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MATERNAL-FETAL MEDICINE

# A randomized controlled study of the effect of hyoscine butylbromide on duration of labor in primigravida women with prolonged labor

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## Abstract

**Objective** To assess the safety and efficacy of hyoscine butyl bromide (HBB) in primipara with prolonged 1st stage of labor.

**Materials and methods** A double-blinded randomized controlled trial included 100 primiparas diagnosed with prolonged labor. They were randomly divided two equal groups. Group I received 40 mg HBB intravenously. Group II received 2 ml of normal saline. The primary outcome was the duration of the 1st stage of labor. Secondary outcomes included success of vaginal delivery, rate of cervical dilation, duration of 2nd and 3rd stages of labor, causes of CS, neonatal outcome and drug side effects.

**Results** The duration of the 1st stage was 322.3 ± 89.8 min in women who received HBB compared with 451.3 ± 198.3 min in the control women ($P < 0.001$). The rate of cervical dilation was increased from 0.4 ± 0.2 to 1.5 ± 0.6 in women who received HBB compared with its increase from 0.4 ± 0.1 to 0.9 ± 0.2 in other women ($P < 0.001$). The rate of CS were significantly higher in control women when compared to those received HBB (34 vs. 20%, $P < 0.001$). The commonest indication for the operation was arrest of cervical dilatation (28 and 16%, respectively).

**Conclusion** HBB is associated with shortening of the 1st stage, lowered rate of CS without any side effects.

**Clinical trial.gov ID** NCT03430362 date of registration 6 February 2018.

Synopsis Hyoscine butyl bromide is associated with shortening of the 1st stage, lowered rate of CS in primiparas with prolonged labor.

**Keywords** Prolonged labor · Primigravida · Hyoscine butylbromide · Duration of labor · Successful vaginal delivery

## Introduction

Dystocia means difficult labor and is characterized by abnormally slow labor progress. It occurs as a result of one or more of three distinct abnormality categories. Insufficient uterine contractions either weak or inappropriately coordinated, abnormal fetal presentation, position, or anatomy and maternal bony or soft tissue abnormalities [1].

The Obstetric care consensus committee of the American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine in 2016 recommended four guides for management of the 1st stage of labor. First, 'a prolonged latent phase is not an indication for cesarean delivery'. Second, "Protraction disorders should be managed through proper observation with assessment of uterine contractions and its stimulation—if needed". Third, "The threshold for active labor is six and not 4 cm of cervical dilatation". Fourth, in cases with active phase arrest, cesarean section is not done except after 4 h of efficient uterine contractions or after 6 h of oxytocin augmentation with inefficient uterine contractions and without cervical dilatation in women with cervical dilatation of 6 cm or more with ruptured membranes [1].

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Cervical dystocia is one of the important causes of prolonged labour [2]. To overcome cervical spasm, antispasmodic drugs were studied in many randomized clinical trials [3].

Atropine was used as spasmolytic effective drug to treat cervical spasm. However, it has remarkable side effects as dryness of secretions, visual disturbances and cardiac manifestations. A series of scopolamine ammonium derivatives were synthesized to avoid these side effects. One of these was hyoscine butyl bromide (HBB) [3].

It is primarily acting through block of neural impulses transmission in the intraneural parasympathetic ganglia by inhibition of cholinergic transmission in the synapses [4].

HBB has a selective action on cervico-uterine plexus and its administration facilitate cervical dilatation and shorten the duration of labour without such undesired effects on uterine contractions of the fetus. In several studies, it has not demonstrated unfavorable side effect on uterine contractions or on the foetus [5].

As HBB does not cross the blood brain barrier unlike atropine, it does not produce the undesirable central effects of atropine at therapeutic doses [6].

The effect of HBB on the duration of active phase of labor is unsure and studies yielded conflicting results [7–11] without reaching a definitive conclusions as these studies had different parities and used different doses of the drug. There is a great need to study the effect of HBB on primipara with prolonged 1st stage of labor and that was the aim of our study.

## Materials and methods

This double-blinded randomized controlled trial was conducted at Kasr Alainy maternity hospital at Cairo University between March 2018 and December 2019. All participants have signed an informed written consent after explanation of the aim, risks and benefits of the study. The study was approved by Kasr Alainy ethical committee and was registered at clinical trials registry ClinicalTrials.gov ID: NCT03430362.

The study involved 100 women between 18 and 38 years of age. All were primigravida with gestational age between 37 and 41 weeks (calculated from sure menstrual dates and confirmed by first trimester ultrasound). All participants had a singleton pregnancy with vertex presentation and had a prolonged 1st stage (defined as cervical dilatation less than 1.2 cm/hour) during the active phase (defined as cervical dilation of 3–6 cm or more, in the presence of uterine contractions) [1]. Exclusion criteria included women indicated for elective cesarean delivery (as women with cephalopelvic disproportion, maternal or fetal distress) and those with medical disorders associating pregnancy as pregnancy induced hypertension or gestational diabetes mellitus. Women with contraindications for HBB as those with sensitivity to atropinics, glaucoma or myasthenia gravis and women who have previous cervical surgery were also excluded from the study.

All participants were subjected to full assessment through history, general and obstetric examination. Obstetric ultrasound examination was done to all participants to ensure stickiness to inclusion and exclusion criteria. After admission, all women were followed-up through partogram.

Once the diagnosis of prolonged labor was done, reevaluation of all women was done assessing the cephalopelvic disproportion (through vaginal examination and performing cephalopelvic disproportion tests), uterine contractions and fetal heart monitoring to exclude any cause of CS. Any women with signs of dehydration received 1000 cc of lactated ringer solution. Women with insufficient uterine contractions received oxytocin at a rate of at 6 mU/min, which is increased by 6-mU/min every 40 min with a maximum dose of 36 mU/min [12].

Amniotomy was done in those with intact membrane and continuous electronic fetal monitoring was done. Women with prolonged labor after these measures were randomly divided using automated web-based randomization system into two equal groups. Group I included 50 women received 40-mg HBB (Buscopan, Memphis Co, Giza, Egypt) intravenous bolus injection. Group II included 50 women received 2 ml of normal saline. The obstetrician, participants and outcome assessor were all blinded to the group assignment. The primary outcome parameter was the duration of the 1st stage of labor defined as the duration from cervical dilatation of 4 cm till the time of full cervical dilatation. Secondary outcomes included success of vaginal delivery, rate of cervical dilation, duration of 2nd and 3rd stages of labor, causes of CS, neonatal outcome and drug side effects.

Sample size calculation was done using the comparison of length of the 1st stage of labor between primiparous women treated with HBB and un-treated mothers as it was the primary outcome of our study. As reported in previous publication [4], the mean ± SD of length of 1st stage of labor in treated group was approximately 186 ± 126 min, while in un-treated group, it was approximately 260 ± 121 min. Accordingly, we calculated that the minimum proper sample size was 46 mothers in each arm to be able to detect a real difference of 74 min with 80% power at $\alpha = 0.05$ level using Student's *t* test for independent samples. We enrolled 50 women to compensate for any dropout cases. Sample size calculation was done using Stats Direct statistical software version 2.7.2 for MS Windows, StatsDirect Ltd., Cheshire, UK.

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using mean, standard deviation,

median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between groups were done using unpaired *t* test in normally distributed quantitative variables, while non-parametric Mann–Whitney test was used for non-normally distributed quantitative variables. For comparing categorical data, Chi-square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 were considered as statistically significant.

## Results

During the study duration, we evaluated 1168 primiparous women, 187 of were diagnosed with prolonged labor. From these, 56 were indicated for CS for various conditions. Thirty one of the residuals responded to proper hydration and oxytocin treatment. We randomized the 100 left for the study intervention (Fig. 1).

No significant difference was detected between women in the HBB group and the control women regarding age, body mass index, gestational age or neonatal birth weight ($P > 0.05$) (Table 1).

The two groups were statistically similar regarding cervical dilatation at the diagnosis of prolonged labor, the number why received epidural analgesia and the neonatal outcome (Table 2).

Although the rate of cervical dilatation was similar in both groups, the rate was significantly faster in women after administration of HBB resulting in shorter 1st stage of labor in these women with similar durations of the 2nd and 3rd stages of labor when compared to control women (Table 2).

The rate of CS was significantly higher in control women when compared to those received HBB. The commonest indication for the operation was arrest of cervical dilatation (Table 2).

There is no significant difference between the two groups regarding side effects as dry mouth, palpitation, flushing, urine retention, nausea, vomiting or blurring of vision. The overall side effects were eight and three in HBB and control group, respectively ($P = 0.2$) (Table 3).

## Discussion

According to our findings, the use of HBB is associated with shortening of the duration of the first stage in women with prolonged labor as a result of increasing the rate of cervical dilatation from $0.4 \pm 0.2$ to $1.5 \pm 0.6$ cm/hour.

In our study, administration of HBB in women with prolonged labor was associated with significantly lower rates of CS. The commonest indication for the operation was arrest of cervical dilatation.

The physiological explanation of our findings is that the primary action of HBB is relaxation of cervical smooth muscle fibers without producing similar effects on uterine muscles. These findings exert maximum efficacy and safety for both the mother and her fetus. Drugs enhance uterine contractions although results in shortening of labor, however, shortening of second stage in such cases will expose the mother to genital birth injuries as cervical, vaginal and perineal tears and expose the neonate to compression decompression injuries as intracranial hemorrhage. On the opposite side, drugs that decreases uterine contractions can expose the women for retained placenta and atonic postpartum hemorrhage [4]. Accordingly, the main aim of management of normal labor is to achieve the vaginal delivery within the shortest duration without exposing the parturient women or her fetus to risk. Therefore, the concept of active management of labor has arisen to achieve rapid and safe vaginal delivery [13].

Prolonged labor is hazardous for both mother and fetus. The duration of labor is mainly affected by the efficiency of uterine contractions and rate of cervical dilation. Therefore, the management of prolonged labor is dependent on our ability to enhance uterine contractility and to help cervical ability to dilate through relaxation of the cervical smooth muscles [14].

Maged and colleagues in 2018 studied 120 primipara during their active phase of labor. They received 20 mg, 40 mg of HBB or placebo. They found that shorter duration of the 1st stage in the former two groups with no difference of side effects or neonatal effects. However, they reported no difference in CS rate. This different finding from our study can be attributed to the nature of participants as they studied all parturient women, while we studied women only with prolonged labor who are exposed to higher risk of CS [11].

Kirim et al. in 2015 randomized 80 women in spontaneous labor to 20 mg of IV HBB or placebo. They reported duration of 1st stage in both groups. They found a significantly shorter 1st stage in HBB group ( $191.1 \pm 43.06$ vs. $248.2 \pm 66.1$ min in the primigravidas and $170.1 \pm 50.8$ vs. $224.06 \pm 53.7$ min in the multigravidas) with no difference in durations of 2nd or 3rd stages of labor, neonatal outcome, maternal or fetal side effects [15].

Sekhavat and colleagues in 2012 randomized 188 multiparas' women in active phase of labor to 20 mg HBB or placebo. The duration of the 1st stage and 2nd stage was shorter in HBB group ($186.8 \pm 125.6$ vs. $260.4 \pm 120.9$ min, $p < 001$ and $20.0 \pm 8.1$ vs. $25.8 \pm 9.4$ min, $p$ 0.03, respectively) with no difference detected in number needed cesarean section, neonatal outcome, or side effects [4]. The difference in their findings related to duration of 1st, 2nd stages and CS rates can be explained by different participants as

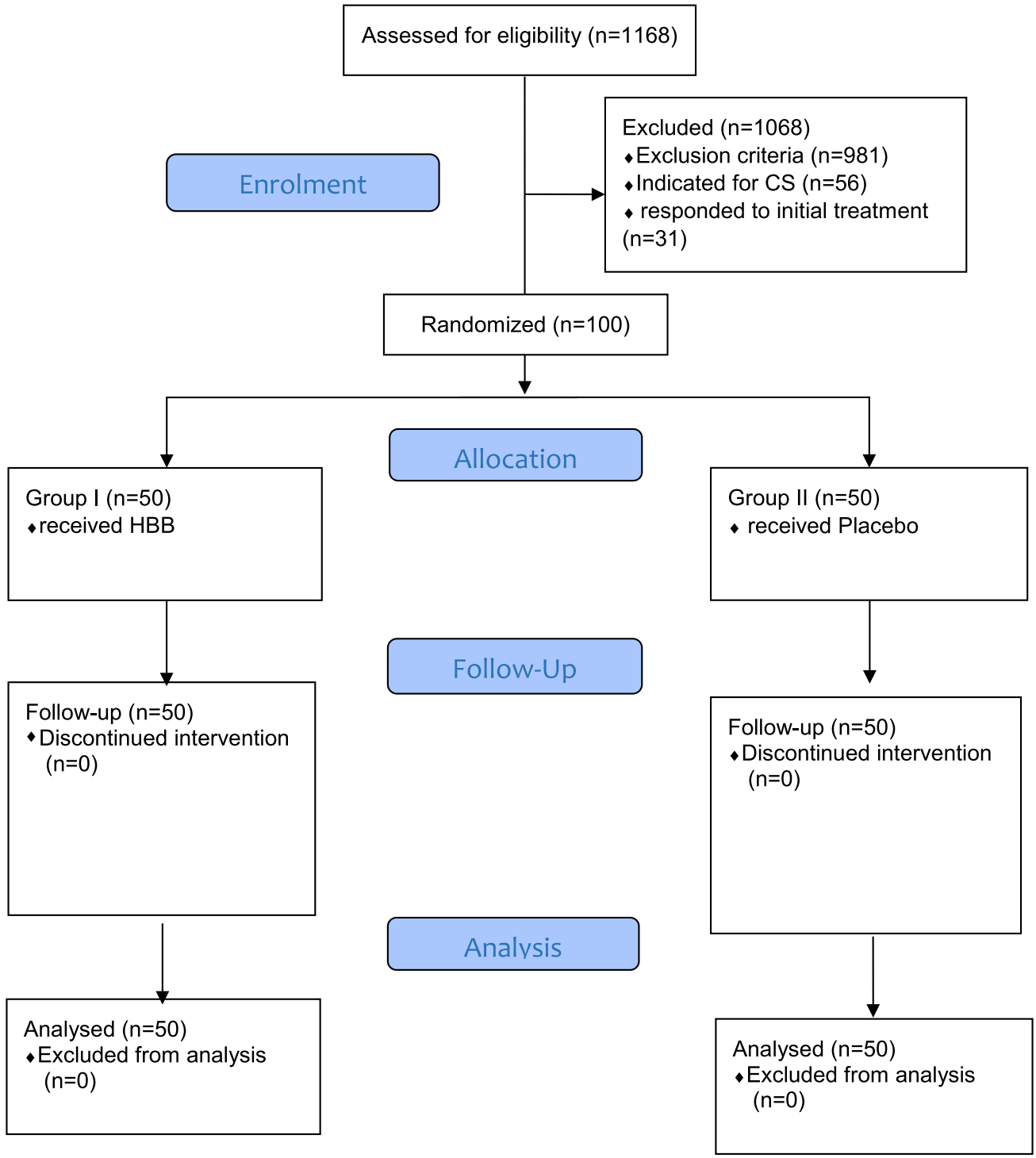


**Fig. 1** Flowchart of participants

their study involved multiparas in normal labor, while our study involved primiparas with prolonged labor.

In our study, the administration of HBB was not associated with occurrence of side effects compared to women who did not receive the drug.

**Table 1** Demographic characteristics of the study population

| | Hyosciene group ($n=50$) | Control group ($n=50$) | $P$ value |
|---|---|---|---|
| Age (years) | 23.60 ± 3.91 | 24.14 ± 3.35 | 0.460 |
| BMI) kg/m$^2$) | 29.69 ± 2.43 | 29.87 ± 2.55 | 0.722 |
| Gestational age (weeks) | 38.4 ± 1.39 | 38.9 ± 1.14 | 0.315 |
| Neonatal birth weight (grams) | 3419 ± 478 | 3501 ± 511 | 0.218 |

Data are presented as mean ± SD

*BMI* Body mass index

**Table 2** Labor characteristics of the study population

| | Hyosciene group ($n=50$) | Control group ($n=50$) | $P$ value |
|---|---|---|---|
| Cervical dilatation at diagnosis | 6.1 ± 0.7 | 6.0 ± 0.8 | 0.729 |
| Rate of cx dilatation (cm/hour) | | | |
| Before | 0.4 ± 0.2 | 0.4 ± 0.1 | 0.534 |
| After | 1.5 ± 0.6 | 0.9 ± 0.2 | < 0.001 |
| Duration of 1st stage (Mins) | 322.3 ± 89.8 | 451.3 ± 198.3 | < 0.001 |
| Duration of 2nd stage (Mins) | 39.5 ± 10.1 | 41.5 ± 11.6 | 0.616 |
| Duration of 3rd stage (Mins) | 8.28 ± 2.14 | 8.64 ± 1.70 | 0.354 |
| Mode of delivery | | | |
| VD | 36 (72%) | 31 (62%) | 0.395 |
| CS | 10 (20%) | 17 (34%) | 0.176 |
| Instrumental VD | 4 (8%) | 2 (4%) | 0.677 |
| Causes of CS | | | |
| Fetal distress | 2 (4%) | 3 (6%) | 1.00 |
| Arrest of cx dilatation | 8 (16%) | 14 (28%) | 0.227 |
| Epidural analgesia | 8 (16%) | 7 (14%) | 0.326 |
| Neonatal outcome | | | |
| Apgar 1 min | 7.2 ± 0.9 | 7.2 ± 0.9 | 0.774 |
| Apgar 5 min | 9.01 ± 0.9 | 9.1 ± 1.0 | 0.615 |
| NICU admission | 3 (6%) | 4 (8%) | 0.712 |

Data are presented as mean ± SD or number (percent)

*Cx* cervix, *VD* vaginal delivery, *CS* Cesarean section, *NICU* Neonatal intensive care unit

**Table 3** Drug side effect

| | Hyosciene group ($n=50$) | Control group ($n=50$) |
|---|---|---|
| Dry mouth | 2 (4%) | 1 (2%) |
| Palpitation | 1 (2%) | 1b(2%) |
| Flushing | 1 (2%) | 0 |
| Urine retention | 2 (4%) | 1 (2%) |
| Nausea & vomiting | 1 (2%) | 0 |
| Blurring of vision | 1 (2%) | 0 |
| Overall side effects | 8 (16%) | 3 (6%) |

Data are presented as number (percent)

To the best of our knowledge, this study is the first randomized controlled double-blind trial to evaluate the effect of HBB on primiparas diagnosed with prolonged labor with properly calculated sample size.

Our study is not without limitations. The main limitation is the relatively small sample size that may be non-conclusive in detection of side effects. The other limitation is being conducted in a single center.

Our findings can provide a key management for parturient women diagnosed with prolonged labor. However, more studies are needed with larger sample size and on women with different parities to confirm our results.

We concluded that the use of HBB is safe and effective in prolonged labor that occurred in primiparas. We recommend its use in all primiparas with protracted cervical dilatation provided that there are no indications for CS with non-distressed mother and fetus. Shortening of the 1st stage has many advantages: it decrease the maternal stress that results from prolonged labor, decrease the needed doses of analgesics during labor with its hazardous effects on neonates and decrease the financial burden of labor. Shortening the duration of labor is associated with lower risk postpartum hemorrhage, puerperal and neonatal infections that is associated with prolonged labor. Also, the use of HBB decreased the possibility of CS with its maternal short- and long-term hazards.

**Author contributions** AM Maged: data analysis, manuscript writing. EH Sorour: project development, data collection, manuscript writing. MM ElSadek: project development, manuscript revision. SM Hassan: data collection, manuscript writing. AY Shoab: data collection, manuscript writing.

## Declarations

**Conflict of interest** The authors report no conflicts of interest in this work.

**Ethical standards** The study was performed in accordance with the Declaration of Helsinki ethical standards. Informed consents were taken from study participants.

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