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ORIGINAL ARTICLE

Effect of intravenous hyoscine-*N*-butyl bromide on active phase of labor progress: a randomized double blind placebo controlled trial

Serpil Kirim[1], Osman Asicioglu[1], Nazli Yenigul[1], Begum Aydogan[1], Neslihan Bahat[1], and Mehmet Bayrak[2]

[1]*Obstetrics and Gynecology Service, Sisli Etfal Research and Training Hospital, Istanbul, Turkey and* [2]*Deparment of Obstetrics and Gynecology, Medeniyet University, Istanbul, Turkey*

Abstract

Introduction: Appropriate cervical dilatation and effacement are essential for the progression of labor. With the active management of labor, number of cesarean deliveries reduces and the duration of labor shortens. Cervical dilatation can be facilitated by mechanical, pharmacological and non-pharmacologic methods. Cervix is richly supplied by autonomic nerves, which may play a role in the dilatation of cervix. Hyoscine-*N*-butylbromide (HBB) is a muscarinic antagonist and acts as a cervical spasmolytic agent. After intravenous administration it is rapidly distributed into the tissues. We aimed to study the effects and safety of a single dose 20 mg HBB injection during the active phase of labor in both primi- and multigravid women.
Materials and method: A randomized, double-blinded, controlled trial, with healthy primigravid and multigravid women in spontaneous labor at term was considered in this study. Once the active phase of labor was achieved, either a single dose of 20 mg (1 mL) of HBB or placebo (1 mL saline) was given intravenously.
Results: The mean duration of the first stage of labor was 191.1 ± 43.06 min in the primigravid patients of the HBB group, while it was 248.2 ± 66.1 min in the placebo group, a statistically significant difference of 57 min ($p < 0.001$). The mean duration of the first stage of labor was 170.1 ± 50.8 min in the multigravid patients of the HBB group, while it was 224.06 ± 53.7 min in the placebo group (difference of 54 min, $p < 0.001$). The mean duration of the first stage of labor was significantly different both for multigravida and primigravid patients. There was no significant change in the times for the second and third stages of labor. There were no significant differences in terms of APGAR scores noted at 1 and 5 min, prepartum and postpartum hemoglobin levels and birth weight. No adverse maternal and fetal effects were observed in both HBB and placebo groups.
Conclusion: A single dose of 20 mg intravenous HBB is effective and safe in shortening the duration of the first stage of labor without any adverse effects on fetus and mother.

Keywords

Active phase of labor, cervix, hyoscine-*N*-butylbromide (HBB), intravenous

History

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Introduction

The concept of active management of labor, first defined by O'Driscoll at the National Maternity Hospital, Dublin, Ireland, in 1968 [1], aims to shorten the duration of labor without increasing maternal or fetal morbidity and mortality. During labor, the fetal head progresses with the presence of regular uterine contractions. The intrauterine pressure generated by repeated uterine contractions and fetal head-to-cervix force plays a role in the cervical dilatation process. Cervical dilatation and effacement are important determinants of the duration of labor. Active management of labor can shorten the duration of labor and reduce the number of cesarean deliveries. Randomized studies have demonstrated the safety of active management of labor [2]. Cervical dilatation can be facilitated by mechanical, pharmacological, and non-pharmacological (i.e. herbal supplements) methods. Pharmacological methods include the use of prostaglandins in various formulations, oxytocin, analgesics, and smooth muscle relaxants. Various anti-spasmodic agents, including hyoscine-*N*-butylbromide (HBB), drotaverine hydrochloride, phloroglucinol, and valethamate bromide, can shorten the first stage of labor [3].

HBB is an anti-spasmodic and anti-cholinergic drug. It relieves spasms in the smooth muscle cells of the female genital tract, especially the cervico-uterine plexus [4,5]. HBB is a muscarinic antagonist that acts as a cervical spasmolytic agent. As it does not cross the blood–brain barrier, HBB does not have central anti-cholinergic action. After intravenous administration, it is rapidly distributed into the tissues, and acts as a cervical spasmolytic agent. Many studies have evaluated the effects of HBB on cervical dilatation, and the majority demonstrated its efficacy in augmenting labor [6–10]. However, Gupta et al. reported no effect of HBB on accelerating labor [11].

Address for correspondence: Dr. Nazli Yenigul, Obstetrics and Gynecology Service, Sisli Etfal Research and Training Hospital, Istanbul, Turkey. E-mail: drnaz84@yahoo.com

Therefore, the present study was performed to examine the effects and safety of a single dose 20 mg of intravenous HBB injection during the active phase of labor in both primigravid and multigravid women.

Materials and methods

This study was conducted at Sisli Etfal Research and Training Hospital, Istanbul, Turkey, between May 2012 and November 2012. Informed consent was obtained from all subjects prior to enrollment. The study was approved by the Institutional Human Ethics Committee. The study was designed as a double-blind, randomized, controlled trial comparing two groups according to intervention: intravenous 20 mg (1 mL) of HBB versus placebo (1 mL of saline) in both primigravid and multigravid female patients (NCT02098889).

Primigravid and multigravid women with singleton pregnancy were included in the study. All fetuses were at vertex presentation. All women were at term (gestational age range: 37–41 weeks), and they did not have a chronic or pregnancy-induced diseases. We excluded cases with premature membrane rupture, preeclampsia, eclampsia, placental abruption, placenta previa, abnormal placental attachment, twin pregnancy, non-cephalic presentation, previous uterine surgery, and cephalopelvic disproportion. During the study period, a total of 1620 patients were admitted to the antepartum unit of our hospital. Of these, 450 fulfilled the inclusion criteria, and 420 agreed to participate in the study. During the trial, 12 patients had cesarean delivery and 1 had vacuum-assisted vaginal delivery in the study group, while 23 and 2 patients, respectively, underwent these procedures in the control group. Therefore, 13 and 25 patients were excluded from the study and control groups, respectively. Finally, 382 women were analyzed (HBB group, $n = 197$; control group, $n = 185$). The subject flow diagram is shown in Figure 1. Randomization was performed using cards. The patients were randomized into two groups by using a sealed enveloped system. 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. Each syringe contained either 1 mL (20 mg) of HBB (Molit ampoule; Adeka, Istanbul, Turkey) or 1 mL of normal saline solution (placebo); both of the liquids were colorless. The participants, nurses, and physicians were all blinded to the syringe designation. The subjects received the contents of the syringe as a single dose given intravenously (i.v.).

A partogram was drawn and vaginal examinations were recorded every 2 h. The active phase of labor was defined as cervical dilatation of 4 cm and 50% cervical effacement in the presence of regular uterine contractions (2–3 contractions every 10 min). The drug was given only once when the active phase was achieved. Iatrogenic amniotomy was performed for patients who did not have spontaneous membrane rupture when cervical ripening was 8 cm. The durations of labor during the first, second, and third stages, oxytocin induction, iatrogenic amniotomy, pre- and post-partum hemoglobin levels, birth weight, and APGAR scores were recorded. Neonatal APGAR scores were determined 1 and 5 min after birth.

Primary outcome was assessment of shortening during the active phase of labor between HBB and placebo groups, and as a primary outcome measure the mean duration (min) of the first stage of labor was measured. Secondary outcome was evaluation of maternal and fetal outcomes, including prepartum–postpartum hemoglobin values, reporting of

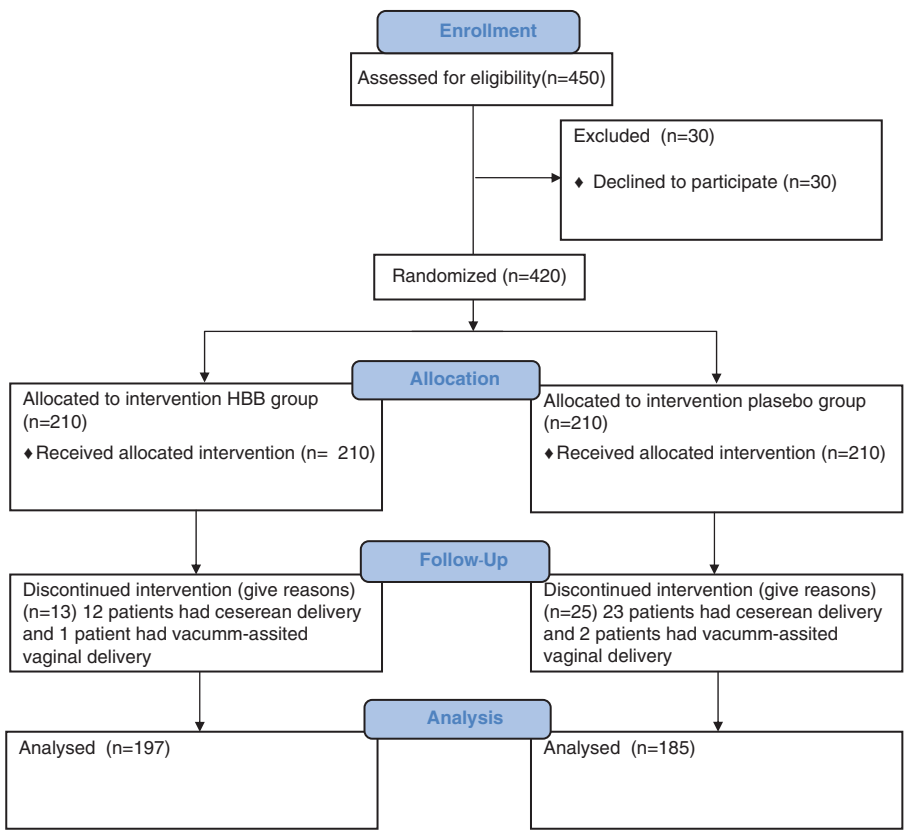

Figure 1. Consort 2010 – flow diagram.

vaginal lacerations, postpartum hemorrhage, chorioamnionitis, postpartum endometritis. APGAR scores were measured to determine the neonatal outcome.

At the start of this randomized controlled trial, we performed pilot trial of 25 patients in each group (placebo and HBB) before the full trial. First stage of labor was 190 ± 60.1 min in the HBB group and 220 ± 97.4 min in the placebo group. On the basis of these sample data, to keep the power of the study at 80% with an α level of 0.05, a sample size of 182 patients in each group was required.

All calculations and statistical analyses were performed using SPSS ver. 17 for Windows (SPSS Inc., Chicago, IL). One-sample Kolmogorov–Smirnov test was used to evaluate the normalilty of the data distribution. Categorical data were assessed using the chi-square test or Fisher's exact test (when chi-square was not applicable). Independent samples *t*-test and Mann–Whitney U-test were used for the comparison of numerical variables. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

A total of 420 patients were enrolled in the study; 38 were excluded from the study in both groups because of cesarean delivery and vacuum-assisted vaginal delivery. Thus, data for 382 patients were included in the analysis. Of these 382 patients, 197 received 1 mL (20 mg) of i.v. HBB and 185 received placebo (1 mL of saline solution). The demographic data of the study population are shown in Table 1. The mean age was 25.9 ± 6.1 in the HBB group and 26.1 ± 5.3 in the control group. The body mass index (BMI) was 27.2 ± 2.9 and 27.4 ± 2.17 in the HBB and placebo groups, respectively. According to parity, 95 primigravidas and 102 multigravidas received HBB, while 85 primigravidas and 100 multigravidas received placebo. There were no significant differences in terms of age, BMI, parity, or gestational age between the two groups (Table 1). The mean cervical ripening and effacement at intervention were 4.1 ± 0.4 cm and $61.7\% \pm 9.4\%$ in the HBB group, and 4.02 ± 0.35 cm and $65.5 \pm 8.5\%$ in the placebo group, respectively. At the time of spontaneous membrane rupture, cervical ripening was 6.9 ± 0.49 cm in the HBB group and 6.8 ± 0.52 cm in the placebo group. When cervical ripening of 8 cm had been achieved, iatrogenic membrane rupture was performed in 48 (24%) and 43 cases (23%) in the HBB and placebo groups, respectively. A total of 90 cases (45.7%) in the HBB group and 88 cases (47.6%) in the placebo group were given oxytocin induction (Table 2). The mean duration of the first stage of labor was 191.1 ± 43.06 min in the primigravid subjects in the HBB group compared with 248.2 ± 66.1 min in the placebo group; the difference of 57 min was statistically significant ($p < 0.001$; Table 3). The mean duration of the first stage of labor was 170.1 ± 50.8 min in the multigravid subjects in the HBB group compared with 224.06 ± 53.7 min in the placebo group; the difference of 54 min was statistically significant ($p < 0.001$). The mean duration of the first stage of labor was significantly different for both multigravid and primigravid subjects. There were no significant differences in the times for the second and third stages of labor (Table 3).

Neonatal outcomes, APGAR scores, birth weight, and blood loss were compared among groups. There were no significant differences in terms of APGAR scores at 1 and 5 min, prepartum and postpartum hemoglobin levels, and birth weight between the two groups (Table 4). The mean APGAR scores at 1 min were 8 ± 0.4 and 8.1 ± 0.3 in the HBB group and the placebo group, respectively. The mean APGAR scores at 5 min were 9.1 ± 0.3 and 9.16 ± 0.35 in HBB and placebo groups, respectively.

No adverse maternal or fetal effects were observed in either the HBB or placebo group.

Discussion

The present study demonstrated a significant decrease in duration of the first stage of labor when a single 20-mg (1 mL) intravenous dose of HBB was injected during the active phase of labor.

The aim of the active management of labor is to shorten the duration of labor without increasing maternal or fetal morbidity and mortality. Cervical dilatation can be facilitated

Table 1. The demographic data of the study population.

	HBB group (*n*:197)	Control group (*n*:185)	*p* value	RR (CI %5)
Maternal age (years) (±SD)	25.90 ± 6.11	26.18 ± 5.31	0.606	–
Body mass index (kg/m^2) (±SD)	27.23 ± 2.92	27.42 ± 2.17	0.353	–
Gestational age (weeks) (±SD)	38.99 ± 1.05	38.94 ± 0.99	0.827	–
Primigravid subjects (*n*,%)	95 (48.2%)	85 (45.9%)	0.656	0.95 (0.77–1.26)

±SD, standard deviation; RR, relative risk; CI, confidence interval.
p value <0.05 statistically significant.

Table 2. Parameters related with the active phase of labor.

	HBB group (*n*:197)	Control group (*n*:185)	*p* value	RR (CI %5)
Cervical dilatation (cm) (±SD)	4.16 ± 0.41	4.02 ± 0.35	0.710	–
Cervical effacement (%) (±SD)	61.74 ± 9.45	65.51 ± 8.52	0.164	–
Cervical ripening at the time of spontaneous membrane rupture (cm) (±SD)	6.98 ± 0.49	6.81 ± 0.52	0.498	–
Number of patients with iatrogenic membrane rupture (*n*,%)	48 (24%)	43 (23%)	0.797	0.95 (0.66–1.36)
Augmentation of labor with oxytocin (*n*,%)	90 (45.7%)	88 (47.6%)	0.712	1.04 (0.84–1.29)

±SD, standard deviation; RR, relative risk; CI, confidence interval. *p* value <0.05 statistically significant.

Table 3. Duration of labor among groups.

	HBB group (*n*:197)	Control group (*n*:185)	*p* value	RR (CI %5)
First stage of labor* (min.)				
Primigravid subjects (±SD)	191.13 ± 43.06	248.21 ± 66.16	<0.001	–
Multigravid subjects (±SD)	170.10 ± 50.87	224.06 ± 53.76	<0.001	–
Second stage of labor (min.) (±SD)	13.24 ± 4.51	14.16 ± 3.86	0.180	–
Third stage of labor (min.) (±SD)	16.88 ± 3.81	18.76 ± 4.63	0.601	–

±SD, standard deviation; RR, relative risk; CI, confidence interval. *p* value <0.05 statistically significant.
*The duration of the active phase.

Table 4. Postpartum comparison of the groups.

	HBB group (*n*:197)	Control group (*n*:185)	*p* value	RR (CI %5)
APGAR score at 1 min (±SD)	8.09 ± 0.41	8.16 ± 0.37	0.064	–
APGAR score at 5 min (±SD)	9.11 ± 0.38	9.16 ± 0.35	0.151	–
Birth weight (g) (±SD)	3351 ± 366	3338 ± 349	0.924	–
Prepartum hemoglobin levels (g/dL) (±SD)	11.58 ± 1.41	11.67 ± 1.27	0.501	–
Postpartum hemoglobin levels (g/dL) (±SD)	10.31 ± 0.81	10.24 ± 0.96	0.489	–

±SD, standard deviation; RR, relative risk; CI, confidence interval. *p* value <0.05 statistically significant.

by mechanical, pharmacological, and non-pharmacological methods. Pharmacological methods include the use of prostaglandins, oxytocin, analgesics, and smooth muscle relaxants. Appropriate cervical dilatation and effacement are essential for the progression of labor. The cervix is richly supplied by autonomic nerves, which may play a role in cervical dilatation. HBB is a derivative of hyoscine, which is extracted from the leaves of the Duboisia tree, and is a peripherally acting anti-cholinergic drug that blocks the action of acetylcholine at parasympathetic sites in smooth muscles and in secretory glands. Oral (tablets) and parenteral (intramuscular, intravenous, rectal suppository) forms are available. After i.v. injection, HBB shows rapid uptake into the tissues ($t_{1/2} = 29$ min). It has high affinity for cholinergic receptors, and has been used in varying doses (20 and 40 mg) and via different routes. Corsen et al. investigated the usage of HBB in management of labor and reported that the most convenient use is the administration of drug at cervical dilatation of 2.5–3 cm [12]. The majority of studies of the effects of HBB on cervical dilatation demonstrated its efficacy in augmenting labor [6–10]. However, Gupta et al. reported no effect of HBB on accelerating labor [11].

A total of 129 female patients were enrolled in a previous randomized double-blind study, and 69 received the placebo, while 60 received 20 mg intravenous HBB [10]. The study population consisted of both primigravid and multigravid subjects; 34 primigravidas and 35 multigravidas received the placebo, while 29 primigravidas and 31 multigravidas received HBB. In the present study, the HBB group consisted of 95 primigravidas and 102 multigravidas, while the placebo control group consisted of 85 primigravidas and 100 multigravidas. The mean duration of the first stage of labor was 228 min in their placebo group and 156 min in the HBB group, a significant decrease of 31.7%. In the present study, the mean duration of the first stage of labor was 191.1 ± 43.06 min in the primigravid subjects in the HBB group compared with 248.2 ± 66.1 min in the placebo group; this difference of 57 min was statistically significant. The mean duration of the first stage of labor was also shortened in multigravid subjects (Table 3). They did not observe any significant difference in the duration of the second or third stage of labor, which is consistent with our findings. Makvandi et al. conducted a randomized double-blinded study in a population of 130 primigravid patients (65 test subjects, 65 controls) to evaluate the effects of a single dose of 20 mg of rectal HBB during labor [13]. They found that both the active phase and the second stage of labor were significantly shorter in the HBB group compared to the placebo controls. There were no significant differences in fetal or maternal heart rate and neonatal APGAR scores between the two groups. In the present study, the mean 5-min Apgar score was 9.11 ± 0.38 in the HBB group, and there were no significant differences in Apgar score between the two groups.

In a previous study, 100 patients received 20 mg of i.v. HBB, 100 patients received 8 mg of valethamate bromide (epidosin) every 20 min at 4-cm dilatation, and 100 patients received no drug. Significant shortening of the first stage of labor in primigravid subjects was observed in both medication groups compared to the controls [14]. In another study, 100 patients received HBB suppositories and 100 received no drug in the first stage of labor [9]. The duration of the first stage of labor was decreased in the HBB group. There were no differences in the duration of the second or third stage of labor between the two groups. Qahtani et al. performed a study in a population of primiparous patients, among whom 52 received 40 mg of i.v. HBB and 45 received placebo. The mean duration of the first stage of labor was significantly reduced in the HBB group (23.3%), but no significant differences were observed in the durations of the second or third stages of labor between the two groups [15]. In another study, 20 mg of i.v. HBB were administered to multiparous patients in the active phase of labor [16]. The durations of both the first and second stage of labor were shorter in the HBB group compared to the controls. On the other hand, some authors concluded that the duration of the active phase was not altered in female patients receiving HBB.

Gupta et al. enrolled 150 patients in a study in which 50 received drotaverine, 50 received HBB, and 50 received no medication [11]. The study population included primigravid and multigravid patients, and 20 mg (1 mL) of i.v. HBB were given every 30 min for a maximum of three doses. However, in the present study, we injected a single dose of HBB. They reported that the mean duration of the active phase of labor and the mean rate of cervical dilation did not differ between the two groups. They also reported side effects, such as nausea, in 20% of cases. In the present study, however, we did not observe any side effects. Mortazavi et al. also reported a longer first stage of labor with the application of intramuscular HBB [17]. Iravani et al. conducted a study in 100 primigravid patients with injection of 20 mg of i.v. HBB versus placebo for the active management of labor [18]. They observed fetal heart rate variation in 24% of fetuses in the HBB group (8% bradycardia and 16% tachycardia). No such fetal heart rate variation was observed in the present study, which may have been due to the method of drug application used; we injected HBB at the time of uterine contractions.

In a recent Cochrane analysis [19], 17 trials ($n = 2617$) were included in the meta-analysis. The anti-spasmodics used included valethamate bromide, HBB, drotaverine hydrochloride, rociverine, and camylofin dihydrochloride. Thirteen trials ($n = 1995$) indicated that the duration of the first stage of labor was significantly reduced by an average of 74.34 min when anti-spasmodics were administered (95% confidence interval (CI): 98.76–49.93). Seven studies ($n = 797$) reported on the total duration of labor, which was significantly reduced by an average of 85.51 min. Six studies ($n = 820$) had data regarding outcome: the rate of cervical dilatation was significantly increased by an average of 0.61 cm/h. Anti-spasmodics did not affect the duration of the second or third stage of labor. Heterogeneity of the data was investigated by subgroup analyses, but remained unexplained. Maternal and neonatal adverse events were not reported in all studies. The meta-analysis indicated low-quality evidence that anti-spasmodics reduce the duration of the first stage of labor and increase the cervical dilatation rate.

Most of the trials reported in the literature were randomized, used different administration routes (intravenous or rectal), and the parity differed among the study groups. Some of the studies were conducted only in primigravid [13] or multigravid [16] subjects. The present study included both primigravid and multigravid subjects. Some of the studies excluded subjects who underwent cesarean delivery during the study, while others included participants undergoing cesarean section in calculation of the mean duration of labor. In the present study, we excluded subjects who underwent cesarean section and assisted vaginal delivery.

The main limitation of the present study was that we included only healthy singleton pregnancies. We excluded cases with premature membrane rupture, twin pregnancy, non-cephalic presentation, and previous uterine surgery. Vaginal birth after cesarean section is becoming more common, and the effects of HBB should be investigated in such cases. In contrast, our sample size was the largest among the studies reported to date, the study was conducted at a single tertiary center, was randomized in a double-blind manner, and the subjects were followed-up by the same individual.

In conclusion, a single dose of 20 mg of i.v. HBB is both an effective and safe means of shortening the duration of the first stage of labor without any adverse effects on the fetus or mother. Further studies are required to evaluate the effects of repeated HBB administration on female patients with active phase arrest and the effects on vaginal birth after cesarean section. The effects of HBB in subjects with epidural anesthesia-assisted vaginal labor should also be investigated in future studies.

Declaration of interest

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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