 3974.01$; $Chi^2 = 62.01$, df = 4 ($p < 0.00001$); $I^2 = 94\%$). The estimated combined MD based on the random-effects model was -12.68 min (95% CI: -70.75 to 45.38), and ($Z = 0.43$, $p = 0.67$).

Promethazine in the Second Stage:

Three studies report data for the effect of Promethazine on the second stage duration (67-69). These studies report the second stage duration as the primary outcome. The observed mean differences for these studies ranged from -8.68 min to 7.26 min, with most estimates being negative (77%). The true outcomes appear heterogeneous ($Chi^2 = 5.47$, ($p = 0.06$); $I^2 = 63\%$). The estimated combined MD based on the random-effects model was 0.7 min (95% CI: -6.55, 7.96, $P=0.85$).

Promethazine in the Third Stage:

Only two studies report data for the effect of Promethazine on the third stage duration (68, 69). These studies report the third stage duration as the primary outcome. The observed mean differences for the two studies are -0.03 min to 1.37 min. The true results appear not heterogeneous ($Chi^2 = 1.73$, ($p = 0.19$); $I^2 = 42\%$). The estimated combined MD based on the fixed-effects model was 0.53 min (95% CI: -0.81, 1.87, $p=0.44$).

HBB vs Promethazine:

Some RCT studies use HBB and Promethazine in combination with other drugs or alone. The analysis included two studies that compared HBB and promethazine effects on separate groups and met the criteria (3, 68). Studies that combine these drugs or other drugs were excluded from the analysis. These studies report the first stage duration as the primary outcome and include 170 participants. The observed mean for these two studies is -107.40 min and 12.50 min. A hetroginty has appeared between studies ($Chi^2 = 8.24$, ($p = 0.004$); $I^2 = 88\%$). Considering this, the combined MD was -42.88 min (95% CI: -160.04 to 74.28, $P=0.47$).

Quality Assessment of the Included Studies:

Based on the Jadad scale, studies get scores from 3 to 8. Most studies (27 studies) have a 6 or 7 score, and two get eight scores. The detailed score for each Study is presented in Table 3 (Supplementary). We considered studies with a score of at least 3 in meta-analysis.

Discussion

Two commonly used drugs to shorten prolonged labor in developing countries are Hyoscine butyl bromide (an anti-spasmodic medicine) and Promethazine (Histamine H1 receptor antagonist).

Several RCT studies have investigated these drugs' efficacy in reducing the active phase of labor duration (3, 16, 19, 25, 34-49, 51, 58, 59, 61-66, 69-75). We conduct this systematic review and meta-analyze to determine the benefit of using these drugs for decreasing labor duration. After a systematic search, we selected 30 studies that meet the inclusion criteria. Among studies, 44 studies administered HBB, two used Promethazine, and three used both in different intervention groups to compare their effectiveness.

The studies were conducted in Iran (15 studies), India (8 studies), Nigeria (6 studies), Egypt (6 studies), Iraq (2 studies), Bahrain (1 study), Kenya (1 study), Mexico (1 study), Saudi Arabia (1 study), Spain (1 study), Tanzania (1 study), Turkey (1 study), which all except Spain, are developing countries. The meta-analysis results regarding the effectiveness of HBB on labor stages showed that HBB shortened the first stage of labor by 66.75 min compared to placebo groups. This reduction is 147.02 min for two studies that use 10 mg HBB (36, 54), and 20 mg and 40 mg doses, shortening the labor first stage duration by 58.95 and 71.60 minutes, respectively. However, 10 mg seems more effective, but because only two studies use this dose, we can't tell if the HBB effect is dose-dependent. On the other hand, Promethazine reduces the first stage duration by 12.68, but it isn't statistically significant (Z = 0.43 (p = 0.67)). Among Promethazine studies, Shahmohammadi (69) and Ebrahimzade-Zagami (3) report the highest reduction (81.42 and 78.60 min); however, two studies (67, 68) report an increase in the first stage duration of the intervention group (21.88 min and 65.97 min increase in duration respectively).

The HBB reduces the second and third stages of labor by 3.27 min (Z = 1.93, $p = 0.05$)) and 0.6 min (Z = 2.27, $p = 0.02$), which are not statistically nor clinically significant. Promethazine increases the duration of the second (0.7 min increase, Z = 0.19 (p = 0.85)) and third (0.53 min increase, Z = 0.77 (p = 0.44)) stages of labor. However, it's not statistically significant. Indeed, we can see that HBB reduces labor duration mainly by affecting the first stage of labor, so we do a subgroup analysis based on first-stage data. We didn't include its data in further analysis because we couldn't find an overall significant effect of Promethazine in any delivery stages.

Next, we consider the participant's pregnancy history effect on HBB efficacy by analyzing 21 studies that report data per parities (3, 16, 19, 32, 35, 38-40, 44, 45, 48, 50-52, 55, 57, 60, 64, 66, 67, 69). Four studies report data for primipara and multiparous women separately, so we use each group's data in specific subgroups (35, 40, 44, 55). We reviewed 23 studies with 1313 primipara women in the HBB intervention group and 1321 in the control group (3, 16, 19, 32, 35, 38-40, 44, 45, 48, 50-52, 55, 57-60, 64, 66, 67, 69). HBB was found to reduce the duration of the first stage of labor in primipara women by 66.04 min (Z = 9.72 ($p < 0.00001$)). We use six studies with 336 multiparous women in the HBB intervention group and 324 in the control group for the multiparous subgroup (35, 40, 44, 55, 61, 65). The HBB reduces the first stage duration by 100.61 min (Z = 6.08 ($p < 0.00001$)). Time reduction in studies that didn't represent separate data for primipara and multiparous women is close to the primipara group (70.37 min, Z = 4.44 (p = 0.00001)). So HBB is more effective in multiparous women compared to primipara women. A recent study by Yousef 2022 found that HBB reduced the duration of the first stage duration in both augmented and non-augmented participants, with a more significant effect on multigravida than primigravida. This study also demonstrated that the average duration of the active first stage of labor was 206.51 minutes in the HBB group compared to 267 minutes in the placebo group (mean difference= 61.44 minutes), which is statistically significant. HBB is an effective and safe drug for reducing the duration of the active first stage of labor (76,77).

One of the main factors in the first stage of labor duration is cervical dilatation; all included studies report the administration time of HBB at 3–4 cm and don't report cervical dilatation rate after administration, so we couldn't involve this factor in the analysis. Two studies use HBB and Promethazine in two separate intervention groups (3, 68). We use these studies to compare HBB and Promethazine directly. The analysis shows that

HBB reduces the first stage duration by 42.88 min compared to Promethazine; however, the effect is not statistically significant (Z = 0.72 p = 0.47). More studies are needed to report accurate results in this regard. We have several limitations here; most studies report comprehensive participant data and don't report subgroup data. All studies report participant age as the mean± SD age, and we couldn't include participants' age in the analysis.

Conclusions

HBB administration reduces labor duration mainly by affecting the first stage of labor. HBB is more effective in multiparous women compared to primipara women. Since 20 mg and 40 mg of HBB both have the same effectiveness, we recommend using 20 mg to minimize side effects in the mother and infant. On the other hand, Promethazine does not reduce total labor duration or any stages of labor, so its use is not recommended.

Abbreviations

MD: Mean Difference

SID: Scientific Information Database

CI: Confidence Interval

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

IG: Intervention Group

CG: Control Group

GA: Gestational Age

HBB: Hyoscine N-Butyl Bromide

Dil: Dilation

FS: First-Stage

SS: Second Stage

TS: Third Stage

PP: Primipara

MP: Multipara

NS: Normal Saline

RCT: Randomized Clinical Trial

HR: Hours

Min: Minutes

IM: Intra Muscular

IV: Intravenously

DW: Distilled Water

NS: Not Specified

HP: Hugo Poin

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Conflicts of interest

The authors declared no conflicts of interest.

Authors' Contributions

MJ, FH, MK, and MA contributed substantially to the design of the study. MJ and FH contributed to data collection. MS had roles in data interpretation. MJ and PY wrote the initial draft and MS critically and substantially revised the final article. All authors reviewed critically and approved the manuscript.

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Supplementary Material

Table 1: Characteristics of the included studies with Hyoscine N-butyl-bromide intervention

Table 2: Characteristics of the included studies with promethazine intervention

Table 3: Quality assessment of the selected studies was presented according to the Jadad score calculation

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