Thai Journal of Obstetrics and Gynaecology
May 2024, Vol. 32, No. 3, pp. 245-253.

OBSTETRICS

The Effect of Hyoscine Butylbromide for Shortening the Active Phase of the First Stage of Labor: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Objectives: To study the efficacy and safety of hyoscine butylbromide for shortening the active phase of the first stage of labor.

Materials and Methods: After receiving informed consent, singleton pregnant women who planned vaginal delivery at Khon Kaen Hospital between July 2022 and April 2023 were randomly allocated into two groups: the control group (n = 61) received 1 mL (20 mg) of intravascular hyoscine butylbromide, while the control group (n = 61) received 1 mL of intravascular normal saline at 5-6 cm cervical dilatation. The duration of the active phase of the first stage of labor and adverse events were analyzed.

Results: Baseline characteristics were not statistically different between groups. Hyoscine butylbromide significantly shortened the active phase of the first stage of labor compared to the control group (88.5 ± 66.7 min vs 188.5 ± 101.9 min, respectively, mean difference -100.02 min (95% confidence interval -130.72 to -69.31, p <0.001)). There were no significant maternal or neonatal adverse outcomes.

Conclusion: Hyoscine butylbromide effectively shortened the active phase of the first stage of labor.

Keywords: hyoscine butylbromide, first stage of labor, duration of labor.

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Received: 27 September 2023, **Revised:** 10 January 2024, **Accepted:** 15 January 2024

ผลของยาฮัยออสซีน-บิวทิลโบรไมด์เพื่อลดเวลาในระยะเร่งของ ระยะที่หนึ่งของการคลอด: การศึกษาแบบสุ่มและปกปิดสองทางเทียบกับยาหลอก

จงรักษ์ คำคง, มนสิชา พงษ์สมัครไทย, มาลีชาติ ศรีพิพัฒนะกุล, ทุมวดี ตั้งรัตนศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพและความปลอดภัยของยาฮัยออสซีน-บิวทิลโบรไมด์ในการลดเวลาระยะเร่งในระยะที่หนึ่งของการคลอด*

วัสดุและวิธีการ: *สตรีตั้งครรภ์เดี่ยวที่วางแผนจะคลอดบุตรทางช่องคลอดที่โรงพยาบาลขอนแก่นระหว่างเดือน กรกฎาคม พ.ศ. 2565 ถึง เมษายน พ.ศ. 2566 ได้รับการเชื้อเชิญให้เข้าร่วมวิจัย หลังจากลงนามในหนังสือยินยอมแล้ว จะมีการสุ่มแบ่งเป็นสองกลุ่ม คือกลุ่มทดลองจำนวน 61 คนจะได้รับยาฮัยออสซีน-บิวทิลโบรไมด์ปริมาณ 1 มิลลิลิตร (ขนาด 20 มิลลิกรัม) แบบฉีดทางหลอดเลือดดำ ในขณะที่กลุ่มควบคุมจำนวน 61 คน ได้รับน้ำเกลือปริมาณ 1 มิลลิลิตร แบบฉีดทางหลอดเลือดดำ เมื่อปากมดลูกเปิด 5-6 เซนติเมตร หลังจากนั้นทำการประเมินระยะเร่งของระยะที่หนึ่งของการคลอดและภาวะแทรกซ้อน*

ผลการศึกษา: *ลักษณะพื้นฐานของประชากรในทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ กลุ่มฮัยออสซีน - บิวทิลโบรไมด์มีระยะเร่งในระยะที่หนึ่งของการคลอดสั้นกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (88.5 ± 66.7 นาที และ 188.5 ± 101.9 นาที ตามลำดับ) โดยค่าเฉลี่ยแตกต่างกัน -100.02 นาที (95%CI: -130.72 to -69.31, p <0.001) ไม่พบผลกระทบหรือผลข้างเคียงจากยาต่อมารดาและทารกในครรภ์อย่างมีนัยสำคัญ*

สรุป: *การได้รับฮัยออสซีน-บิวทิลโบรไมด์ทางหลอดเลือดดำสามารถช่วยลดเวลาในระยะเร่งในระยะที่หนึ่งของการคลอดได้*

คำสำคัญ: *ยาฮัยออสซีน-บิวทิลโบรไมด์, ระยะที่หนึ่งของการคลอด, ระยะเวลาคลอด*

Introduction

Prolonged labor can increase maternal and neonatal morbidity and mortality, including postpartum hemorrhage, rupture of the uterus, maternal death, neonatal injury, and perinatal asphyxia[1]. Active labor management can shorten labor duration and reduce the cesarean delivery rate[2]. In 1968, O'Driscoll et al were the first to define the concept of active labor management, which proposed to reduce the duration of labor without increasing maternal or neonatal morbidity and mortality[2]. Cervical dilatation and effacement are essential determinants of the duration of labor and can be facilitated by medical and non-medical procedures[3]. Medical procedures such as oxytocin, analgesics, prostaglandins, muscle relaxants, and antispasmodic drugs can shorten the first stage of labor[3]. Hyoscine butylbromide (HBB) is an anticholinergic agent, also known as scopolamine, which inhibits cholinergic transmission in the pelvic parasympathetic ganglia, and alleviates spasms in the smooth muscles of female genitalia, particularly the cervico-uterine plexus. Thus, HBB acts as a spasmolytic agent at the cervix and promotes cervical dilatation without the effect on uterine contractions so that it can reduce the active phase of the first stage of labor[4-6]. Common adverse effects of HBB include dry mouth, flushing, nausea, blurred vision and dizziness. Mohaghegh et al reported some adverse effects, including maternal tachycardia and dry mouth but without other major maternal adverse effects[7]. Although it is unclear whether it crosses the placenta to the fetus, many studies have not found neonatal adverse effects as evidenced by no difference in Apgar scores[8-12].

Several studies[7-13] on HBB have reported that it can shorten labor time compared to control groups, whereas Duada et al reported the contrary effect[14]. While many studies[7-13] suggest a potential reduction in labor duration with the use of HBB, the underlying mechanism and robust evidence for its efficacy remain unclear. The current study aimed to elucidate the impact of HBB on labor duration by assessing its effectiveness in promoting cervical dilatation and shortening the active phase of the first stage of labor. Additionally, safety evaluations of HBB were conducted as secondary outcomes.

The primary outcome was duration in the active phase of the first stage of labor. The secondary outcomes were the duration of the second and third stages of labor, drug adverse effects, and maternal and neonatal outcomes.

Materials and Methods

Before the initiation of the research, the study protocols were reviewed and approved by the Khon Kaen Hospital Institute Review Board in Human Research. This randomized, double-blind, placebo-controlled trial was conducted at the labor room.

Recruited participants included term singleton pregnant women 18 or older with a cephalic presentation and planned vaginal delivery. Participants were excluded if they (a) received epidural anesthesia; (b) had unstable fetal status (e.g., placental abruption, meconium-stained amniotic fluid, fetal anomaly, non-reassuring fetal status); (c) had contraindications for HBB; and/or, (d) had medical complications during the pregnancy (e.g., maternal fever, thyroid diseases, cardiovascular diseases, autoimmune diseases, gestational diabetes mellitus, pregnancy-induced hypertension).

After giving written informed consent, the participants were assigned to one of two groups, either the HBB or the control group, using computer-generated block-of-four randomization. Allocation concealment was done using sealed opaque envelopes. Baseline characteristics were recorded: age, body mass index (BMI), parity, induction by misoprostol/ oxytocin/ ruptured amniotic membrane before the active phase, and meconium-stained amniotic fluid. Participants were informed about the outcomes that they were observed and recorded, including the duration of the active phase of the first, second, and third stages of labor, adverse effects, and maternal and neonatal outcomes.

All participants received intrapartum care by standardized physicians and labor room nurses with

the same protocol as follows. In the latent phase of the first stage of labor, participants underwent pelvic examinations every 4 hours and observed uterine contractions and fetal heart rate every hour. In the active phase of the first stage of labor, participants underwent pelvic examinations every hour to early detect the cervical progression and accurately accessed duration of the active phase of the first stage of labor. One participant underwent a pelvic examination from one physician who had to standardize using corrections from a cervical dilatation chart. Uterine contractions and fetal heart rate were observed every 30 minutes. The progression of labor was closely documented. Induction or augmentation was performed according to obstetric indications. When cervical dilatation reached 5-6 cm, the eligible participants were masked and randomly allocated into the HBB group or the control group for receiving the intervention. The HBB group was administered 1 mL (20 mg) of HBB intravenously, while the control group was administered 1 mL of normal saline solution (placebo) intravenously. The pharmacist prepared the HBB and placebo in an identical type of syringe using aseptic technique. Participants and healthcare providers were blinded to the treatment groups.

When the cervical dilatation reached 10 cm, the participants were transferred to the delivery room. The primary outcome was duration in the active phase of the first stage of labor, which was recorded using a standard digital clock. The secondary outcomes were recorded, including the duration of the second and third stages of labor, estimated blood loss, uterine atony, postpartum hemorrhage, adverse drug effects, neonatal birth weight, Apgar score at 1 and 5 minutes, and the rate of admission to neonatal intensive care unit (NICU).

The sample size was calculated based on a pilot study of 30 patients with a power of 90%, an α level of 0.05, we get different duration 69 min between two groups from this formula and a dropout rate of 15%. Thus, 122 participants (61 in each group) were required. Data were analyzed based on an intention-to-treat analysis using STATA version 14. The student's t-test and Mann-Whitney U test were used to analyze continuous data. Chi-squared and Fisher's exact test were used to analyze categorical data. A p value < 0.05 was considered statistically significant.

Results

Between July 2022 and April 2023, 122 participants were randomly assigned, 61 to the HBB group and 61 to the control group. Two participants were dropped out, 1 cesarean section in HBB group and 1 cesarean section in control group due to cephalopelvic disproportion. The dropout rate was 1.6% (2/122), and all 60 participants in each group were analyzed by intention-to-treat as shown in Fig. 1.

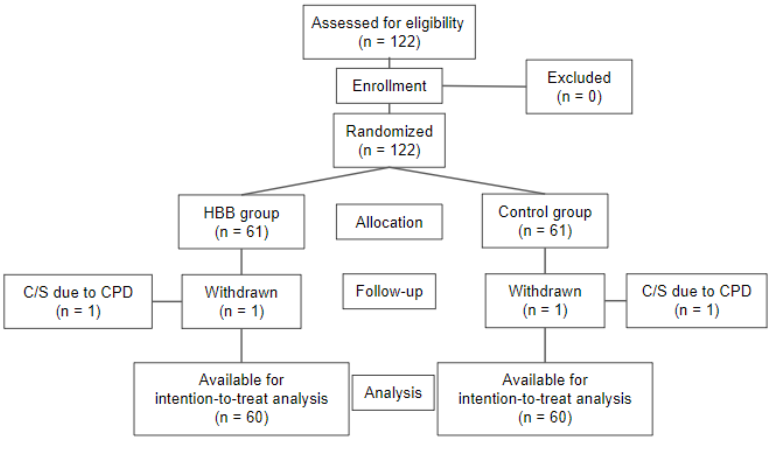


Fig. 1. Study flow.
C/S = cesarean section, CPD = cephalopelvic disproportion

Baseline characteristics including age, BMI, parity, induction by misoprostol or oxytocin or combined misoprostol with oxytocin, ruptured amniotic membrane before the active phase, and meconium-stained amniotic fluid were similar between groups as shown in Table1.

Table 1. Demographics and clinical characteristics of the participants.

Characteristics	HBB group	Control group	p value
Maternal age (years)	26.9 ± 5.9	27.5 ± 5.4	0.523[t]
Gestational age (weeks)	39.1 ± 1.1	39.2 ± 1.0	0.544[t]
Body mass index (kg/m^2)	28.5 ± 4.5	27.1 ± 4.1	0.088[t]
Multipara	34 (56.7)	35 (58.3)	0.853[c]
Amniotic membrane rupture before the active phase	34 (56.7)	37 (61.7)	0.577[c]
Meconium-stained amniotic fluid	1 (1.7)	3 (5)	0.619[f]
Induction of labor with misoprostol	10 (16.7)	9 (15)	0.803[c]
Augmentation of labor with oxytocin	16 (26.7)	19 (31.7)	0.547[c]
Combination of misoprostol and oxytocin used	5 (8.3)	3 (5)	0.717[f]

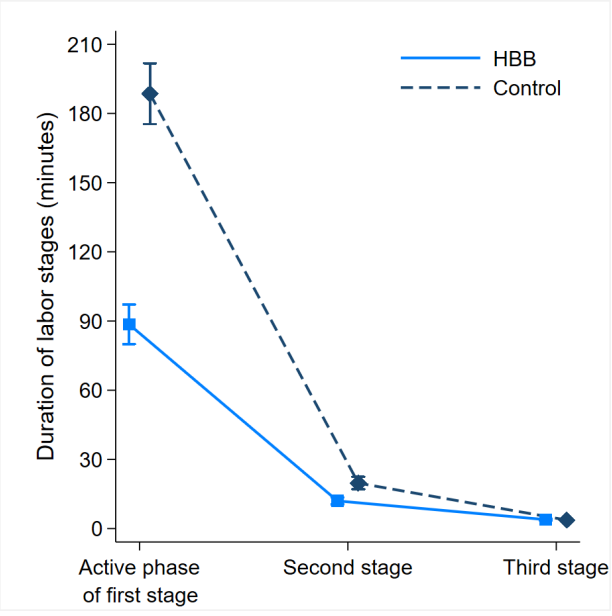
HBB: hyoscine butylbromide
Data are presented as number (%), mean ± standard deviation, or median (interquartile range).
p value corresponds to t = independent samples t-test, c = chi-square test, f = Fisher's exact test. * Significant at p value < 0.05

The HBB group had a significantly shorter time in the active phase of the first stage of labor than the control group (88.5 ± 66.7 min vs 188.5 ± 101.9 min, mean difference -100.02 min, 95%CI -130.72 to -69.31, p < 0.001). The HBB group also had a significantly shorter time in the second stage of labor than the control group (12.0 ± 11.7 min vs 19.7 ± 20.9 min, mean difference -7.73 min, 95%CI -13.8 to -1.67, p = 0.012). Notwithstanding, no significant differences were observed in the duration of the third stage of labor (3.8 ± 2.4 min vs 3.7 ± 2.7 min, mean difference 0.18 min, 95%CI -0.75 to -1.12, p = 0.7) (Table 2, Fig. 2).

Table 2. Duration of the active phase of the first stage, second stage and third stage of labor between the HBB group and the control group.

Duration of labor stage (min)	HBB group	Control group	Absolute difference (95%CI)	p value
All participants (n = 120)	(n = 60)	(n = 60)		
Active phase of first stage	88.5 ± 66.7	188.5 ± 101.9	-100.02 (-130.72 to -69.31)	< 0.001*
Second stage	12.0 ± 11.7	19.73 ± 20.9	-7.73 (-13.8 to -1.67)	0.012*
Third stage	3.8 ± 2.4	3.70 ± 2.7	0.18 (-0.75 to 1.12)	0.700
Nullipara (n = 51)	(n = 24)	(n = 27)		
Active phase of first stage	109.6 ± 70.9	201.8 ±83.0	-92.15 (-134.19 to -50.11)	< 0.001*
Second stage	17.6 ± 15.3	26.3 ± 28.5	-8.74 (-21.27 to 3.78)	0.171
Third stage	3.6 ± 1.9	3.0 ± 2.0	0.62 (-0.46 to 1.69)	0.260
Multipara (n = 69)	(n = 36)	(n = 33)		
Active phase of first stage	72.3 ± 59.3	179.0 ± 113.8	-106.70 (-149.05 to -64.36)	< 0.001*
Second stage	7.7 ± 5.0	15.0 ± 11.5	-7.29 (-11.44 to -3.15)	0.001*
Third stage	4.0 ± 2.8	4.2 ± 3.1	-0.11 (-1.55 to 1.28)	0.875

HBB: hyoscine butylbromide, CI: confident interval
[†] Absolute difference is the mean difference with 95%CIs estimated by generalized linear models with a robust error variance.



HBB: hyoscine butylbromide

Fig. 2. Mean duration of the active phase of the first stage, second stage and third stage of labor between the HBB group and control group.

For the subgroup analysis, in multipara women, the active phase of the first stage of labor was significantly shorter in the HBB group (72.3 ± 59.3 min) compared to the control group (179.0 ± 113.8 min), with a mean difference of -106.70 min ($p < 0.001$). For nullipara women, the HBB group also had a significantly shorter active phase of the first stage of labor (109.6 ± 70.9 min) compared to the control group (201.8 ± 83.0 min), with a mean difference of -92.15 min ($p < 0.001$). In multipara women, the second stage of labor was significantly shorter in the HBB group (7.7 ± 5.0 min) compared to the control group (15.0 ± 11.5 min), with a mean difference of -7.29 min ($p = 0.001$). However, in nullipara women, the duration of the second stage of labor did not show a significant difference between the HBB and control groups (17.6 ± 15.3 min vs 26.3 ± 28.5 min, mean difference -8.74 min, $p = 0.171$). The duration of the third stage of labor showed no significant difference between the HBB and control groups in both multipara women (4.0 ± 2.8 min vs 4.2 ± 3.1 min, mean difference -0.11 min, $p = 0.875$) and nullipara women (3.6 ± 1.9 min vs 3.0 ± 2.0 min, mean difference 0.62 min, $p = 0.260$) (Table 2).

Maternal outcomes, including uterine atony, estimated blood loss (mL), postpartum hemorrhage, and adverse drug effects, were not significantly different between the two groups. No abnormal neurologic ocular or urological manifestations were reported. Neonatal outcomes, including Apgar score at 1 and 5 minutes and neonatal birth weight, were not significantly different between groups, there were no admissions to the NICU in both groups (Table 3).

Table 3. Obstetric outcomes and adverse drug effects between the HBB group and the control group.

	HBB group (n = 60)	Control group (n = 60)	p value
Estimate blood loss (mL)	120 (100 - 150)	120 (100 - 175)	0.442[m]
Maternal complication			
Uterine atony	9 (15)	10 (16.7)	0.803[c]
Postpartum hemorrhage	1 (1.7)	1 (1.7)	1.000[f]
Adverse drug effects			
Dry mount	10 (16.7)	6 (10)	0.283[c]
Palpitation	3 (5)	2 (3.3)	1.000[f]
Flushing	3 (5)	2 (3.3)	1.000[f]
Nausea	4 (6.7)	4 (6.7)	1.000[f]
Vomiting	2 (3.3)	1 (1.7)	1.000[f]
Neonatal birth weight (g)	3,107.6 ± 376.4	3,126.5 ± 410.7	0.794[t]
Apgar score			
at 1 min	8 (8-9)	8 (8-9)	0.774[m]
at 5 min	9 (9-10)	9 (9-10)	0.935[m]

HBB: hyoscine butylbromide
Data are presented as number (%), mean ± standard deviation, or median (interquartile range).
p value corresponds to [m] = Mann-Whitney U test, [c] = chi-square test, [f] = Fisher's exact test, or [t] = independent samples t-test

Discussion

The current study showed that compared to the placebo, intravascular administration of HBB when cervix dilate 5-6 cm reduce the duration of the active phase of the first stage of labor with 100.02 min compared with the control group (88.5 ± 66.7 min vs 188.5 ± 101.9 min (95%CI -130.72 to -69.31, $p < 0.001$). The results of the current study were similar to the findings of Yousuf[8] and Samules et al[9] and others[10-12], HBB was clinically effective in both nullipara and multipara for shortening the first stage of labor. These results support that the mechanism of HBB action is by inhibiting cholinergic neurotransmission in the pelvic parasympathetic ganglia and alleviating spasms in the smooth muscles of the cervix and promoting cervical dilatation[4-6,15].

In contrast, Duada et al[14] reported that administering 20 mg via intramuscular injection in the active phase did not significantly shorten the first stage of labor, while the current study administered the same dose of HBB, but intravenously. The reason for these results might be due to the different routes of drug administration that consistent with Brand et al reported that the peak activity of HBB administered by intramuscular injection was 1-2 hours[16] whereas after intravenous administration, the peak effect was 20-60 minutes, the onset of action was about 10 minutes, and the action lasted 2 hours[4-6,15]. However, intramuscular administration of HBB 40 mg reported by Al Qahtan et al and Kandi et al showed significant shortening of the active phase of the first stage of labor[17-18]. In the current study, the mean time difference of the first stage of labor between the two groups was 100 min, while Samuels et al found the mean time difference was 72 min[9], the result might be due to the different times of drug administration. Our study administered the drug at 5-6 cm of cervical

dilatation, while Samuels et al administered the drug at 3-4 cm of cervical dilatation[9]. In the second stage of labor, the HBB group also had a significantly shorter time, similar to Yousuf[8], but in contrast to other studies[10-12]. Subgroup analysis among nullipara and multipara women revealed that the second stage of labor duration between the HBB and control groups was significantly shortened only in the multipara women. This might be supported by the studies reviewed that during labor, multiparous had less uterocervical resistance and increased uterine efficiency than nulliparity[19, 20], so, this might be the reason for the shorter time in second stage of labor among multipara women.

There was no difference in the duration of the third stage of labor between the HBB and control groups in this study. This was similar to the findings of Yousuf[8], Imaralu et al[10], and others[11-12], which supported that HBB did not affect uterine contractions[4-6, 15]. In the current study, HBB did not significantly affect the rate of cesarean section and the delivery route, similar to Samuels et al and other studies[10, 13]. The estimated blood loss, uterine atony, and postpartum hemorrhage were not significantly different in both groups. This observation suggested no adverse effect on uterine contraction during the postpartum period. This was similar to the findings of other authors[9,11]. However, it contrasted with the study by Imaralu et al, which showed that HBB was also associated with significantly less postpartum blood loss. This can be explained by shorter durations of labor causing less myometrial exhaustion that might reduce postpartum hemorrhage (PPH)[21].

The median Apgar score at one and five minutes was not different between the two groups. Moreover, both groups had no neonatal admission to the intensive care unit. This was similar to the findings of other studies, explaining that HBB did not cross the placenta and, therefore, did not cause respiratory depression in neonates[7-12, 14]. In the current study, maternal adverse effects were not statistically significant between the two groups. This observation was consistent with other reports. No significant major adverse effects were associated with intravascular HBB use[11, 12]. This study provides evidence that HBB significantly diminishes the duration of the active phase of the first stage of labor. In alignment with the 2018 World Health Organization recommendations[23], which revised the definition of the active phase of labor to commence at cervical dilation of 5 cm, the current study administered the drug when the cervix was dilated between 5-6 cm, while other studies[9-11] administered it at 3-5 cm. The observed mean time difference in this study, compared to other studies[9-11], suggests that administering the drug at an appropriately timed dilation can lead to a more substantial reduction in the duration of the active phase of the first stage of labor. Additionally, adverse effects from HBB were mild and manageable. Therefore, HBB emerges as a potential drug of choice for promoting cervical dilatation during the active phase of the first stage of labor.

Although, the current study showed no different effect to maternal and neonatal outcomes, but reducing 100 min in labor process could reduce not only the time that pregnant women suffered from labor pain which one of the most painful conditions that women typically experience in life but also stress during labor process that might have negative impact on the pregnancy mental health[22].

The main strengths of this study were that it was a randomized, double-blind, placebo-controlled trial with an adequate sample size. The study's limitations were that it lacked a cost-effectiveness analysis. Further studies are required to determine the effect of HBB in the difference of dosage, time to administration, and route of administration to reduce complications in prolonged labor.

Conclusion

In summary, compared to the placebo, intravascular hyoscine butylbromide significantly shortened the active phase of the first stage of labor without any adverse effect on maternal and neonatal outcomes.

Acknowledgments

We thank (a) the participants for their cooperation, (b) the labor room nursing staff and physicians for their assistance, (c) the staff from the Obstetrics and Gynecology Department at Khon Kaen Hospital for their support, (d) the pharmacist for preparing drug and placebo, and (e) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript under the aegis of the Publication Clinic, Research Affairs, Khon Kaen University.

Potential conflicts of interest

The authors declare no conflicts of interest.

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