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The efficacy of intravenous hyoscine-n-butylbromide for the acceleration of labour in primiparous women: a randomised controlled trial

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Abstract

Background: Antispasmodic agents have been used to hasten labour despite little high-quality evidence to support their efficacy.
Objective: To establish the safety and efficacy of hyoscine-N-butylbromide in accelerating labour in primiparous women.
Methods: A randomised, double-blinded, placebo-controlled clinical trial was conducted at the Aga Khan University Hospital Nairobi, Kenya. Consenting primiparous women in spontaneous labour at term were randomised to receive either 40mg of hyoscine-N-butylbromide or sterile water-for-injection intravenously once confirmed to be in active labour. The dose could be repeated once after four hours. The main outcome measure was the duration of labour. Secondary outcome measures were rate of cervical dilatation and postpartum satisfaction score. Safety aspects such as drug adverse effects, APGAR scores and postpartum hemorrhage were also explored.
Results: Between October 2009 and July 2010 a total of 85 women were randomised and 79 yielded data for analysis. Of these 37 received hyoscine-N-butylbromide and 42 received placebo. There was no significant difference in the mean duration of active labour to second stage between the drug and placebo arms (396.2 versus 389.3 minutes, respectively, p=0.881, 95% CI -85.9 to 99.8). The mean rate of cervical dilatation in the drug arm was 1.17 centimetres per hour (cm/hr) compared to 1.22cm/hr in the placebo arm. This difference was not statistically significant (p value=0.832). The postpartum satisfaction scores were similar between the two arms. Hyoscine-N-butylbromide was well tolerated without any major adverse effects observed in either arm.
Conclusion: Hyoscine-N-butylbromide does not shorten the duration of labour in first time parturients in spontaneous labour. It also does not change maternal satisfaction with care received and is not associated with major adverse outcomes in the mother or newborn.

Keywords: Antispasmodics, Hyoscine-N-butylbromide, Labour

Introduction

The global maternal and infant mortality and morbidity ratios are unacceptably high and developing nations bear the greatest burden (1). Labour protraction disorders have been associated with increased perinatal morbidity and mortality (2). Other sequelae of protracted of labour include postpartum hemorrhage and pelvic floor injury. Obstructed labour is the fourth leading cause of maternal mortality worldwide. It is desirable to develop strategies that can safely shorten labour to prevent such eventualities.

The progress of labour is a sum result of a complex interplay of fetal (size, presentation, position), uterine (normal development, contractions) and pelvic (shape and size) factors among others. Active management of labour means putting in place measures aimed at controlling the labour process, other than passive observation (3). Early amniotomy and oxytocin augmentation is one of the key approaches of active management of labour, others being strict criteria for diagnosing labour, and continuous professional support in labour. To achieve progressive labour, cervical dilatation is just as important as sufficient uterine activity.

Hyoscine-N-butylbromide (in the form of Buscopan®, Boehringer Ingelheim) has been used in Kenya, and indeed other parts of the world with a view of speeding up labour. It is a quaternary ammonium derivative, which exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary, and genitourinary tracts by blocking the action of acetylcholine at parasympathetic sites in smooth muscle. After intravenous (IV) administration, Buscopan® is rapidly distributed into the tissues with onset of action in 10 minutes. Duration of action after IV administration is 2 hours. Hyoscine-N-butylbromide does not pass the blood–brain barrier, and plasma protein binding is low. The half-life of the terminal elimination phase is about 4.8 hours. Approximately

half the clearance is renal, and the main metabolites found in urine have no significant clinical action. Side effects may include dry mouth, facial flushing, dryness of the skin, photophobia, loss of accommodation, urinary urgency and retention, and constipation. The mechanism by which it may act in the context of labour has not yet been elucidated. It is labelled by the Food and Drug Administration (FDA) in pregnancy class C.

There are few prospective studies on the safety and efficacy of hyoscine-N-butylbromide in labour (4-6). They include different parities, dosages, dosing frequencies, routes and timing of administration. Sirohiwal *et al* (4) used a non-randomised prospective design to test the effect of hyoscine-N-butylbromide suppositories on first stage of labour. The conclusion was that hyoscine-N-butylbromide significantly reduced the duration of first stage of labour. This study included both primiparous and multiparous women yet it is known that the rate of cervical dilatation and progress of labour in these groups is different (7). Samuels *et al* (5), employed a randomised controlled double-blind design to test the effect of intravenous hyoscine-N-butylbromide on first stage of labour. They showed a significant reduction in the duration of first stage of labour by 31.7%. This study also included a mix of both primiparous and multiparous women. The numbers recruited were also too small to make significant conclusions on either group alone. Secondly, their institutional protocol employed active management of labour which is not routine practice in most maternity units in East Africa. Lastly, the dose of hyoscine-N-butylbromide used was 20mg intravenous as a single dose while a dose of 40mg is used in our set-up. Gupta *et al* (6) examined drotaverine (intramuscular) versus hyoscine-N-butylbromide (intravenous) in the first stage of labour. The randomisation procedure was, however, not clear. The study was also not blinded, making bias possible. The results conflicted with the earlier two studies concluding that there was no difference in the rate of cervical dilatation between hyoscine-N-butylbromide, drotaverine and no drug. It also included both first time parturients and multiparae. Two related studies have been done locally with conflicting findings. Odongo (8) examined the effect of intramuscular hyoscine-N-butylbromide (Buscopan®) compared to placebo on the rate of cervical dilatation in first time parturients given between 4 and 6cm of cervical dilatation. The design was quasi-randomised and no blinding was applied. The dose of hyoscine-N-butylbromide was 20mg as single dose intramuscularly. Hyoscine-N-butylbromide was found to significantly increase the rate of cervical dilatation. However no difference in duration of second and third stages of labour, APGAR score or blood loss. Mabeya (9) examined the effect of hyoscine-N-butylbromide 40mg intramuscularly as a single dose on rate of cervical dilatation from 7 to 8cm. The design was randomised but not placebo controlled and no blinding was employed. Both first time parturients and multiparae were included. No significant difference in the rate of cervical dilatation, duration of second and third stages of labour, blood loss and APGAR scores was found. Both local studies reported no adverse events to hyoscine-N-butylbromide concluding that it is safe for use in labour.

This study therefore aims to establish the safety and efficacy of hyoscine-N-butylbromide in accelerating labour in primiparous women using a more robust methodology. The study had two specific objectives. Firstly, to compare the combined duration of active labour and second stages in first time parturients receiving intravenous hyoscine-N-butylbromide and those receiving placebo. Secondly, to evaluate for differences in participant satisfaction between the first time parturients receiving hyoscine-N-butylbromide and those receiving placebo.

Materials and Methods

Study design: A randomised, placebo-controlled, double-blinded clinical trial.

Outcome measures: The primary outcome measure was the combined duration of labour from diagnosis of active phase to delivery of the baby. The secondary outcome measures were the rate of cervical dilatation and the patient satisfaction scores.

Study setting: The study was carried out at the Antenatal Clinics (ANC) and maternity unit of the Aga Khan University Hospital, Nairobi- Kenya.

Study population: The study population consisted pregnant women at or above 18 years delivering at the Aga Khan University Hospital Nairobi. Women were eligible for the study if they met the following criteria; Primiparous, singleton term pregnancy, cephalic fetal presentation, suitable for vaginal delivery and had no contraindications to using hyoscine-N-butylbromide (e.g. myasthenia gravis, megacolon and narrow-angle glaucoma, hypersensitivity to hyoscine-N-butylbromide). In addition, a woman could be recruited in the delivery suite and consented if she met the above criteria and presented in spontaneous latent phase of labour. Women who required induction of labour or presented before 38 weeks were excluded from the study.

Sample size: In calculating the sample size several assumptions were made. The minimal clinically relevant difference in mean duration of labour was taken to be 60 minutes (1 hour). This was set following discussions with consultants in the department as well as from a similar study (5). The standard deviation of the mean duration of labour was taken as 80.7 minutes

based on a previous study (4). One sided alpha (α) was set at 0.05 and β was set at 0.10, therefore, power (1-β) at 0.90. It was calculated that a minimum of 39 participants would be required in each arm-hyoscine-N-butylbromide arm and placebo arm.

Randomisation and data collection: Study participants were recruited from the antenatal clinic and labour ward (only if in latent phase of labour). All potential participants were approached by the researcher after 30 weeks gestation and screened for eligibility. Eligible women then received written-English and Kiswahili- and verbal explanation of the purpose and procedure of the study. Written signed informed consent was then sought. Those women giving written informed consent were enrolled into the study. Their files and revisit cards were tagged with a special orange sticker for ease of identification when admitted in labour.

Using a computer program, random sequence of numbers were generated. Each of the random numbers was sequentially assigned either drug or placebo. This randomisation code was then handed over to a designated pharmacist. On admission of a recruited patient, the pharmacist was alerted and proceeded to prepare-with aseptic precaution- a pair of syringes per code number. Each syringe of a pair contained either 2ml (40mg) hyoscine-N-butylbromide (Buscopan®) or 2ml sterile water for injection depending on the next available number on the randomisation code. Two syringes were prepared per code to allow for a repeat dose four hours after the first administration. Each pair was labelled with only the randomization code number and handed over to the labour ward staff. Fresh syringes were prepared as need arose using the code. Both hyoscine-N-butylbromide and sterile water for injection are colourless and, therefore, indistinguishable from each other. Once a recruited client was diagnosed to be in active labour at 3 to 6 cm cervical dilatation, she received the contents of one of the syringes intravenously. Those women progressing in labour and not delivered four hours after the first dose received the second dose.

During labour, data on labour and delivery progress, interventions and outcome were collected. The monitoring of labour was done using the revised WHO partograph. The application of interventions such as amniotomy, augmentation of labour and decision for operative delivery was at the discretion of the team on duty as per the existing policies and protocols. Prior to discharge, each participant was interviewed on their views on the labour and delivery experience. Based on prior studies examining maternal satisfaction with various aspects of the delivery experience (10, 11), a five point Likert type questionnaire with four items was developed. The four questions asked the participants to rate, based on expectations, their overall experience of labour, the pain control during labour, the duration of labour and whether they would consider receiving the study 'drug' in their next labour. The maternal satisfaction questionnaire was, prior to the start of the study piloted on twenty postnatal women. They all easily completed the questionnaires and on enquiry had no difficulties in understanding of language or content. Statistically the scale was found to be reliable with a Cronbach alpha of 0.68. This was interpreted as acceptable reliability (12).

Statistical analysis: All verified raw data were coded and entered into the Statistical Package for Social Sciences (SPSS) program, version 11.5 (SPSS Inc, Chicago, IL, USA). Data analysis was performed using the same software. Quantitative variables were compared using unpaired independent t test while categorical variables were compared using chi ($\chi 2$) test. A p-value of <0.05 was considered statistically significant. The data on duration of labour and rate of cervical dilatation were analysed on an intention-to-treat basis. However, data for adverse events, maternal satisfaction scores, postpartum haemorrhage, and postpartum haemoglobin were analysed per treatment.

Ethics: Written ethical approval for this study was sought and obtained from the Aga Khan University Hospital ethics committee prior to commencement of the study.

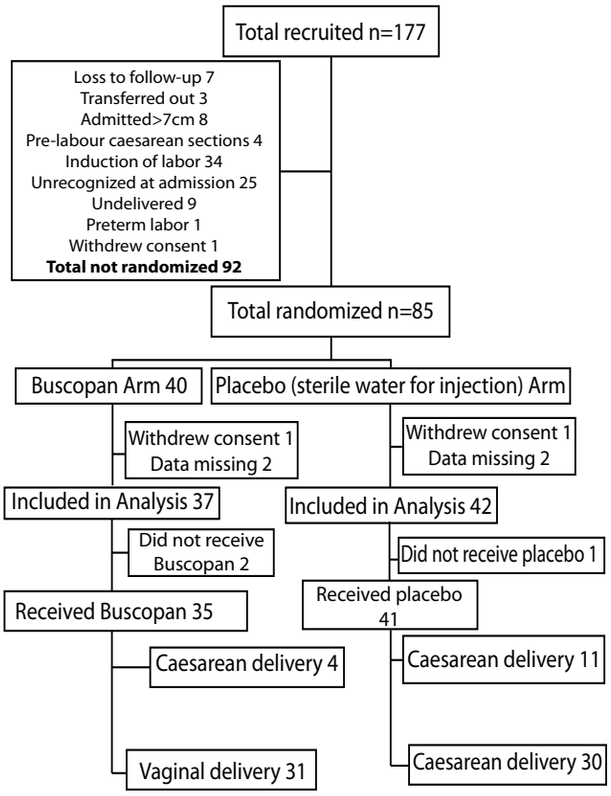
Results

Data collection was carried out over ten months-between October 2009 and July 2010. A total of one hundred and seventy seven participants were recruited. Ninety-two participants were not randomised: 7 were lost to follow up, 3 transferred out, 8 were admitted at a cervical dilatation beyond 7 centimeters, 4 had prelabour caesarean sections, 34 had induction of labour for various indications, 25 were not recognized as recruited at admission into labour, 9 were undelivered at the time of data analysis, and 1 withdrew consent and another had preterm labour and delivery at 32 weeks gestation. It was found necessary in the course of data collection to recruit more participants than initially planned due to a greater number of losses during the study than previously projected.

Eighty-five participants were randomised. Two participants, one allocated to hyoscine-N-butylbromide and the other to placebo arms, withdrew consent after randomisation and were excluded from analysis. Four of the randomised patients (2 in the

hyoscine-N-butylbromide arm and 2 in the placebo arm) had missing data and were also excluded from analysis. Seventy-nine participants were included in the data analysis. Three participants did not receive their allocation-two in the hyoscine-N-butylbromide and one in the placebo arm-two had short labour and delivered before they received their allocation and one had an early caesarean section due to non-reassuring fetal status. However, these participants were included in the intention-to-treat analyses. Thirty-five participants received hyoscine-N-butylbromide and 41 received placebo. Of these thirty-one in the hyoscine-N-butylbromide arm and 30 in the placebo arm delivered vaginally (Figure 1).

Figure 1: Flow diagram of study participants



Baseline characteristics of randomised participants: The two arms of the study were similar in terms of baseline characteristics. There was no significant difference in age, cervical dilatation at randomisation, birth weight, and APGAR scores at 5 minutes between the participants allocated to hyoscine-N-butylbromide and placebo. There was no significant difference between the arms in events in labour such as amniotomy, oxytocin augmentation, mode of delivery, postpartum anaemia (haemoglobin concentration less than 10.0g/dl) and development of postpartum haemorrhage (Table 1).

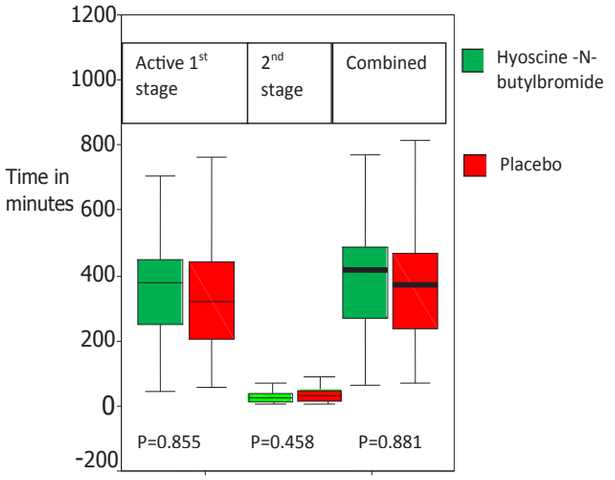
Table 1: Baseline characteristics of study participants

Variable	Hyoscine-N-butylbromide arm mean±1SD	Placebo arm mean ± 1SD	
Age (years)*	26.7±4.2	27.5±3.5	0.387
Gestational age (weeks)*	39.9±0.8	40.0±0.9	0.798
Cervical dilatation at randomisation (centimetres)*	4.3±1.0	4.3±0.9	0.942
Birth weight (grams)*	3134±422	3286±334	0.079
APGAR score at 5 minutes**	10.0(8,10)	10.0(7,10)	-
Amniotomy	24/37 (64%)	33/42 (79%)	0.175
Oxytocin augmentation	16/37 (43%)	26/42 (62%)	0.097
Caesarean delivery	5/37(14%)	11/42 (26%)	0.162
Post-partum Hb <10g/dL §	13/28 (46%)	13/29 (45%)	0.903

*values represent mean and ± 1 standard deviation
**values represent median, with minimum and maximum values in parentheses
§ number of those receiving allocation and delivering vaginally
***p value of <0.05 was considered significant

Primary outcome: This was the time interval from the first diagnosis of active labour to the delivery of the infant. This includes the duration of active and second stages of labour. Data for 63 participants (those recruited, randomised and delivered vaginally) were analysed for the primary outcome on the intention to treat; 32 from hyoscine-N-butylbromide arm and 31 from placebo arm. There was no significant difference in the mean duration of combined active labour and second stage in the hyoscine-N-butylbromide and placebo arms (hyoscine-N-butylbromide 396.2 minutes, placebo 389.3 minutes, mean difference 7.0 minutes, 95% confidence interval -85.9 to 99.8, p value=0.881). The mean duration of active labour in the hyoscine-N-butylbromide arm was 362.8 minutes compared to 354.7 minutes in the placebo arm. This was not statistically significant (mean difference 8 minutes, 95% confidence interval -79.6 to 95.6, p value 0.855). Likewise, there was no significant difference in the duration of second stage between the arms (hyoscine-N-butylbromide 29.9 minutes, placebo 33.7 minutes p value= 0.458) (Figure 2).

Figure 2: Comparison of the duration of active labour, second stage and combined active and second stage between hyoscine-N-butylbromide and placebo arms. (P values calculated by the unpaired t-test)



Secondary outcomes: Data from 65 participants (33 from hyoscine-N-butylbromide and 32 from placebo arms) were analyzed for the rate of cervical dilatation on an intention to treat. The average rate of cervical dilatation in the hyoscine-N-butylbromide arm was 1.17 cm/hr compared to 1.22cm/hr in the placebo arm. This difference was not statistically significant (mean difference 0.5, 95% CI -0.5 to 0.4, p value=0.832).

Fifty-eight (76%) of the participants who received their allocation filled the satisfaction questionnaire, 38 (80%) from the hyoscine-N-butylbromide arm and 30 (73%) from the placebo arm. Satisfaction data were analysed according to the actual treatment received. The mean composite satisfaction score in the hyoscine-N-butylbromide arm was 13.7 and in the placebo arm 14.4 (mean difference 0.7, 95% CI -2.5 to 1.1; (p value=0.447).

Discussion

Hyoscine-N-butylbromide used as an intravenous injection at a dose of 40mg in early active labour (and repeated once in four hours) does not accelerate labour compared to placebo. However, the drug is safe without significant short term adverse effects to either the mother or baby. The drug did significantly affect maternal satisfaction with the labour process.

Previous studies have reported conflicting results. Gupta and colleagues (6) found that hyoscine-N-butylbromide did not shorten the duration of labour or hasten cervical dilatation, even though, Samuels *et al* (5) reported hyoscine-N-butylbromide to shorten labour by 31.7% or 72 minutes (p=0.001). Sirohiwal *et al* (4) found the mean duration of active labour to be significantly shortened by 244 minutes in the hyoscine-N-butylbromide group compared to the control group (p<0.001). This study was non-randomised and not placebo controlled increasing risk of bias and hyoscine-N-butylbromide was administered as a single 20mg rectal suppository. In a case control study from Kenya (8), hyoscine-N-butylbromide significantly increased the rate of cervical dilatation compared to control, but there was no difference in the durations of second stage. In this study, hyoscine-N-butylbromide was administered as a single 20mg intra-muscular injection.

There are therefore glaring differences in the methodology used in these studies. Our study was superior in that we had a more stringent eligibility criteria compared to the studies mentioned. It is also difficult to make objective comparisons of these studies considering the differences in dosage, timing and route of administration of the drug. It is not surprising that, a Cochrane review including 21 studies (3286 participants) done after and incorporating our study's results, assessing various antispasmodics for shortening labour (13) found low quality evidence on their efficacy in reducing the duration of first stage of labour. However, there are other basic considerations when examining interventions to reduce the duration of labour. First, there is no evidence-based threshold reduction in labour duration that is associated with improvement in important clinical outcomes including patient satisfaction. Furthermore, other interventions that have been shown to reduce the duration of labour, such as active management, have not been shown to change maternal and neonatal morbidity (14).

On the positive side, it is encouraging that despite its low efficacy, our study and similar other studies do not find hyoscine-N-butylbromide to have any significant adverse effects both to the mother and baby. Only one participant in the hyoscine-N-butylbromide arm reported transient palpitations which could not be directly associated to the drug. All published studies reviewed either reported no adverse effects (4, 5, 8, 9) with hyoscine-N-butylbromide or an adverse effect rate similar to placebo (6). However, no long-term follow up safety studies in mothers and infants are available.

Conclusion

This study, using a robust clinical design found that hyoscine-N-butylbromide as an intravenous injection of 40mg in early active labour (and repeated once in four hours) did not accelerate labour. However, it is a safe drug without significant maternal and infant short term adverse effects. Its administration does not affect maternal satisfaction significantly. However, since a subsequent Cochrane review showed low quality evidence suggesting benefit of antispasmodics, it is advised that large, well-designed multicenter studies need to be conducted on this subject.

Conflict of interest: None to declare.

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