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RESEARCH ARTICLE

PREVENTION OF PROLONGED LABOR BY ACTIVE MANAGEMENT OF FIRST STAGE USING SPASMOLYTIC DRUGS A DOUBLE BLIND RANDOMIZED CONTROLLED CLINICAL STUDY

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ABSTRACT

Background: Dystocia remains the most common indication for emergency cesarean section especially for primigravidae. As such, it is a major contributor to operative and instrumental intervention. **Type of Study:** A double-blind, randomized, controlled clinical trial**. Objective:** This study aimed to evaluate the effect of 2 spasmolytic drugs, Drotaverine and Hyoscine-N-Butylbromide on shortening of first stage of labor. **Setting:** Obstetrics and Gynecology Departments of Al-Azhar university hospital (Assiut)**,** Egypt**. Patients & Methds:** 150 full term primigravidae in labor (cervical dilatation 3-4cm with regular progressive uterine contractions 3-4/ 10 minutes, each lasting for at least 40 seconds) were recruited for this study during the period from June 2018 to december 2018. Patients were divided into three equal groups (50 patients for each). **Group I:** Received (40mg) drotaverine hydrochloride by slowly IV infusion. **Group II:** Received (20mg) hyoscine-n-butylbromide by slowly IV infusion. **Group III: (control):** Received Sterile water for injection (placebo). **Results:** the rate of cervical dilation was significantly higher in group 1&II compared to the control group; also duration of 1st stages was significantly shorter in the same groups while no significant difference in duration of 2nd stage were present among the 3 groups, the degree of severe pain and the need for oxytocin augmentation doses were significantly lesser in both groups compared to control ($p<0.001$). The neonatal outcomes in the form of APGAR score was higher and need for NICU admission was significantly lower in group I&II compared to group III. **Conclusion:** both drugs used in this study have significant effects on shortening of 1st stage of labor with lesser units of oxytocin needed for augmentation with good analgesic effect and good neonatal outcome, however, Drotaverine hydrochloride was better as it was more effective beside it has the strongest labor pain relieve and lesser maternal adverse effects. **Recommendations:** We recommend using of either drug in enhancing first stage of labor however; Drotaverine hydrochloride is preferable as it is more effective with minimal maternal adverse effects.

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INTRODUCTION

Labor is a natural physiological process characterized by progressive increase in frequency, intensity and duration of uterine contractions, effacement and dilatation of cervix with descent of the fetus through the birth canal (Archie and Biswas, 2003). 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 (PPH), puerperal sepsis, and maternal death (Hofmeyr, 2004). The two major factors that determine duration of labor are uterine contractility and rate of cervical dilation.

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In addition to mechanical factors such as sweeping of membranes, cervical stretching and amniotomy, various pharmacological agents have been found to facilitate cervical dilation. (Tan *et al.*, 2006, and Kandil *et al.,* 2017). WHO stated that, the expected duration of the active phase of the first stage of labor depends on the reference threshold used for its onset. The established boundaries for the active first stage were rounded 95th percentile values from evidence on the duration of the progress of cervical dilatation from 5 cm to 10 cm. The median duration of active first stage is 4 hours in first labors and 3 hours in second and subsequent labors, when the reference starting point is 5 cm cervical dilatation (WHO; 2018). The cervix is made up of only 10-15 % smooth muscle with the remaining tissue comprised primarily of extracellular connective tissue. Constituents of the latter include type I, III, and IV collagen, glycosaminoglycans, proteoglycans, and elastin (Canty *et al.,* 2005).

Cervical softening results from increased vascularity, stromal hypertrophy, glandular hypertrophy and hyperplasia, and compositional or structural changes of the extracellular matrix (Word *et al*; 2007). Various pharmacological agents have been found to facilitate cervical dilation. The role of oxytocin and prostaglandins has been established worldwide in augmentation of labor (Sharami *et al.,* 2005). Spasmolytic drugs as hyoscine N-butylbromide and Drotaverin are frequently employed to overcome cervical spasm and thus reduce the duration of labor. Hyoscine N-butylbromide has been used to shorten the duration of labor. It acts primarily by blocking the transmission of neural impulses in the intraneural parasympathetic ganglia of abdominal organs, apparently inhibiting the cholinergic transmission in the synapses. After intravenous administration, exerts a spasmolytic action on the smooth muscles of the gastrointestinal tract, biliary and genitourinary tracts. The mechanism by which it acts in the context of labor has not yet been elucidated, and the evidence for its efficacy was previously largely anecdotal (Sekhavat *et al.,* 2012). The drugs acts primarily as an analgesic for the pain associated with labor, intravenous Hyoscine-N-butylbromide smoothens the passage of labor effects by affording pain relive of up to 36% and also shortening the duration of active phase without any fetal or maternal complications (Samuel *et al.,* 2007).

Drotaverine is highly effective in reducing the duration of active phase of labor by hastening cervical dilatation, more effective when given in more dilated cervix than with less dilatation and more effective in multigravida than in primigravida (Tahira *et al.,* 2018). There was no interference with uterine contractility and no increase in operative delivery. It reduces the incidence of traumatic postpartum hemorrhage by reducing the incidence of cervical tear (Roy *et al.,* 2007) and (Singh *et al.,* 2004).

Objectives: to evaluate the effect of 2 different spasmolytic drugs, Drotaverine and Hyoscine-N-Butylbromide in enhancement of first stage of labor to prevent prolongation of labor.

PATIENTS AND METHODS

The study is a double-blind, randomized, controlled clinical trial. 150 patients were enrolled in the study from attendants of antenatal care clinic and labor ward in Al Azhar University Hospital in Assiurt – Egypt during the period from June 2018 to December 2018. After proper history taking, examination (general, abdominal and local obstetric examinations), routine investigations and ultrasound examination were done to fulfill the inclusion criteria; a Full informed consent was obtained from all participants.

Inclusion Criteria: Primigravidae , Singleton pregnancy, Term gestation i.e. 37- 42 weeks, Sure reliable dates, Vertex presentation, occipitoanterior position, spontaneous onset of labor, Regular uterine contractions 3- 5 /min ,each lasting for 40 sec, Cervical dilatation of 3-5cm,with or without rupture of membranes with no evidence of maternal or fetal distress.

Exclusion Criteria: Mal-presentations, Mal-positions, Multifetal pregnancy, Cephalopelvic disproportion, history of cervical surgery or injury.

Patients were classified into 3 equal groups according to type of IV medication used (50 patients each);

- **Group I:** (Received 40mg of Drotaverine hydrochloride).
- **Group II: (**Received 20mg of Hyoscine-n-butylbromide).
- **Group III (control):** (received normal saline)**.**

METHODS

The syringes containing the drugs and placebo were prepared by the same investigator, under aseptic conditions. Each syringe contained either 1 ml of, drotaverine hydrochloride (40mg), hyoscine butylbromide (20 mg), or 1 ml of normal saline; all liquids are colorless, so the syringes containing the drugs were indistinguishable from those containing placebo. A computer program was used to generate a random sequence of numbers. Sequentially numbered, sterile syringes were then prepared using the random numbers to determine their content: drugs or placebo. Only the principal investigator knew the correlation between the labels of the syringes and their contents, and this was only showed after the study was completed. Participants received drugs as a single dose, given intravenously, when they were assessed as being in labor, with cervical dilatation of 3–5 cm, as confirmed and documented by residents in the Obstetrics and Gynecology departments. The woman and the caregivers were blinded as to whether the active drug or placebo was being administered. The progress of the participants was closely documented, with the conduct of labor for both the drugs and control groups in accordance with our normal labor ward protocol, which is based on the principle of active management. Thus, routine amniotomy was performed for all women in established labor who were found to have cervical dilatation of 3 cm or more, and who had not had spontaneous rupture of membranes. Oxytocin augmentation was initiated if the initial progress of labor (as assessed through partographs) was unsatisfactory. Intervention through instrumentation or caesarean delivery was dictated by the usual obstetric determinants. Laboring mothers were monitored in bed, and the use of electronic cardiotocography assisted in the monitoring of fetal wellbeing. All data sheets (containing the raw data obtained during the study) were collected by the principal investigator and kept in a combination locked filing drawer in his office. At the end of the study, the data were disaggregated by the principal investigator, using the record of randomization sequences and the label of the syringes to sort the participants and their data into the appropriate groups (drugs or control).

Statistical analysis: data was collected, tabulated and statistically analyzed using SPSS (statistical program for social science version 12). Descriptive data were reported as frequency, percentage, mean and standard deviation (S.D.), for the comparison of result, Student t-test, chi-Square and and ANOVA tests were used. A p-value of less than 0.05 was considered significant.

RESULTS

Table (1) shows socio demographic and clinical characteristics among the studied groups, there was no statistically significant difference as regard to maternal age, BMI, GA, cervical dilatation and cervical effacement at start of study *(p* > 0.05).
Table (2) shows post treatment cervical effacement, durations of labor (1st and 2nd stages), dose of oxytocin used and labor pain among the studied groups, the rate of cervical dilation was significantly higher in group 1&II compared to the control group; also duration of 1st stages was significantly shorter in the same groups while no significant difference in duration of 2nd stage were present among the 3 groups, the dose of

Table 1. Socio-demographic and clinical characteristics of the studied groups

variables	Group I (n=50)	Group II (n=50)	Group III (n=50)	P
Maternal Age (Years)	22.3 ± 2.05	22.5 ± 1.81	22.3 ± 1.49	0.33
BMI (kg/m^2)	24.1± 0.63	24.0± 0.65	24.2± 0.60	0.42
Gestational Age (Wks)	39.1± 0.87	39.0 ± 0.77	39.4±0.60	0.09
Cervical dilatation (cm) onadmission	4.4± 0.67	4.4± 0.64	4.3± 0.53	0.45
Cervical effacement (%) on admission*				
•<50%	24(48%)	25(50%)	23(46%)	0.155
•≥ 50%	26(52%)	25(50%)	27(54%)	
Values are given as mean ± SD unless otherwise mentioned				
*Values are given as no.%				

Table 2. Post treatment cervical effacement, durations of 1st & 2nd stages, dose of oxytocin used and labor pain among the studied groups

	Group I (n=50)	Group II (n=50)	Group III (n=50)	P
Rate of cervical dilatation (cm/hr)	1.9± 0.54	1.8± 0.58	0.98± 0.55	0.001
Duration of 1st stage (hours)	2.1± 0.54	2.3± 0.61	3.1± 0.78	0.001
Duration of 2nd stage (minutes)	31.0± 7.53	31.4± 7.19	33.9± 7.2	> 0.05
units of Oxytocin	5.3± 0.54	7.2± 0.74	14.7± 0.65	0.001
Labor pain*				
•Moderate	35 (70%)	30(60%)	18 (36%)	< 0.05*
•Severe	15(30%)	20(40%)	32(64%)	
Values are given as mean ± SD unless otherwise mentioned				
*Values are given as no.%				

Table 3. Neonatal outcome in the studied groups

	Group I (n=50)	Group II (n=50)	Group III (n=50)	P
Birth weight (kg)	2.9± 0.14	3.0± 0.18	3.1± 0.19	>0.05
APGAR score				
•1 minute	7.2± 1.08	6.8± 1.04	7.0± 1.00	0.01
•5 minute	9.30.69	8.4± 0.70	8.1± 0.73	0.01
NICU admission*	1(2%)	4(8%)	6(12%)	0.01
Values are given as mean ± SD unless otherwise mentioned				
*Values are given as no.%				

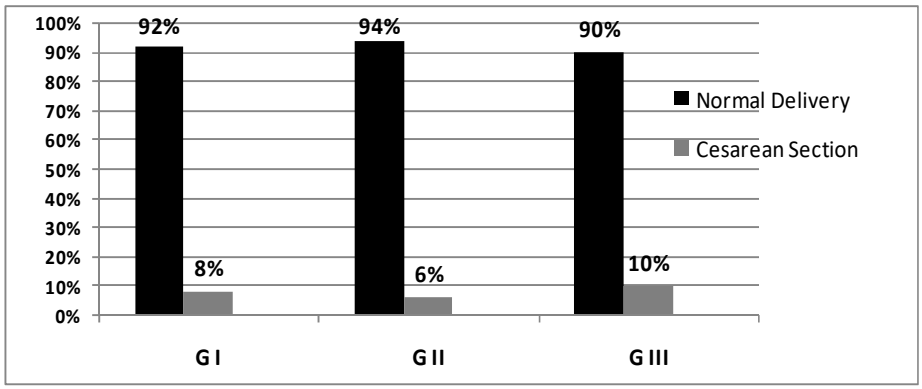

Figure 1. Mode of Delivery among the Studied Groups (p>0.05)

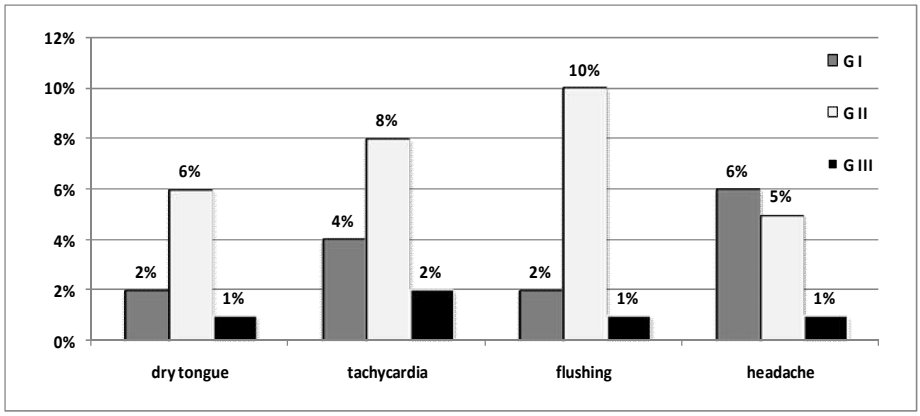

Figure 2. Adverse Effects among the Studied Groups (P < 0.05)

oxytocin needed for augmentation of labor and the degree of severe pain were significantly lesser in both groups compared to control ($p<0.001$). Figure (1) shows mode of delivery among studied groups, no statistically significant difference was found between groups ($p>0.05$). Table (3) shows neonatal outcomes among the studied groups, no statistically significant difference was present as regard to birth weight ($p>0.05$) on the other hand APGAR score was significantly higher and NICUE admission was significantly lesser in group I&II compared to control group ($p<0.01$). Figure (2) shows adverse effects among the studied groups, there were statistically significant difference in the occurrence of maternal adverse effects (dry tongue, headache, tachycardia and flushing) in group I&II compared to control groups ($p<0.05$).

DISCUSSION

Reducing the length of labor is a highly desirable goal of intrapartum care, both from a perspective of maternal and fetal well-being, and for the providers of the birth services. Avoiding along, protracted labor entails shorter exposure to pain, anxiety and stress and would thus translate into a major improvement in maternal satisfaction with the childbirth experience (Dhungana *et al.,* 2019). Drotaverine, an isoquinolone derivative is a superior smooth muscle relaxant which acts specifically on spastic sites and corrects the cAMP and calcium balance relieving smooth muscle spasm. This inhibitory action is detected only in lower uterine segment during labor since muscle fibers in upper uterine segment are strongly affected by contractile effect of oxytocin. Use of drotaverine during pregnancy was proved to be free of any teratogenic and embryotoxic effects (Tahira *et al.,* 2018). In this study there was no statistically significant difference among studied groups as regard to maternal age, BMI, GA, cervical dilatation and cervical effacement at start of study ($p > 0.05$). The rate of cervical dilation was significantly higher in group 1&II compared to the control group; also duration of 1st stages was significantly shorter in the same groups while no significant difference in duration of 2nd stage were present among the 3 groups, the degree of severe pain and the need for oxytocin augmentation doses were significantly lesser in both groups compared to control ($p<0.001$). These finding are in agreement with Sekhavat *et al.,* 2012 and Dhungana *et al.,* 2019.

Sharma *et al.,* 2001 reported a reduction of 218 minutes in the duration of labor. Singh *et al.,* 2004 also demonstrated a mean reduction of 15% and 19% in the duration of the 1st and 2nd stages of labor, respectively with the use of drotaverine. On the other hand these results are in contrary to what was reported by Gupta *et al.,* 2008 who showed no significant effect of drotaverine hydrochloride on cervical dilation. Hyoscine-N-butylbromide is a muscarinic antagonist that acts as a cervical spasmolytic agent. Our study showed a significant effect of Hyoscine-N-butylbromide on shortening duration of 1st stage of labor which agreed with what had been reported by Sekhavat *et al.,* (2012) who showed a reduction of first stage duration in primigravida and multigravida. Sirohiwal *et al.,* ;2005 evaluated the effect of Buscopan suppositories in the active management of labor and found a significant difference in the duration of labor between the control and study groups (368.05 ±133.0 min versus 123.86±68.89 min, respectively), however our results were against what was reported by Al Dohami and Al Matari 2002 and Gupta *et al.,* 2008 who found no effect on either the duration of the active phase of labor or the rate of cervical dilation. In this study there was no statistically significant difference among studied groups as regard to mode of delivery, duration of 2nd stage of labor and these results agreed with what was reported by Tar *et al.,* 2002. As regard to severity of labor pain, it was lesser in groups I and II compared to group III (30% & 40% vs. 64% respectively) $p<0.05$ this is due to spasmolytic analgesic effect of both drugs. These finding were in agreement whith Sirohiwal *et al.,* 2005, Samuel *et al.* 2007, Roy *et al*., 2007 and Aggarwal *et al.,* 2008. As regard to adverse effects of drugs used in this study, there were statistically significant difference in the rate of dry tongue, headache, tachycardia and flushing in group I&II compared to control groups ($p<0.05$) these finding were comparable to Mandal *et al.,* 2018 and Dhungana *et al.,* 2019. As regard to neonatal outcomes, no statistically significant difference was present as regard to birth weight ($p>0.05$) on the other hand APGAR score was significantly higher and NICUE admission was significantly lesser in group I&II compared to control group ($p<0.01$) these finding were agreed with what was reported by Tewari *et al.,* 2003 and Sharma *et al.,* 2009.

Conclusions

Both spasmolytic drugs used in this study have significant effects on shortening of 1st stage of labor with lesser units of oxytocin need for augmentation with good analgesic effect and good neonatal outcome however, Drotaverine hydrochloride is preferred as it was more effective beside it has the strongest labor pain relieve and lesser maternal adverse effects.

Recommendations

We recommend using of either drug in enhancing first stage of labor however, Drotaverine hydrochloride is preferable as it is more effective with minimal maternal adverse effects. More randomized trials on a larger scale are needed to evaluate the efficacy and safety of these drugs in labor**.**

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