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Effect of valethamate bromide in accelerating labor: a prospective randomized controlled trial

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Summary

Objective: This prospective randomized study aimed to investigate the effect of valethamate bromide on the length of labor. *Materials and Methods:* A total of 200 pregnant women, who were in the 37-41 weeks of gestation, and in the active phase of labor with cervical dilatation of 6-7 cm, were included in the study. Twenty-four pregnant women that underwent cesarean section and 33 pregnant women that required oxytocin were not included in the final statistical analysis. Finally, 71 nulliparous and 72 multiparous women were randomized to four groups according to whether they received valethamate bromide or not. Groups 1 and 2 consisted of 35 nulliparous and 37 multiparous women, respectively receiving 16 mg of valethamate bromide, whereas groups 3 and 4 consisted of 36 nulliparous and 35 multiparous women, respectively, not receiving any medication, and both groups were considered as the control group. *Results:* There was no statistically significant difference between the groups in terms of mean maternal age and gestational age ($p > 0.05$). Evaluating the groups in terms of drug side effects such as maternal tachycardia, dry mouth, flushing, headache, nausea, and vomiting, no statistically significant difference was determined between the valethamate bromide groups (groups 1 and 2) and the controls ($p > 0.05$). There was no statistically significant difference between the study groups (group 1 *vs.* 3 and groups 2 *vs*. 4) in terms of the time from the rupture of the membranes to the second stage of labor ($p > 0.05$). Contrarily, the median length of the second stage of labor was 35 (5-70) minutes and 42.5 (10-70) minutes for groups 1 and 3, respectively, in the nulliparous women and the difference between the groups was considered statistically significant ($p = 0.045$). For the multiparous women, the median length of the second stage of labor was 12 (5-30) minutes in group 2 and 15 (5-40) minutes in group 4 and no statistically significant difference was determined between the groups ($p > 0.05$). The median time from the rupture of the membranes to the delivery was 100 (10-235) minutes and 87.5 (20-395) minutes in groups 1 and 3, respectively, and 50 (25-365) minutes and 50 (10-390) minutes in groups 2 and 4, respectively. No statistically significant difference was determined between the groups ($p > 0.05$). *Conclusion:* Valethamate bromide significantly shortens the second stage of labor in nulliparous women.

Key words: Valethamate bromide; Delivery; Duration; Cervical dilatation; Spasmolytic; Labor.

Introduction

Cervical alterations and progression of labor have been a matter of debate for years for obstetricians. Unfavorable effects of prolonged labor on the mother and infant have been documented. From the point of expectant approach, the risk of maternal burn out, postpartum bleeding, sepsis, fetal distress, and fetal asphyxia increases with prolonged labor. Current trend is decreasing the length of labor by active management of labor considering both maternal and fetal safety into consideration [1, 2]. Active management of labor was conceptualized by O'Driscoll, has been widely accepted and demonstrated to be beneficial [3]. There are different mechanical and pharmacological methods that might facilitate cervical dilatation. These methods include membrane stripping, balloon catheter, amniotomy, different forms of prostaglandins, and oxytocin. The pharmacological methods that facilitate the labor include hyoscine N-butyl bromide, drotaverine hydrochloride, and valethamate bromide [1, 4].

Valethamate bromide, which is the subject of the present study, decreases the length of labor allowing rapid relaxation of cervical muscles. The literature comprises studies with conflicting results about this medication. There are studies reporting that valethamate bromide has no effect on labor [5-7], as well as the studies reporting that valethamate bromide decreases the length of labor [4, 8-10]. The present study aimed to investigate the effect of intravenous valethamate bromide on the length of labor and to observe potential maternal side effects of the drug.

Materials and Methods

The present study was prospectively performed in women undergoing normal vaginal delivery in T.R.M.H. Etlik Zubeyde Hanim Maternity and Women's Health Teaching and Research Hospital between May 7, 2009 and July 30, 2010. The study was approved by the local ethics committee (2009-32). Informed consents for participating in the study were obtained from the patients. Nulliparous and multiparous women who were in the 37-41

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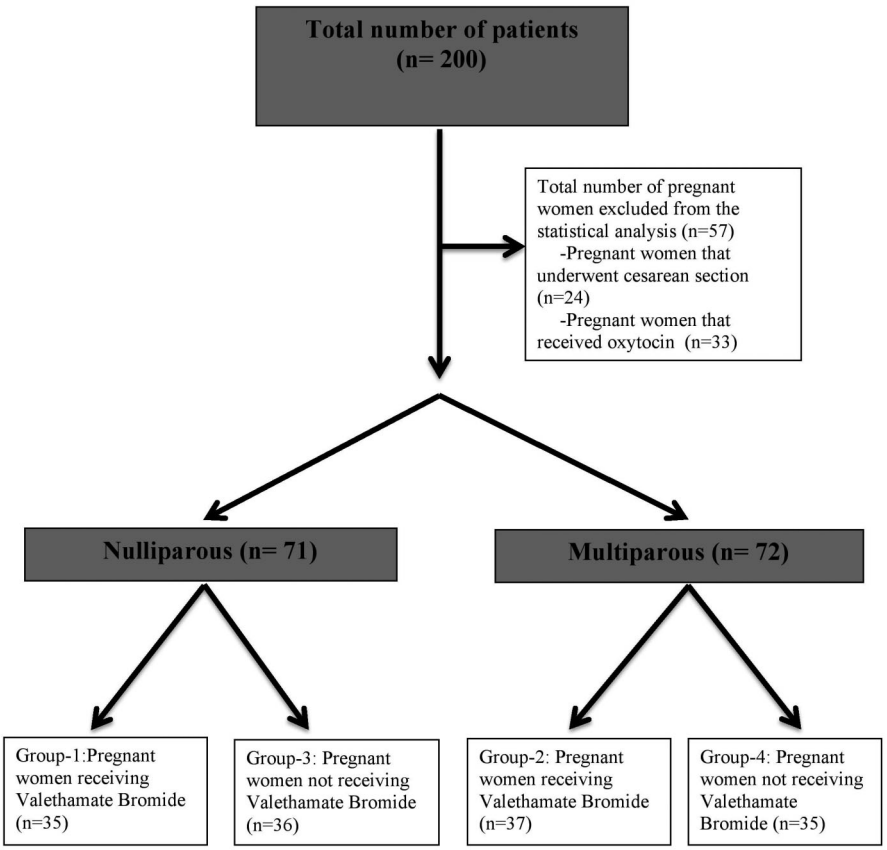

Figure 1. — Flow chart of the randomization.

weeks of gestation were included in the study. Gestational week was determined based on the last menstrual period. However, sonographic week was used to determine the gestational age in case the difference between fetal biometric measurement in the first trimester and the last menstrual period was longer than seven days.

Women who had singleton pregnancies and were in active phase of labor, with cervical dilatation of 6-7 cm, had a fetus with vertex presentation, and had intact membranes were included in the study. Physical, obstetric, and sonographic examinations were performed in each patient. The study population was determined based on these examinations. All pregnant women participated in the study underwent amniotomy.

Pregnant women with medical or surgical complications such as early rupture of the membranes, intrauterine growth retardation, oligohydramnios, polyhydramnios, placenta previa, antepartum bleeding, preeclampsia, hypertension, diabetes mellitus, fetal macrosomia (estimated fetal weight > 4,000 grams), or remarkably narrow pelvis were excluded. Again, pregnant women, in whom the labor was induced by prostaglandin analogues, who received oxytocin, who had a fetus with occiput posterior presentation, who had multiple pregnancies, a Müllerian anomaly, and of whom the previous pregnancy was terminated by cesarean section, were excluded because of the potential impact on labor. The study was planned with 200 pregnant women (Figure1). Fifty-seven pregnant women were not included in the statistical analysis as they did not meet the study criteria (24 underwent cesarean section and 33 received oxytocin).

The study comprised of 71 nulliparous and 72 multiparous women. Software was used to randomize the patients to the study groups. A single dose of 16 mg valethamate bromide was administered via intravenous route in randomly selected 35 nulliparous and 37 multiparous women. Remaining 36 nulliparous and 35 multiparous women did not receive valethamate bromide and were considered as the control group (Figure 1).

Amniotomy was performed in each participant when cervical dilatation reached up to 6-7 cm. A single dose of 16 mg of valethamate bromide was administered via intravenous route following amniotomy procedure in 35 nulliparous women in group 1 and in 37 multiparous women in group 2. Amniotomy was also performed in 36 nulliparous women in group 3 and in 35 multiparous women in group IV without administering valethamate bromide when cervical dilatation reached up to 6-7 cm.

Vaginal examination was performed in all patients at two-hour intervals by the same physician to evaluate the progression of labor. The patients were examined at 15-minute intervals when cervical dilatation reached up to 9 cm. All patients were regularly monitored at one-hour intervals in terms of blood pressure (mmHg), pulse rate (beat/minute), uterine contraction (Montevideo unit) and fetal heart rate (beat/minute), and side effects of valethamate bromide (tachycardia, dry mouth, flushing, fever, headache, and nausea-vomiting). Time of drug administration, vaginal examinations during drug administration, time of rupture of the amnion membrane, time of complete cervical dilation and effacement, postpartum changes in the infant, and first- and fifth- minute APGAR scores were recorded.

Table 1. — *Demographic characteristics of the cases according to the groups.*

Groups	Age (years)	Parity	Gestational week
Nulliparous			
Group I	23.2±4.2	-	39.3±0.9
Group III	22.3±3.9	-	39.2±0.9
p	0.329	-	0.588
Multiparous			
Group II	27.3±5.2	2±.1	39.3±1.0
Group IV	27.3±5.2	2±1	39.3±1.0
p	0.993	0.715	0.789
Total			
Receiving Valethamate bromide	25.3±5.2	1±1	39.3±0.9
Not receiving Valethamate bromide	24.7±5.2	1±1	39.3±0.9
p	0.542	0.716	0.578

Table 2. — *Distribution of the cases in terms of side effects of valethamate.*

Variables	Not receiving valethamate bromide (n=71)	Receiving valethamate bromide (n=72)	*p*
Side effects	19 (26.8%)	17 (23.6%)	0.664
Tachycardia	7 (9.9%)	4 (5.6%)	0.334
Dry mouth	4 (5.6%)	6 (8.3%)	0.745
Flushing	2 (2.8%)	7 (9.7%)	0.166
Fever	-	1 (1.4%)	1.000
Headache	4 (5.6%)	3 (4.2%)	0.719
Nausea-vomiting	4 (5.6%)	5 (6.9%)	1.000

In order to determine the length of labor, which was the primary objective of the present study, the time (minutes) from valethamate bromide administration to the complete cervical dilation and effacement, as well as to the delivery, was recorded. Pregnant women were evaluated for placental retention after delivery. Whether the pregnant women had tachycardia (pulse rate > 100 beats/minute), dry mouth, nausea-vomiting, fever, flushing, or headache was recorded.

The data were analyzed using SPSS for 22.0 package program. Whether the distribution of continuous variables was close to normal was analyzed by Shapiro Wilk test. Descriptive statistics were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables. Nominal variables were presented as the number of subjects (n) and percentage (%). Whether the mean maternal age and gestational week showed differences between parity and drug groups was analyzed by two-way analysis of variance. Whether the times from the rupture of the membranes to complete cervical dilatation, from complete cervical dilatation to delivery, and from the rupture of the membranes to delivery showed significant differences according to the parity and receiving valethamate bromide was assessed by Mann Whitney U test. Nominal variables were analyzed using Pearson's Chi-square or Fisher's Exact Chi-square tests. The results with $p < 0.05$ were considered statistically significant.

Results

The mean maternal age was 23.2 and 27.3 years in groups 1 and 2, respectively, and 22.3 and 27.3 years in groups III and IV, respectively. Mean gestational age was 39.3 weeks in both groups 1 and 2, whereas it was 39.2 and 39.3 weeks in groups 3 and 4, respectively. In pregnant women that received valethamate bromide, the mean maternal age was 25.3 years, mean gestational age was 39.3 weeks, and mean parity was 1±1. In the control group, the mean maternal age was 24.7 years, mean gestational age was 39.3 weeks, and mean parity was 1±1. No statistically significant difference was determined between the groups in terms of mean maternal age and gestational age ($p > 0.05$) (Table 1).

The incidences of the side effects determined in 71 cases that did not receive valethamate bromide were as following: tachycardia 9.9%, dry mouth 5.6%, flushing 2.8%, headache 5.6%, and nausea-vomiting 5.6%. Fever was not determined in any case. The incidences of the side effects determined in the cases that received valethamate bromide were as following: tachycardia 5.6%, dry mouth 8.3%, flushing 9.7%, fever 1.4%, headache 4.2%, and nausea-vomiting 6.9%. No statistically significant difference was determined between the groups that received and not valethamate bromide in terms of these symptoms and signs ($p > 0.05$) (Table 2).

The median time from the rupture of the membranes to the second stage of labor was 50 (5-345) minutes and 32.5 (5-385) minutes in nulliparous and multiparous women, respectively ($p > 0.05$). The median length of the second stage of labor was 40 (5-70) minutes in nulliparous women and 15 (5-40) minutes in multiparous women. The median time from the rupture of the membranes to the delivery was 90 (10-395) minutes in nulliparous women and 50 (10-390) minutes in multiparous women. All these differences between the groups were considered significant ($p < 0.05$). The median time from the rupture of the membranes to complete cervical dilatation was 47.5 (5-350) minutes in the groups that received valethamate and 35 (5-385) minutes in the groups that did not receive valethamate. The median time from complete cervical dilatation to the delivery was 20 (5-70) minutes in the groups received valethamate bromide and 25 (5-70) minutes in the groups that did not receive valethamate bromide. The median time from the rupture of the membranes to the delivery was 77.5 (10-365) minutes in the groups received valethamate bromide and 75 (10-395) minutes in the groups not received valethamate bromide. No statistically significant difference was determined between the groups.

The median time from the rupture of the membranes to the second stage of labor was 80 (5-185) minutes in group 1, 40 (10-345) minutes in group 3, 35 (15-350) minutes in group 2, and 30 (5-385) minutes in group 4. No statistically significant difference was determined between the groups

Table 3. — *Times in terms of parity and drug.*

Variables	Group 1	Group 2	Group 3	Group 4	*p (Groups 1 - 3).*	*P (group II - IV)*
From the rupture of membranes to complete cervical dilatation (min)	8 (5-185)	35 (15-350)	40 (10-345)	30 (5-385)	0.375	0.202
From complete cervical dilatation to delivery (min)	35 (5-70)	12 (5-30)	42.5 (10-70)	15 (5-40)	0.045	0.345
From the rupture of membranes to delivery (min)	100 (10-235)	50 (25-365)	87.5 (20-395)	50 (10-390)	0.600	0.513

($p > 0.05$) (Table 3). The median length of the second stage of labor in groups I and 3 was 35 (5-70) minutes and 42.5 (10-70) minutes, respectively; the difference was considered statistically significant ($p = 0.045$). In the multiparous women, the median length of the second stage of labor was 12 (5-30) minutes in group 2 and 15 (5-40) minutes in Group 4. No statistically significant difference was determined between the groups. The median time from the rupture of the membranes to the delivery was 100 (10-235) minutes and 87.5 (20-395) minutes in group I and group 3, respectively, whereas it was 50 (25-365) minutes and 50 (10-390) minutes in groups II and 4, respectively. No statistically significant difference was determined between the groups in terms of these values (Table 3).

All pregnant women that completed the study gave birth vaginally. The first- and fifth-minute APGAR scores of the infants were assessed. None of the fetuses had low APGAR score or developed perinatal asphyxia. Placenta retention after delivery was not determined in any of the women.

Discussion

Active management of labor reduces maternal morbidity and perinatal mortality. Valethamate bromide is an agent used for this purpose for a long time to decrease cervical spasm. Valethamate Bromide, which is used to decrease the length of labor, is a quaternary ammonium compound. It has an anti-muscarinic effect and is a cholinergic receptor blocker in the ganglia. It is thought to help cervical dilatation by affecting cervical smooth muscle. As it is not selective, it has cholinergic side effects such as tachycardia, flushing, dry mouth, and mydriasis-related photophobia [1, 5, 6, 8].

It is known for a long time that anticholinergic drugs such as valethamate bromide have side effects. An earlier randomized controlled study determined that maternal tachycardia was almost doubled in pregnant women receiving valethamate bromide (primigravida RR 1.97, 95% CI 1.3-3.0; multigravida RR 2.16, 95% CI 1.3-3.6) [5]. In the subsequent two studies, however, drug-related maternal tachycardia was observed, but it was not statistically significant [7, 11]. Batukan *et al.* detected maternal tachycardia in the valethamate bromide group (35%) and considered it as a significant side effect compared to the control group (1%) [9]. In their study, Yılmaz *et al.* [7] found significantly more prevalent dry mouth and tachycardia. Köstü *et al.* found maternal tachycardia (33%, $p = 0.05$) and flushing (13%, $p = 0.04$) to be statistically significantly more prevalent in the Valethamate bromide group as compared to the control group [6]. However, no significant difference was determined in terms of dry mouth, fever, headache, nausea or vomiting. Many studies comparing drotaverine with valethamate bromide observed that anticholinergic side effects were less common with drotaverine *vs*. valethamate bromide [4, 10, 12-16].

In the present study, the side effects determined in 71 cases not receiving valethamate bromide were tachycardia (9.9%), dry mouth (5.6%), flushing (2.8%), headache (5.6%), and nausea-vomiting (5.6%). There was no case with high fever. Tachycardia (5.6%), dry mouth (8.3%), flushing (9.7%), fever (1.4%), headache (4.2%) and nausea-vomiting (6.9%) were determined in 72 cases receiving valethamate bromide. No statistically significant difference was determined between the patient groups receiving and not valethamate bromide in terms of the incidences of these symptoms and signs. In the present study, the authors did not find any statistically significant side effect. They believe this might be associated with the drug administered during advanced cervical dilatation when there is less time to delivery and at a single dose of 16 mg different from the earlier studies.

Dahal *et al.* [12] compared valethamate bromide with drotaverine in a group comprising both nulliparous and multiparous women, and they found that both valethamate bromide and drotaverine shorten the active phase and length of labor and that drotaverine is superior to valethamate bromide**.** Similar results were found in another prospective, randomized, controlled study conducted by Madhu *et al.* [4] to compare valethamate bromide with drotaverine, where both nulliparous and multiparous women were in the same group. They enrolled 146 low-risk pregnant women, 49 pregnant women (24 nulliparous and 25 multiparous women) in group 1 received drotaverine, 49 pregnant women (25 nulliparous and 24 multiparous women) in group 2 received valethamate bromide, and 48 pregnant women (23 nulliparous and 25 multiparous women) were assigned to the control group (group 3). The mean length of labor with treatment was found to be 183.2 minutes in group 1, 206.5 minutes in group 2, and 245 minutes in group 3. Compared to the control group, it was found that both drotaverine ($p = 0.0001$) and

valethamate ($p = 0.0074$) significantly decreased the length of labor. Moreover, it was determined that drotaverine is more effective than valethamate bromide in decreasing the length of labor ($p = 0.0404$)

Some of the studies in the literature about the effects of valethamate bromide on the length of labor in nulliparous women demonstrated that the length of labor was not decreased [5, 7]. Sharma *et al.* [8] found the time between the injection and delivery to be 220.68 minutes in the valethamate group and 412.84 minutes in the control group; the length of labor has been decreased by 46.5%. Batukan *et al.* [9] administered 8 mg/ml of valethamate bromide via intramuscular route randomly at one-hour intervals for three times in the beginning of active phase of labor (when cervical dilatation is 4-5 cm), and they found the length of active phase of labor to be statistically significantly shorter in primiparous women receiving valethamate bromide (210.3±93.5 minutes) as compared to the primiparous women receiving placebo (287.1±130.3 minutes) ($p = 0.015$). Köstü *et al.* [6] conducted a prospective randomized trial in nulliparous women and found the mean length of active phase to be 225.5±67.2 minutes in the study group after one ampoule of valethamate bromide administered at one-hour intervals maximum for three times in the active phase of labor when cervical dilatation was 3-5 cm and 219.6±76.5 minutes in the control group with statistically significant difference determined between the groups ($p > 0.05$).

In the literature, there are some studies about drotaverine *vs.* valethamate bromide reporting that both valethamate bromide and drotaverine shortens the active phase of labor compared to the control group and that drotaverine is superior to valethamate bromide in this respect [10-12, 15, 16].

Sarbhjit *et al.* [1] determined the length of active phase in the first stage of labor to be 154.48 minutes in group 1 receiving camylofin dihydrochloride and 215.55 minutes in group 2 receiving hyoscine N-butyl bromide together with valethamate bromide, which is the control group; the difference was considered significantly shorter ($p < 0.01$). Jayashree *et al.* [13] and Sangetaa Raman Jogi [14] compared the effects of drotaverine and valethamate bromide on the length of the active phase of labor, and they found that the length of the active phase of labor to be significantly shorter in the nulliparous women receiving drotaverine hydrochloride compared to the group receiving valethamate bromide. Thapa *et al.* [17] found no statistically significant difference between the group receiving drotaverine and the group receiving valethamate bromide together with hyoscine N-butyl bromide in terms of the length of the first stage of labor. ($p = 0.72$).

In the present study, as well as the results of some other studies, the authors determined that valethamate bromide does not shorten the first stage of labor in nulliparous women [5-7]. In the present study, the median time from the rupture of the membranes to the second stage of labor was 80 (5-185) minutes in group 1 and 40 (10-345) minutes in group 3. No statistically significant difference was determined between the groups ($p > 0.05$). The median length of the second stage of labor was 35 (5-70) minutes and 42.5 (10-70) minutes in groups I and 3, respectively, and this difference was considered statistically significant. The median time from the rupture of the membranes to the delivery was 100 (10-235) minutes and 87.5 (20-395) minutes in groups 1 and 3, respectively. No statistically significant difference was determined between the groups regarding these values.

With regard to the studies conducted with Valethamate Bromide in multiparous women, Kruvila *et al.* [5] found no statistically significant difference between multiparous women receiving Valethamate bromide and the control group in terms of mean rate of cervical dilatation. In the study conducted by Batukan *et al.* [9], the result of which was similar to that of the present study, there was no significant difference between valethamate bromide group (187.1±81.4 minutes) and the control group (241.9±131.1 minutes) in terms of the time to the beginning of the second stage of labor in multiparous women (p=0.11). Khosla *et al.* [11] found that valethamate bromide and drotaverin significantly shortened the length of the active phase of the first stage of labor in multiparous women. In the study conducted by Thapa *et al.* [17], the time from the injection to the delivery in multiparous women was shorter in the drotaverine group compared to the group receiving hyoscine N-butyl bromide together with valethamate bromide ($p = 0.03$). Sarbhjit *et al.* [1] determined the length of active phase of the first stage of labor to be 128.82 minutes in group 1 receiving camylofin dihydrochloride and 153.05 minutes in group 2 receiving valethamate bromide and hyoscine N-butyl bromide, which was the control group ($p < 0.05$). This difference was significantly shorter. Jayashree *et al.* [13] and Sangetaa Raman Jogi [14] compared drotaverine and valethamate bromide and found that the length of active phase was significantly shorter in the group of multiparous women receiving drotaverine. Both Pradnya Rajendra Changede [10] and Hema Sinhasane [16] found significantly shorter active phases of the first stage of labor both in the multiparous women receiving drotaverine and in the multiparous women receiving valethamate bromide. Moreover, drotaverine was determined to be superior to valethamate bromide.

Similar to the studies conducted by Kruvila *et al.* and Batukan *et al.*, the present study determined no significant decrease in the first stage of labor in the multiparous women. With regards to the multiparous women in the present study, the median time from the rupture of the membranes to the second stage of labor was 35 (15-350) minutes in group 2 and 30 (5-385) minutes in group 4. No statistically significant difference was determined between the groups ($p > 0.05$). The second stage of labor in multiparous women was found to be 12 (5-30) minutes in group 2 and 15 (5-40) minutes in group 4, with no statistically significant difference determined between the groups. The median time from the rupture

of membranes to delivery was 50 (25-365) minutes in group 2 and 50 (10-390) minutes in group IV. No statistically significant difference was determined in terms of these values.

In the Cochrane review published in 2013 that investigated the effects of antispasmodics on delivery in the term pregnancies, the antispasmodics were compared between the placebo or the patient groups not receiving any medication. This review comprised 21 randomized controlled trials including a total of 3,286 pregnant women. It was determined that each type of spasmodic shortened the first stage of labor by 49-98 minutes. In addition, such medications shortened the total length of delivery from the onset of labor to birth by 49-121 minutes. Since both maternal and neonatal side effects have been reported scarcely, more information is required to make a conclusion regarding the safety of these drugs during labor. The studies included were usually of poor quality, and more powerful studies are required to assess what would be when these drugs are given to the women with prolonged labor.

In conclusion, there are evidences of poor quality that antispasmodics decrease the length of the first stage of labor and increase the rate of cervical dilatation. There are evidences of very poor quality that antispasmodics decrease the total length of delivery. There are evidences of moderate quality that antispasmodics do not influence the prevalence of normal births with vertex presentation. The evidences are limited in number to draw any conclusion about the safety of these drugs for both mother and baby. Large-scale, randomized and controlled studies are required to evaluate the effects of antispasmodics on prolonged labor as well as on delivery [2].

Conclusion

Valethamate bromide administered in the further period of active phase does not shorten the time from drug administration to the second stage of labor, either in nulliparous or multiparous women, or the second stage of labor in nulliparous women without significant maternal or fetal impacts.

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