

**Supplementary Table S1** Investigated studies

No.	First author last name	Publication date	Journal	Title
1	Maged	March 2015	Journal of Maternal Fetal & Neonatal Medicine	Carbetocin vs. oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high-risk women
2	Maged	June 2015	Reproductive Sciences	Delayed start vs. conventional GnRH antagonist protocol in poor responders pretreated with estradiol in luteal phase: a randomized controlled trial
3	Maged	December 2015	International Journal of Gynaecology Obstetrics	A randomized placebo controlled trial of preoperative tranexamatic acid among women undergoing elective cesarean delivery
4	Maged	August 2015	Gynaecological Endocrinology	The adjuvant effect of metformin and N-acetylcysteine to clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome
5	Maged	February 2016	Reproductive Sciences	Endometrial scratch injury induces higher pregnancy rate for women with unexplained infertility undergoing IUI with ovarian stimulation: a randomized controlled trial
6	Maged	May 2016	Archives of Gynaecology and Obstetrics	Carbetocin vs. oxytocin in the management of atonic postpartum hemorrhage after vaginal delivery: a randomized controlled trial
7	Maged	December 2016	Journal of Maternal Fetal & Neonatal Medicine	Role of antioxidants in gestational diabetes mellitus and relation to fetal outcome: a randomized controlled trial
8	Maged	April 2017	Journal of Maternal Fetal & Neonatal Medicine	Carbetocin vs. syntometrine for prevention of postpartum hemorrhage after cesarean section
9	Maged	August 2017	Taiwanese Journal of Obstetrics and Gynaecology	Effect of oral contraceptives on balance in women: a randomized controlled trial
10	Maged	August 2017	Journal of Maternal Fetal & Neonatal Medicine	The effect of HBB on the duration and progress of labor in primigravidae: a randomized controlled trial
11	Maged	February 2018	International Journal of Gynaecology Obstetrics	Randomized controlled trial of the effect of endometrial injury on implantation and clinical pregnancy rate during the first ICSI cycle
12	Maged	February 2018	The European Journal of Contraception and Reproductive Health care	Benefit of vaginal misoprostol prior to IUD insertion in women with previous cesarean delivery: a randomized controlled trial
13	Maged	April 2018	Archives of Gynaecology and Obstetrics	Effect of swimming exercise on premenstrual syndrome
14	Maged	June 2018	Journal of Maternal Fetal & Neonatal Medicine	Subcuticular interrupted vs. continuous skin suturing in elective cesarean section in obese women: a randomized controlled trial
15	Maged	June 2018	Taiwanese Journal of Obstetrics and Gynaecology	Comparison of local and intravenous dexamethasone on postoperative pain and recovery after cesarean section: a randomized controlled trial
16	Maged	October 2018	Reproductive Sciences	Effect of prolonged GnRH agonist downregulation of ICSI outcomes in patients with endometriomas less than 5 cm: a randomized controlled trial
17	Maged	May 2019	Journal of Maternal Fetal & Neonatal Medicine	The value of aminopatch in pregnancies associated with spontaneous preterm premature rupture of fetal membranes: a randomized controlled trial

**Supplementary Table S1** (Continued)

No.	First author last name	Publication date	Journal	Title
18	Maged	July 2019	American Journal of Perinatology	Effect of low level laser therapy vs. electroacupuncture for postnatal scanty milk secretion: a randomized control trial
19	Shaltout	July 2019	Journal of Ovarian Research	A randomized controlled trial of a new technique for laparoscopic management of ovarian endometriosis preventing recurrence and keeping ovarian reserve
20	Maged	July 2019	International Journal of Gynaecology Obstetrics	A randomized controlled trial of the safety and efficacy of preoperative rectal misoprostol for preventing of intraoperative and postoperative blood loss at elective cesarean delivery
21	Shoab	October 2019	International Journal of Gynaecology Obstetrics	The value of endocervical and endometrial lidocaine flushing before office hysteroscopy: a randomized control trial
22	Maged	December 2019	International Journal of Gynaecology Obstetrics	Carbetocin vs. rectal misoprostol for management of third stage of labor among women with low risk of postpartum hemorrhage

Abbreviations: HBB, hyoscine butylbromide; GnRH, gonadotropin-releasing hormone agonists; ICSI, intracytoplasmic sperm injection; IUD, intrauterine device; IUJ, intrauterine insemination.

<b>Supplementary Table S2</b> Bibliographic comparison of Gebril 2017 and Maged 2017	
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<b>Author affiliations</b> Obstetrics and Gynecology Department, Al Azhar University, Cairo Egypt, Agouza Hospital, Giza, Egypt	<b>Author affiliations</b> Obstetrics and Gynecology Department Kasr Aini Hospital Cairo University
<b>Title</b> Role of intravenous hyoscine butylbromide injection on the duration and progress of first stage of labor in primigravidae	<b>Title</b> The effect of hyoscine butylbromide on the duration and progress of labor in primigravidae: a randomized controlled trial
The Egyptian Journal of Hospital Medicine (October 2017) Vol.69, Page 2052–2058	The Journal of Maternal–Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2017.1359828
<b>Study center</b> Outpatient Gynaecological Clinic at Al Azhar University Maternity Hospital	<b>Study center</b> Conducted at Kasr Alainy Medical School at Cairo University
<b>Conducted</b> Between January 2017 and June 2017	<b>Conducted</b> July 2015 to December 2016
<b>Submitted</b> April 2, 2017 (note the inconsistency between submission date and the end of recruitment)	<b>Submitted</b> April 7, 2017
150 women  Group A: 50 pregnant patients received 2 mL of normal saline intravenously as a placebo Group B: 50 pregnant patients received (20 mg) hyoscine butylbromide (1 mL HBB + 1 mL saline) intravenously Group C: 50 pregnant patients received 2 mL (40 mg) hyoscine butylbromide intravenously	120 women  20 mg hyoscine butylbromide, $n = 40$ 40 mg hyoscine butylbromide, $n = 40$ 2 mL of normal saline $n = 40$

**Supplementary Table S3** Clinical trial registration of 22 randomized controlled trials and study period

No.	Study	Registration Start	Registration End	Study period (M = Y)	Date registered (DMY)	Article submission (MY)	No. randomized per month
1	Maged 2015a	May 2013	December 2014	January 2014	January 2015	10	
2	Maged 2015b	January 2014	April 2015	November 2013	NA	10	
3	Maged 2015c	ACTRN12615000312549 <sup>a</sup>	March 2014	September 2012	January 2015	17	
4	Maged 2015d	January 2010	January 2015	January 2014	January 2015	6	
5	Maged 2016a	NCT02349750 <sup>a</sup>	January 2013	June 2014	January 29, 2015	NA	3
6	Maged 2016b	NCT02304055	January 2013	January 2015	December 1, 2014	May 2015	5
7	Maged 2016c	NCT0235197 <sup>a</sup>	January 2013	July 2015	February 4, 2015	January 2016	8
8	Maged 2017a	NCT0204549	January 2015	December 2015	January 24, 2015	February 2016	16
9	Maged 2017b	NCT02855294 <sup>a</sup>	January 2015	July 2016	August 4, 2016	NA	11
10	Maged 2017c	NCT03430362 <sup>a</sup>	July 2015	December 2016	February 12, 2018	April 2017	7
11	Maged 2018a	NCT02660125	January 2016	Mar 2017	January 21, 2016	May 2017	20
12	Maged 2018b	NCT03081442	April 2017	November 2017	March 16, 2017	November 2017	15
13	Maged 2018c	NCT03264612 <sup>a</sup>	April 2016	May 2017	August 29, 2017	October 2017	7
14	Maged 2018d		April 2017	December 2018	March 2018	December 2017	10
15	Maged 2018e	NCT02784340 <sup>a</sup>	May 2014	December 2015	May 27, 2016	December 2017	6
16	Maged 2018f		April 2016	October 2017	NA	5	
17	Maged 2019a	NCT03473210 <sup>a</sup>	January 2016	December 2017	March 22, 2018	November 2018	5
18	Maged 2019b	NCT03806062 <sup>a</sup>	January 2018	December 2018	January 16, 2019	April 2019	5
19	Shaltout 2019	NCT02947724	October 2016	January 2019	October 28, 2016	January 2019	8
20	Maged 2019c	NCT03680339	September 2018	February 2019	September 21, 2018	January 2019	36
21	Shoab 2019	NCT03530488	May 2018	February 2019	May 21, 2018	March 2019	26
22	Maged 2019d	NCT03556852	July 2018	May 2019	June 14, 2018	June 2019	14

Abbreviation: NA, not applicable.  
<sup>a</sup>Retrospective registration.

<b>Supplementary Table S4</b> Other investigated studies				
Other	Gebril	October 2017	The Egyptian Journal of Hospital Medicine	Role of intravenous hyoscine butylbromide injection on the duration and progress of first stage of labor in primigravidae

<b>Supplementary Table S5</b> Textual similarities between Gebril 2017 and Maged 2017				
<b>Abstract</b>				<b>Abstract</b>
<p><b>Background:</b> Labor is a physiologic process that results in expulsion of the products of conception outside the uterus throughout three stages. It is achieved with changes in the biochemical connective tissue and with gradual effacement and dilatation of the uterine cervix as a result of rhythmic uterine contractions of sufficient frequency, intensity, and duration. HBB belongs to the parasympatholytic group of drugs and is a semisynthetic derivative of scopolamine. It is a quaternary ammonium derivative, which exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary, and genitourinary tracts.</p> <p><b>Methods:</b> A case-control study conducted on 150 women coming to Al Azhar University Maternity Hospital. Patients who meet the inclusion criteria were asked to participate in the study and a verbal consent was obtained from each patient. Patients were divided into three equal groups (A, B, and C). A single dose of the drug (placebo or HBB of 20 mg or HBB of 40 mg) was injected intravenously slowly to groups A, B, and C, respectively. Laboring mothers were monitored in bed. Vaginal examination was conducted every 2 h. The duration of the first stage was calculated from the time of cervical dilatation of 3 to 4 cm in active labor until a fully dilated cervix was observed</p> <p><b>Results:</b> The study showed significant difference between the three groups regarding the progress of labor. There was a significant decrease in the duration of the active phase of first stage of labor in study groups who received HBB compared to placebo group. The decrease in the duration of active phase of first stage of labor was not related to the drug dose. There was no significant difference between the three groups regarding the second stage duration. There were no significant adverse effects of HBB on either mothers or neonates.</p> <p><b>Conclusion:</b> HBB helps to decrease the duration of active phase of labor in primigravida with no side effects on either the mother or the neonate. This decrease is not related to the dose of the drug. HBB belongs to the parasympatholytic group of drugs and is a semisynthetic derivative of scopolamine. It is a quaternary ammonium derivative, which exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary, and genitourinary tracts. Role of intravenous HBB injection on the duration and progress of first stage of labor in primigravida</p>				Objective: The study aimed to assess the effect of HBB on duration of the first stage of labor in primigravida.
				Methods: A case-control study conducted on 120 primigravida at term admitted in active labor were divided into three equal groups. A single dose of the drug (placebo or HBB of 20 mg or HBB of 40 mg) was injected intravenously slowly to groups A, B, and C, respectively. The duration of the first stage was calculated from the time of cervical dilatation of 3 to 4 cm in active labor until a fully dilated cervix was observed.
				Results: The duration of first stage was significantly shorter in women receiving 20 and 40 mg of HBB when controlled to control women ( $187.73 \pm 20.92$ , $186.41 \pm 19.40$ vs. $231.39 \pm 33.14$ min). There was no significant difference between the three study groups regarding duration of second stage ( $36.76 \pm 9.98$ , $35.72 \pm 9.97$ , and $37.55 \pm 10.57$ , respectively, $p > 0.05$ ), number of cases delivered by cesarean section (12.5, 12.5, and 15%, respectively, $p > 0.05$ ) and Apgar's score of the neonates ( $p > 0.05$ ). There was no significant difference between the three study groups regarding occurrence of side effects named dry mouth (7.5, 12.5, 5%, respectively, $p > 0.05$ ), flushing (2.5, 5 and 0%, respectively, $p > 0.05$ ), tachycardia (2.5, 2.5, and 2.5% respectively, $p > 0.05$ ) or urinary retention (2.5, 0 and 0% respectively, $p > 0.05$ ).
				Conclusion: Intravenous injection of HBB decreases the duration of active phase of labor in primigravida with no side effects.
				Keywords: normal labor, augmentation of labor, HBB
<b>Introduction</b>				<b>Introduction</b>
<p>Normal labor is a continuous process which has been divided into three stages for the purposes of study, with first stage further subdivided into two phases. The first stage of labor is the interval between the onset of labor and full cervical dilatation. The second stage of labor is the interval between full cervical dilatation and delivery of the fetus. The third stage of labor is the period between the delivery of the fetus and delivery of the placenta.<sup>1</sup></p> <p>The first stage begins with regular uterine contractions and ends with complete cervical dilatation at 10 cm. First stage is divided according to Friedman's landmark studies of 500</p>				Parturition can be arbitrarily divided into four overlapping phases that correspond to the major physiological transitions of the myometrium and cervix during pregnancy. <sup>1</sup> These phases of parturition include a prelude to it, the preparation for it, the process itself, and recovery. <sup>2</sup>
				The first stage begins when spaced uterine contractions of sufficient frequency, intensity, and duration are attained to bring about cervical thinning or effacement. This labor stage ends when the cervix is fully dilated—about 10 cm—to allow passage of the term-sized fetus. The first stage of labor therefore is the stage of cervical effacement and dilatation. <sup>2</sup>

**Supplementary Table S5** (Continued)

<p>nulliparous women into an early latent phase and an ensuing active phase. The latent phase starts with mild, irregular uterine contractions that soften and shorten the cervix. The contractions become progressively more rhythmic and stronger. This is followed by the active phase of labor, which usually begins at about 3 to 4 cm of cervical dilation and is characterized by rapid cervical dilatation and descent of the presenting fetal part.<sup>2</sup> Measurement of the length of labor is inherently imprecise for several reasons. The starting point cannot be identified by objective means. The cervix undergoes various structural alterations in late pregnancy, and women do not begin labor with identical cervical anatomy. Labor onset is a self-diagnosis, and women vary in their recognition and response to painful contractions. As such, the duration of the latent phase is particularly difficult to quantify. Therefore, cervical dilatation on admission to the hospital is often used as the first data point.<sup>3</sup> The principle of active management of labor was introduced in Dublin to shorten the length of labor while achieving or maintaining a low rate of cesarean delivery, the active management of labor refers to active control, rather than passive observation over the course of labor by the obstetric provider.<sup>4</sup></p> <p>When necessary obstetricians use cervical ripening agents to decrease the duration of labor. Intravaginal misoprostol (prostaglandin E1 analog) and dinoprostone (prostaglandin E2) are the most commonly used agents for cervical ripening.<sup>5</sup> Hyoscine-N-butylbromide is a derivative of hyoscine which is extracted from leaves of the Duboisia tree found mainly in Australia. It is known by its spasmolytic action and has been arisen since 1951.<sup>6</sup> HBB belongs to the parasympatholytic group of drugs and is a semisynthetic derivative of scopolamine. It is an effective antispasmodic drug without the untoward side effects of atropine as it does not cross the blood-brain barrier; therefore, no central action is seen. It is a quaternary ammonium</p>	<p>The progress of labor in nulliparas has particular significance because curves reveal a rapid change in the slope of cervical dilatation rates between 3 and 5 cm. Thus, cervical dilatation of 3 to 5 cm or more, in the presence of uterine contractions, can be taken to reliably represent the threshold for active labor. The mean duration of active-phase labor in nulliparas was 4.9 h. But the standard deviation of 3.4 h is large, hence, the active phase was reported to have a statistical maximum of 11.7 h.<sup>3</sup> Indeed, rates of cervical dilatation ranged from a minimum of 1.2 up to 6.8 cm/h. The ideal management of labor and delivery requires two potentially opposing viewpoints on the part of clinicians. First, birthing should be recognized as a normal physiological process that most women experience without complications. Second, intrapartum complications, often arising quickly and unexpectedly, should be anticipated.<sup>4</sup></p> <p>According to Orji (2008), the WHO partograph is similar for nulliparas and multiparas. Labor is divided into a latent phase, which should last no longer than 8 h, and an active phase. The active phase starts at 3 cm dilatation, and progress should be no slower than 1 cm/h. A 4-h wait is recommended before intervention when the active phase is slow.<sup>5</sup> Lavender and colleagues (2006) randomized 3,000 nulliparous women to labor interventions at 2 vs. 4 h as recommended by WHO.<sup>6</sup> More than 30 years ago, O'Driscoll and associates (1984) pioneered the concept that a disciplined, standardized labor management protocol reduced the number of cesarean deliveries for dystocia. Their overall cesarean delivery rate was 5% in the 1970s and 1980s with such management.<sup>7</sup> The approach is now referred to as active management of labor. Two of its components—amniotomy and oxytocin—have been widely used.</p> <p>Wei and associates (2009) in a Cochrane database review found a modest reduction in cesarean delivery rates when active management of labor was compared with standard care.<sup>8</sup> Frigoletto and coworkers (1995) reported another randomized trial with 1934 nulliparous women at Brigham and Women's Hospital in Boston. Although they found that such management somewhat shortened labor, it did not affect the cesarean delivery rate.<sup>9</sup> These observations have since been reported by many others.<sup>10</sup> Oxytocin has amino acid homology similar to arginine vasopressin. Because of this, it has significant antidiuretic action, and when infused at doses of 20 mU/min or more, renal free water clearance decreases markedly. If aqueous fluids are infused in appreciable amounts along with oxytocin, water intoxication can lead to convulsions, coma, and even death.<sup>11</sup> The American College of Obstetricians and Gynecologists recommends the use of amniotomy to enhance progress in active labor, but cautions that this may increase the risks of infection and maternal fever.<sup>12</sup></p> <p>When necessary obstetricians use cervical ripening agents to decrease the duration of labor. Intravaginal misoprostol (prostaglandin E1 analog) and dinoprostone (prostaglandin E2) are the most commonly used agents for cervical ripening.<sup>13</sup> Hyoscine-N-butylbromide is a derivative of hyoscine which is extracted from leaves of the Duboisia tree found mainly in Australia. It is known by its spasmolytic action and has been arose since 1951.<sup>14</sup> HBB belongs to the parasympatholytic group of drugs and is a semisynthetic derivative of scopolamine. It is an effective antispasmodic drug without the untoward side effects of atropine as it does not cross the blood-brain barrier; therefore, no central action is seen. It is a quaternary ammonium</p>
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**Supplementary Table S5** (Continued)

	<p>derivative, which exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary, and genitourinary tracts.<sup>15</sup> It acts primarily by blocking the transmission of neural impulses in the intraneuronal parasympathetic ganglia of abdominal organs, apparently inhibiting cholinergic transmission in the synapses of the abdominal and pelvic parasympathetic ganglia, thus relieving spasms in the smooth muscles of gastrointestinal, biliary, urinary tract, and female genital organs, especially the cervico-uterine plexus, thus aiding cervical dilatation.<sup>16</sup></p> <p>The aim of this study is to assess whether the intravenous injection of HBB is effective in hastening cervical dilatation, thus shortening the duration of the first stage of labor in primigravidae.</p>
<b>Results</b>	<b>Results</b>
This study was conducted at Al Azhar University Maternity Hospital during the period between January 2017 and June 2017. A total of 150 primigravid women in the active phase of the first stage of labor were recruited in this study. Patients who met the inclusion criteria were asked to participate in the study and a verbal consent was obtained from each patient. Patients were divided into three equal groups, each group consisted of 50 patients. Group A: received 2 mL of normal saline intravenously as a placebo. Group B: received 20 mg (HBB (1 mL HBB + 1 mL saline) intravenously. Group C: received 2 mL (40 mg) HBB intravenously.	There was no significant difference between the three study groups regarding age, weight, height, or gestational age ( <b>Table 1</b> ). The duration of first stage was significantly shorter in women receiving both doses of HBB when controlled to control women ( <b>Table 2</b> ). There was no significant difference between the three study groups regarding duration of second stage, neonatal birth weight, number of cases delivered by cesarean section, and Apgar's score of the neonates ( <b>Table 2</b> ). There was no significant difference between the three study groups regarding occurrence of side effects named dry mouth, flushing, tachycardia, or urinary retention ( <b>Table 3</b> ). The women excluded from the study and the causes of exclusion are shown in <b>Table 4</b> .
(1) Duration of active phase of first stage of labor.	
The duration of active phase was measured from the point of cervical dilatation of 3 to 4 cm to full dilatation. Comparing range, mean and SD of the duration of active phase of first stage of labor between control group and group, which was given 20 mg of HBB showing statistically significant differences ( <i>p</i> -value < 0.05), which indicates the effect of HBB on the course of labor. Comparing range, mean and SD of the duration of active phase of first stage of labor between control group and group, which was given 40 mg of HBB showing statistically significant differences ( <i>p</i> -value < 0.05), which indicates the effect of HBB on the course of labor. Comparing range, mean and SD of the duration of active phase of first stage of labor between group which was given 20 mg of HBB and group which was given 40 mg of HBB showed no statistically significant differences ( <i>p</i> -value > 0.05), which indicated that the dose of the drug has minor effect on the duration of active phase of first stage of labor.	
Neonatal outcome	
Fetal weight was measured after delivery. The insignificant <i>p</i> -value (>0.05) indicated that fetal weight had no effect on the study results. Apgar's score was measured after delivery. The insignificant <i>p</i> -value (>0.05) indicated that the HBB has no effect on neonatal well-being.	
Side effects of hyoscine-N-butylbromide	
The following table showed the common side effects of HBB and their prevalence among study groups. There were no statically significant differences between study groups concerning side effects.	
<b>Discussion</b>	<b>Discussion</b>
The management of normal labor is both an art and a science. Prolongation of labor is one such dilemma that every obstetrician tries to avoid.	The management of normal labor is both an art and a science. Prolongation of labor is one such dilemma that every obstetrician tries to avoid.
The ultimate aim of the obstetrician is to accomplish the delivery in the shortest possible time without compromising maternal and fetal safety.	The ultimate aim of the obstetrician is to accomplish the delivery in the shortest possible time without compromising maternal and fetal safety.
For decades, health providers have worked for shortening the duration of painful labor. Reduction of cesarean sections and	For decades, health providers have worked to manage labor actively and safely, with the goal of shortening the duration of

**Supplementary Table S5** (Continued)

<p>other fetal and maternal complications is also an important aspect of labor management.<sup>9</sup></p> <p>Active management of labor was introduced in 1960s as a method to prevent prolonged labor.</p> <p>Prolonged labor is one of the most important risk factors for perinatal compromise and, if caused by obstructed labor, it carries the risk of uterine rupture, postpartum hemorrhage. The two major factors that determine duration of labor are uterine contractility and rate of cervical dilation.<sup>10</sup></p> <p>Spasmolytic drugs are frequently employed in India to overcome cervical spasm and thus reduce the duration of labor. One of these spasmolytics is hyoscine-N-butylbromide, which has been used to shorten the duration of labor. It exerts a spasmolytic action on the smooth muscle of the gastrointestinal tract, biliary and genitourinary tracts.<sup>11</sup></p> <p>The study was done on age group ranging from 18 to 35 years old, patients aging less than 18 years or more than 35 years were excluded from our study as pregnancy in this age group consider high risk pregnancy.<sup>12</sup> Patients with occiput posterior position were excluded from the study as this position is associated with prolonged first and second stages of labor.</p> <p>Al Qahtani and Al Hajeri<sup>7</sup> conducted a randomized, double blind, controlled trial. Ninety-seven primigravid term pregnant women in spontaneous labor received either HBB or a placebo intramuscularly once the women entered the active phase of labor.</p> <p>A total of 97 women yielded data for analysis. Of these, 45 women received the placebo and 52 received HBB.</p> <p>The mean duration of the first stage in the control group was 215 min, compared with 165 min in the study group, representing a decrease of 23.3% (<i>p</i>-value = 0.001). There were no significant changes in the duration of the second (<i>p</i>-value = 0.063) or third (<i>p</i>-value = 0.0618) stages of labor.</p> <p>The difference in result may be because different administrative route.</p> <p>The results of the current study are compatible with results of Samuel et al<sup>4</sup> in their randomized, double-blinded a total of 129 women yielded data for analysis. Of these, 69 women received the placebo and 60 received 20 mg of HBB intravenously in the beginning of active phase of first stage of labor. The mean time for the first stage in the control group was 228 min, compared to 156 min in the drug group, representing a decrease of 31.7% (<i>p</i>-value = 0.001). There was no significant change in the duration of the second and third stages of labor.</p> <p>The difference in the results between this study and Samuel et al<sup>4</sup> may be because this study was on both prime and multigravida off different ethnic groups.</p> <p>Our study results are compatible with results of Kirim et al.<sup>9</sup> A randomized, double-blinded, controlled trial, with healthy primigravid and multigravid women in spontaneous labor at term was considered in this study. A total of 80 patients were categorized into two equal groups. 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.</p> <p>Assessment of cervical dilatation was done every 1 h.</p> <p>The mean duration of the first stage of labor was <math>191.1 \pm 43.06</math> min in the primigravid patients of the HBB group, while it was <math>248.2 \pm 66.1</math> min in the placebo group, a statistically significant difference of 57 min (<i>p</i>-value &lt; 0.001). The mean duration of the first stage of labor was <math>170.1 \pm 50.8</math> min in the multigravid patients of the HBB group, while it was <math>224.06 \pm 53.7</math> min in the placebo group (difference of 54 min, <i>p</i>-value &lt; 0.001). The mean duration of the first stage of labor was significantly different both for multigravida and</p>	<p>painful labor.</p> <p>Reduction of cesarean sections and other fetal and maternal complications is also an important aspect of labor management.<sup>19</sup></p> <p>Prolonged labor is one of the most important risk factors for perinatal compromise.</p> <p>The two major factors that determine duration of labor are uterine contractility and rate of cervical dilation.<sup>20</sup></p> <p>Spasmolytic drugs are frequently employed to overcome cervical spasm and thus reduce the duration of labor. One of these spasmolytics is hyoscine-N-butylbromide, which exerts a spasmolytic action on the smooth muscle of the gastrointestinal tract, biliary and genitourinary tracts.<sup>21</sup></p> <p>Our study found that administration of HBB in 20 or 40 mg has significantly decreased the duration of first stage of labor without exerting such effect on second and third stages of labor.</p> <p>The physiological explanation of that is the primary site of action of HBB which is the cervix without effect on uterine contractility. That's very important as enhancement of uterine contractions that shorten the second stage is exposing both the parturient women and her fetus to risks, especially injuries. On the other hand, if it exerted an inhibitory action on uterine activity, it can expose the woman to hazards of atonic postpartum hemorrhage and retained placenta.<sup>18</sup></p> <p>The study was done on age group ranging from 18 to 35 years old, patients aging less than 18 years or more than 35 years were excluded from our study as pregnancy in this age group consider high-risk pregnancy.<sup>22</sup> Patients with occipitoposterior position were excluded as it is associated with prolonged first and second stages of labor.<sup>23</sup></p> <p>Al Qahtani and Al Hajeri (2011) conducted a randomized, double blind, controlled trial on 97 primigravid term pregnant women in spontaneous labor received either HBB or a placebo intramuscularly once the women entered the active phase of labor.</p> <p>The mean duration of the first stage in the control group was 215 min, compared with 165 min in the study group, representing a decrease of 23.3% (<i>p</i>-value = 0.001). There were no significant changes in the duration of the second (<i>p</i>-value = 0.063) or third (<i>p</i>-value = 0.0618) stages of labor.<sup>15</sup></p> <p>Kirim et al in 2015 performed a randomized, double blinded, controlled trial done on healthy primigravid and multigravid women in spontaneous labor at term. A total of 80 patients were divided into two equal groups to either a single dose of 20 mg (1 mL) of HBB or placebo (1 mL saline) intravenously.</p> <p>The mean duration of the first stage of labor was <math>191.1 \pm 43.06</math> min in the primigravid patients of the HBB group, while it was <math>248.2 \pm 66.1</math> min in the placebo group, a statistically significant difference of 57 min (<i>p</i>-value &lt; 0.001).</p> <p>The mean duration of the first stage of labor was <math>170.1 \pm 50.8</math> min in the multigravid patients of the HBB group, while it was <math>224.06 \pm 53.7</math> min in the placebo group (difference of 54 min, <i>p</i>-value &lt; 0.001). 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's 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.<sup>24</sup></p> <p>Sekhavat et al (2012) conducted a single-blinded randomized clinical trial study on 188 multiparas women in early active phase of labor divided into two groups hyoscine group (<i>n</i> = 94) received 20 mg (1 mL) of hyoscine and control group</p>
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**Supplementary Table S5** (Continued)

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's scores noted at 1 and 5 min, prep partum and postpartum hemoglobin levels and birth weight. No adverse maternal and fetal effects were observed in both HBB and placebo groups.

The results of our study are also compatible with those of Sirohiwal et al.

Samuel et al<sup>410</sup> nonrandomized controlled prospective study was carried out on 200 women in labor. In the active phase of labor, at 3 cm or more cervical dilatation, 100 women were administered HBB via suppository and 100 women (control) were not given any drug. The duration of first stage of labor was  $123.86 \pm 68.89$  (mean  $\pm$  standard deviation) min in the study group and  $368.05 \pm 133.0$  min in the control group. These differences were statistically significant. There were no differences in the duration of the second and third stages of labor. There was no increased incidence of operative deliveries in the study group. No adverse effects were noted on the mother or fetus. The difference in results may be because different route of administration.

The results of our study are also compatible with those of Makvandi et al.<sup>11</sup> A randomized double-blind placebo-controlled clinical trial was carried out on 130 primigravid women admitted for spontaneous labor. The women were recruited and randomized into the experimental ( $n=65$ ) and control group ( $n=65$ ). In the beginning of the two active phase of labor, 20 mg of HBB rectal suppository was administered to the experimental group, while a placebo suppository was administered to the control group. Cervical dilatation and duration of active phase and second stage of labor were recorded. The rate of cervical dilatation was 2.6 cm/h in the experimental and 1.5 cm/h in the control group ( $p$ -value  $<0.001$ ). The active phase and the second stage of labor were significantly shorter in the experimental group ( $p$ -value = 0.001 and  $p$ -value  $<0.001$ , respectively).

There was no significant difference between the two groups in the fetal heart rate, maternal pulse rate, blood pressure, and the Apgar's score at 1 and 5 min after birth.

Sekhavat et al<sup>12</sup> conducted a single-blinded randomized clinical trial study, 188 multiparas women in early active phase of labor who admitted to Shahid Sadoughi Hospital were evaluated. They were divided hyoscine group ( $n=94$ ) received 20 mg (1 mL) of hyoscine and control group ( $n=94$ ) received 1 mL of normal saline was given as placebo intravenously. The effects of hyoscine in shortening labor time, and neonatal Apgar's score were compared. Duration of the first (mean  $\pm$  SD:  $186.8 \pm 125.6$  min vs.  $260.4 \pm 120.9$  min,  $p$ -value = 0.001) and second stage of labor (mean  $\pm$  SD:  $20.0 \pm 8.1$  min vs.  $25.8 \pm 9.4$  min,  $p$ -value = 0.03) was shorter in hyoscine group. Frequency of cesarean section and mean of neonatal Apgar's score at 1 and 5 min were not different in both groups. No serious adverse events were seen in the two groups.

Sekhavat et al<sup>12</sup> concluded that HBB is effective in significantly reducing the duration of the first and second stages of labor and that it is not associated with any obvious adverse outcomes in mother or neonate. Different results may be due to inclusion of multiparas women in the study.

Our study results are compatible with results of Fardiazar et al.<sup>13</sup> In a single blind randomized clinical trial, 120 term pregnancies in early active phase of first stage of labor were enrolled from July 2009 to March 2011. A parallel design was used to randomly assign subjects into two equal groups including 60 participants in each group. Hyoscine-N-

( $n=94$ ) received 1 mL of normal saline was given as placebo intravenously. Duration of the first stage was  $186.8 \pm 125.6$  vs.  $260.4 \pm 120.9$  min,  $p$ -value = 0.001) and duration of second stage of labor was  $20.0 \pm 8.1$  vs.  $25.8 \pm 9.4$  min,  $p$ -value = 0.03) in hyoscine group vs. controls, respectively. Frequency of cesarean section and mean of neonatal Apgar's score at 1 and 5 min were not different in both groups. No serious adverse events were seen in the two groups.<sup>18</sup> The difference in results related to second stage may be acquired from nature of participants as multigravida may respond in a different way when compared to primigravida. Our study is an important randomized-controlled and double-blinded study limited to primipara women who are more suspected to abnormal progress of labor and subjected to more hazards of prolonged labor. Our intervention led to shortening of the duration of first stage of labor. That's is unquestionably beneficial as such shortening of duration alleviate the needs for more doses of analgesics with its potential fetal and neonatal effects and lower the cost of labor. Shortened labor is associated with lower risk of chorioamnionitis, puerperal, and neonatal sepsis associated with prolonged labor. It also decreased the risk of postpartum hemorrhage which is markedly increased after prolonged labor. Also, shortened labor raise maternal tolerability to vaginal delivery decreasing the risk of cesarean section resulted from maternal exhaustion or psychological troubles associated with labor pain, especially in developing areas without high availability of epidural analgesia. We think that will be also associated with less postpartum depression, which is needed to be evaluated in future studies. We also observed no effect on the rate of cesarean section among the study groups. However, we do believe that this finding is related to small sample size and if the trial is repeated with large sample size ,decreased rate of cesarean will be imminent. Fetuses with limited reserve or those with diminished liquor and women with medical disorders can tolerate uterine contractions for a limited time and we think that will decrease the rate of cesarean section in these high-risk pregnancy. We also found that HBB has no effect on the second and third stages of labor. That's also beneficial as hastened second stage will be associated with increased risk of maternal and fetal birth injuries In conclusion, intravenous injection of HBB helps to decrease the duration of active phase of labor in primigravidae with no side effects on either the mother or the neonate. We recommend the small dose (20 mg) intravenously as there was no significant changes with higher dose.

**Supplementary Table S5** (Continued)

butylbromide was administered 40 mg intravenously in the first group and intravenous atropine was given in second group at a dose of 0.5 mg. The participants of the two trial arms were similar according to the distribution of background variables. Mean length of the first stage of labor was 218.5 min (SD: 81.4) in hyoscine vs. 339 min (SD: 83.3) in atropine group (*p*-value < 0.001).

Our study results are compatible with those Manpreet et al.<sup>14</sup> A randomized comparative study was carried out on 100 women in labor. They were randomly allocated to one of the two groups. Group A included 50 women who were given injection drotaverine hydrochloride and Group B included 50 women who were given injection HBB intravenously in the first stage of labor. The main outcome measures were the time taken for full dilatation, rate of cervical dilatation, the duration of first and second stages of labor and blood loss in third stage of labor, all calculated separately for nulliparas and multiparas of the two groups. Average time to full cervical dilatation was significantly less in Group B in both nulliparas (*p*-value < 0.01) and in multiparas (*p*-value < 0.05). Similarly, the average rate of cervical dilatation was significantly more in Group B, both in nulliparas (*p*-value < 0.007) and in multiparas (*p*-value < 0.02). No significant difference in the side effects of either drug was observed. The difference in the duration of second and third stages of labor and the blood loss were statistically insignificant. The study concluded that HBB is more efficacious than drotaverine hydrochloride for cervical effacement and dilatation with no increase in the side effects, duration of second and third stages of labor and the third stage blood loss.

Our study results are compatible with those of Aggarwal et al.<sup>15</sup> This prospective randomized control trial was carried out on 104 primigravidae with single live fetus in cephalic presentation, with spontaneous onset of labor, between 37 and 40 weeks of gestation. Women were consecutively randomized into study (group I) and control (group II) groups, each with 52 patients after excluding high-risk factors like preeclampsia, antepartum hemorrhage, previous uterine scar, and any contraindications to vaginal delivery. Group I received 40 mg of HBB as a slow intravenous injection early in the active phase of labor, while group II received 2 mL of normal saline. Cervical dilatation was assessed at baseline and 2 h later. Secondary outcome measures compared were mode of delivery and neonatal condition at birth. Statistical significance was assessed by using Student's *t*-test and Chi-square test. A *p*-value < 0.05 was taken as significant. Mean duration of labor was 3 h 46 min in group I compared to 8 h 16 min in Group II (*p*-value < 0.001).

Mode of delivery and neonatal outcome were comparable. No adverse maternal effects were noted. The study concluded that Intravenous hyoscine N-Butyl bromide shortens the duration of active phase of first stage of labor without any untoward short term fetal or maternal effects.

The result of this study was in contrast to that of Gupta et al<sup>16</sup> who studied and compared the efficacy and side effects of Drotaverine (group 1 included 50 women given 40 mg), Hyoscine-nbutylbromide (group 2 included 50 women given 20 mg) and a placebo (group 3 included 50 women) in augmentation of labor and found that the mean duration of active phase of first stage of labor was  $4.48 \pm h$ ,  $3.9 \pm h$  and  $3.6 \pm h$  in group 1, 2, and 3, respectively. The differences were not statistically significant. There were no differences in the duration of the second or third stages of labor. They concluded that drotaverine and hyoscine-N-butylbromide do not have a role in augmentation of labor.

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**Supplementary Table S5** (Continued)

The result of this study was on contrast to that of Aldahhan et al.<sup>4</sup> (17). A double-blind study included 200 women attending labor ward in the first stage of labor either latent or active phases. They were categorized into two groups; group A (cases) received HBB 20 mg IV and group B (controls) received placebo intravenously. Assessment of cervical dilatation was carried out every hour postinjection. The duration of the stages of labor, maternal and neonatal outcome was determined. The study revealed that cervical dilatation at 1 h was significantly lesser in role of Intravenous HBB injection... group A ( $6.8 + 1.8$ ) cm compared to ( $7.6 + 2.1$ ) cm in the control group (*p*-value < 0.05). The duration of the first stage of labor was significantly longer among group A ( $4.1 + 1.8$ ) hours as compared with the controls ( $3.4 + 1.6$  h) *p*-value <0.05. The frequency of caesarean section was significantly higher among group A (12%) compared to controls (4%), *p*-value < 0.05. Fetal heart rate was significantly higher among group A ( $137.8 + 11.2$  beat/min) compared to control ( $133.5 + 9.9$  beat/min), *p*-value < 0.001; they conclude that the administration of HBB decelerate the cervical dilatation in the first stage of labor and causes prolongation in its duration. Also, it is associated with small, but obvious fetal risk, and an increase in the rate of cesarean section.

Abbreviation: HBB, hyoscine butylbromide.