Comparison of 60mg and 40mg doses of hyoscine butylbromide on labor outcomes at Moi teaching and referral hospital, Eldoret, Kenya

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Received: 2nd June, 2018 **Accepted:** 14th August, 2018

Abstract

Introduction: Effects of 40mg of Hyoscine butylbromide (HBB) in reducing duration of active phase of labor are well documented. However effects of 60mg have not been well studied despite the fact that it is often used.

Objectives: To compare the effect of 60mg and 40mg of HBB on the duration of labor.

Materials and Methods: A single-blind randomized controlled clinical trial was carried out at Moi Teaching and Referral Hospital from January to April 2014. At the onset of active phase of labor (4–5 cm) they were randomized into two arms. Those in the control arm received 40mg of HBB intravenously while those in the study arm received 60mg. Information on progress of labor; mode of delivery, amount of blood loss and neonatal APGAR scores was recorded.

Results: A total of 114 primigravid women were recruited into the study and randomized into the control arm (n=59) and study arm (n=55). The 40mg and 60mg arms were comparable for socio-demographic and obstetric characteristics. Injection to delivery time was 340 (223–483) minutes in the 40mg arm and 305 (253–475) minutes in the 60mg arm, a difference that is not statistically significant (p=0.905). Seven (12 %) and five (9 %) of patients in the 40mg and 60mg arm respectively needed delivery via caesarean section (p=0.602). 5 minute APGAR scores were 9.7 in the 40mg arm and 9.8 in the 60mg arm (p=0.727. Estimated blood loss was 300mls in the 60mg arm and 350mls in the 40mg arm (p=0.152).

Conclusion: Head to head, 60mg of parenteral HBB is not superior to 40mg on their effects on duration of labor and feto-maternal outcomes.

Keywords: Hyoscine Butylbromide, Buscopan, Labor.

Introduction

Prolonged Obstructed labor is one of the leading causes of maternal morbidity and mortality (Say et al. 2014). Safe, proven and affordable measures employed to accelerate labor include use of Uterotonics such as oxytocin and early Amniotomy (Smyth, Markham, and Dowswell 2013; Bidgood and Steer 1987; Akoury Hani A; MacDonald Francis J; Brodie Glen; Caddick Robert; Chaundry 1991). Some anti-spasmodics have also been used for this purpose, including Hyoscine Butylbromide (HBB), Drotaverine Hydrochloride, Valethamate Bromide, Rociverine, and Camylofin Dihydrochloride (Rohwer, Khondowe, & Young, 2013). Of these, HBB has been better studied and commonly used at Moi Teaching and Referral Hospital (MTRH) and in many other maternity units. Several randomized controlled trials have evaluated the effect of HBB on the active phase of labor, most showing a positive effect of reducing the duration of active phase of labor without triggering any maternal or neonatal adverse effects. In a Jamaican Teaching Hospital, 129 women in labor were given either 20mg of HBB or 1cc of normal saline intravenously in the early active phase. The duration of active phase was shorter by an average of 31.7% in the HBB arm without significant change in the duration of the second and third stages of labor, and no difference in blood loss or in APGAR scores (Samuels et al. 2007). Other studies have shown similar effects (Makvandi, Tadayon, and Abbaspour 2011) (Qahtani & Hajeri, 2011).

HBB is an alkaloid that acts by inhibiting cholinergic transmission in the abdominal and pelvic parasympathetic ganglia. Through this it relieves spasm in the smooth muscles of the female genital organs, aiding cervical dilatation (Aggarwal, Zutshi, and Batra 2008). It can be administered via the parenteral route, oral route or as a suppository and does not cross the blood brain barrier. Many of the listed undesirable effects, assigned to its anticholinergic properties are generally mild and self-limited. HBB has an excellent safety profile and as such has been approved by the Food and Drug Administration in the USA for preoperative use in women scheduled for caesarean section. The drug is also compatible with breastfeeding (Kauffman, R. E., Banner, W., Berlin, C. M., Blumer, J. L., Gorman, R. L., Lambert, G. H., & Wilson 1994).

Doses commonly studied in literature include 20mg or 40mg of HBB. At MTRH we had observed that 60mg of parenteral HBB is administered with a general believe that the higher the dose the shorter the labor. In this study we thus set out to establish whether 60mg of HBB further shortens active phase labor without adverse maternal and fetal effects.

Materials and Methods

Study Design: This was a single-blind randomized controlled clinical trial carried out at the maternity unit of MTRH, Eldoret, Kenya with data collected between 1st January and 30th April 2014. There were two arms; control arm with 59 participants and study arm with 55 participants. The investigator knew what arm the participants fell but the participants were blinded.

Study Setting: The study was carried out at the maternity unit of MTRH. This is the second National Referral Hospital in Kenya, located in Uasin Gishu county, western part of Kenya. The hospital has a bed capacity of 800 and serves population of western Kenya, parts of Eastern Uganda, and the southern Sudan. Its Obstetrics unit has a bed capacity of approximately 160 of which 28 are specifically for antenatal mothers and 17 for labor and delivery. In the year 2014, an average of 30 - 35 deliveries were conducted every 24 hours in MTRH. Of these about 15% were via Caesarian Section.

Study Population: The study population was expectant mothers in labor. The target population was expectant mothers in labor seeking care at MTRH.

Sample Size: The number required in order to be 95% sure that we detect at least one hour reduction in the duration of labor when 60mg of HBB is used compared to the 40mg of the same drug was determined using the following formula (Hulley S.B, Cummings S.R, Browner W.S, Grady D.G 2007).

$$n = 4\left(\frac{Z_{\beta} + Z_{1-\alpha/2}}{\delta}\right)^2 \sigma^2$$

$z_{1-\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the standard normal distribution under type I error assumed to be 5% while $z_{1-\beta}$ is the $100(1-\beta)$ percentile of the standard normal distribution under type II error assumed to be 20%, δ is the margin of error, taken to be one hour in this case, σ^2 is the pooled variance. That is the, combined variance when the 40mg of HBB is used and when the 20mg of the same drug is used. However, in this study we assumed that the variance under the arm with 60mg and the variance under the arm with 40mg are equal. We cross examined a couple of studies that had been done previously (Qahtani and Hajeri 2011) (Samuels et al. 2007) (Sirohiwal, Dahiya, and De 2005) to help us estimate the standard deviation for use in sample size estimation. We chose to use a standard deviation of 1.6 which is equal to 100/60 because their unit for time was minutes but we are using hours in this study.

The sample size arrived at in this case is 41 for each arm, giving a total of 82.

Data Collection Procedure: We recruited prim gravid women with term gestation (>37 weeks and <42 weeks), 18 years or older, singleton gestation, cephalic presentation & spontaneous labor while excluding those with hypersensitivity to HBB, Contra-indication to vaginal delivery and scarred uterus. At the point of administering the drug those with chorioamnionitis, ante-partum hemorrhage, those who withdrew their consent, had intra-uterine fetal demise or cervical dilatation > 5cm were excluded from the study. Patients who met the inclusion criteria were included in the study (Fig. 1).

Study participants were recruited from the MTRH antenatal ward by two research assistants, both qualified midwives. There were two arms; control arm (40mg) and study arm (60mg). The investigator knew what arm the participants fell but the participants were blinded. In the control arm the participants were given 40mg of intra-venous HBB in the early active phase of labor i.e. 4 – 5cm while in the intervention arm the participants received 60mg of intra-venous HBB, also in the early active phase of labor.

Sampling Technique: Simple random sampling was employed. The participants did not know which arm of the study they were in. The investigator knew which arm of the study the participants were in. A computer generated program was used to generate a random sequence of numbers and assign each into either 40mg or 60mg in equal proportion. Sequentially numbered, sterile syringes were then prepared using the random numbers and placed in an opaque box. The moment a participant was due to receive HBB, the principal investigator opened the box and blindly picked the syringe he encountered, counter-checked the number on the syringe with the database to determine whether to give 40mg or 60mg of HBB. He then loaded the drug and administered it. There were two identical registers, one maintained by the principal investigator and the other by the maternity unit research assistant. They both had the participant's in-patient number, code number and the dose of drug given. Every evening the two registers were reconciled to ensure data accuracy. The drugs and consumables used in administering the drugs were locked up in a cabinet accessible by only the principal investigator. The participant's in-patient chart also had a sticker with the code of the dose of HBB given.

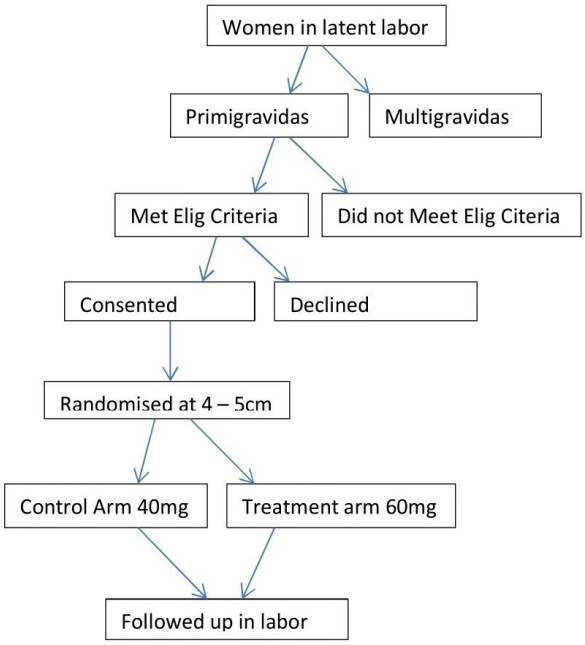

Fig. 1: Study procedure

The investigator was working with two research assistants, both qualified midwives working in the maternity unit. Study participants were recruited from the MTRH antenatal ward. They were primigravidas at term. Once a client that fits the study criteria was identified, the research assistant spent some time with her and explained the purpose of the study. She was given a chance to seek clarification and raise any concerns. After this she was asked to make a decision whether or not to participate in the study. Those willing were asked to sign a consent form.

In the control arm the participants were given 40mg of intra-venous HBB in the early active phase of labor i.e. 4 – 5cm while in the intervention arm the participants received 60mg of intra-venous HBB, also in the early active phase of labor. The investigator administered the drug. This was after assessing the participant and ascertaining that she falls within the study criteria. He then immediately labeled the chart according to the code on the syringe and recorded the chart details in a register. The brand of HBB used was Buscopan manufactured by Boehringer Ingeiheim. Labor progress was monitored with the standard WHO partograph. Vaginal exams were done every four hours or earlier if it was deemed necessary. Fetal status was monitored by intermittent auscultation every thirty minutes in active phase labor and every 15 minutes in second stage labor. This was done by the principal investigator and the primary midwife taking care of the patient. The outcomes under investigation all had a place on the partograph and were routinely recorded in all deliveries. After delivery the principal investigator or the research assistant in-putted the data both from the in-patient chart and the partograph on a semi-structured questionnaire.

Stopping Rules: The study was to be stopped if any life threatening feto-maternal adverse reactions attributed to HBB occurred. This was to include respiratory failure, anaphylactic reaction and perinatal mortality.

Data Collection: Interviewer administered semi-structured questionnaire were used to collect data by the research assistants. They also cross-checked to make sure patients recruited met the eligibility criteria. Other data was obtained from medical records i.e. antenatal card, in-patient chart and the partograph. It contained bio-data, demographic data and information on labor progress from admission till end of third stage.

Data Analysis

Age was categorized into 18 – 22 years, 23 – 27 years and 28 – 32 years. Data analysis was done using SAS version 9.3. Categorical variables were summarized as frequencies and the corresponding percentages. Continuous variables that assumed the Gaussian distribution were summarized as mean and the corresponding standard deviation (SD). Continuous variables that violated the Gaussian assumptions were summarized as median and the corresponding inter quartile range (IQR). Gaussian assumptions were assessed using Shapiro-Wilks normality test. Association between categorical variables was assessed using Pearson's Chi Square test while the association between skewed continuous and categorical variables was assessed using Wilcoxon two sample test (Mann Whitney U test). The association between normally distributed continuous variables and categorical variables was assessed using two sample t-test. Association between dependent continuous variables was assessed using paired t test for normally distributed continuous variables and sign rank test between skewed continuous variables. Results were presented using tables and graphs.

Ethics

1. Approval was sought from and granted by Moi University IREC and the MTRH administration.
2. Individual informed consent was sought from each participant before carrying out the study. The participants were informed that their decision to participate or not to participate in the study would NOT affect their medical care. Informed consent was obtained by the research assistants who were not directly providing care to minimize coercion.
3. Those who declined to give informed consent were not in any circumstance denied medical care that best suited their needs.
4. Cross over effects among patients on 60mg and 40mg of HBB was checked by clear recording of their individual data at two points. First in the antenatal ward where the research assistant recorded the dose given and the patient's in-patient

number. Secondly the principal investigator recorded the dose given and the patient's in-patient number soon after giving the drug in a separate register. Later the two registers were reconciled and validated.

5. Privacy and confidentiality of information was guaranteed by keeping questionnaires in key locked data cabinets, password-coded databases, limiting access to data only to the principal investigator. Consenting process took place in private consultation room.

Results

One hundred and seventy patients met the initial eligibility criteria, 114 of who were eventually recruited (Fig. 2). 48% (n=55) received 60mg of HBB while 52% (n=59) received 40mg.

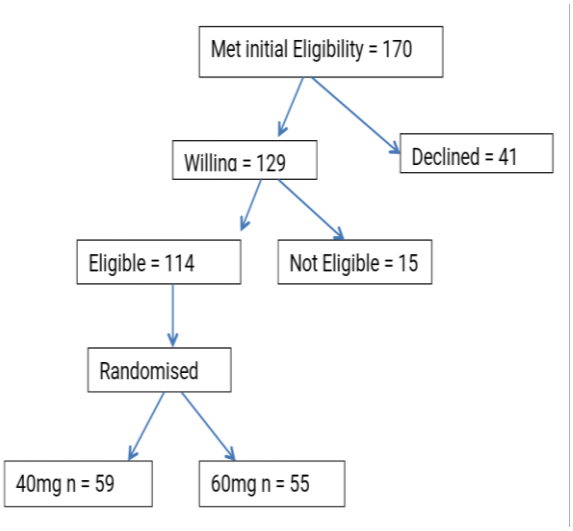

Fig. 2: Study execution

Socio-demographic and Clinical Characteristics: Age, marital status, education level, occupation and religion were similar between the 40mg and the 60mg arm. Mean gestational age was 39.6 weeks and 39.4 weeks respectively in the control and study arm. The full socio-demographic and clinical characteristics are shown in table 1.

Table 1: Socio-demographic and clinical characteristics stratified by arm

Variable	40mg arm (n=59, 52%), n(%) or Mean(SD) or Median(IQR)	60mg arm (n=55, 48%), n(%) or Mean(SD) or Median(IQR)
AGE	**22**	**21**
18 – 22 years	32	30
23 – 27 years	17	18
28 – 32 years	10	7
Marital Status		
Married	37	32
Single	19	15
Separated	4	7
Divorced	0	0
Widowed	0	0
Education Level		
Primary	18	12
Secondary	25	33
Tertiary	15	11
Occupation		
Formal employment	17	9
Self employed	40	28
Unemployed	8	12

Injection to Delivery Time: Compared to the controls, the participants who received 60mg had a shorter, though non-significant labor period, 305(253-475)minutes vs. 340(223-483) minutes, p=0.905, as shown in table 2. Estimated blood loss was 300mls in the 60mg arm and 350mls in the 40mg arm (p=0.152). 1st minute APGAR scores were 8.7 in both arms (p=0.922) while 5th minute APGAR scores were 9.8 and 9.7 in the 60mg arm and 40mg arm respectively (0.727).

Table 2: Outcomes stratified by arm

Variable	Dose		P=value
	40 mg n=59) Mean (std) or median (IQR) or n(%)	60 mg (n=55) Mean (std) or median (IQR) or n (%)	
Age	22(20-24)	21(20-23)	0.137
Gestational Age	39.4(1.2)	39.6(1.0)	0.438
Baby admitted to the newborn unit	2(4%)	3(6%)	0.670[f]
APGAR Score at 1st Minute	8.7(0.9)	8.7(1.1)	0.922
APGAR Score at 5th Minute	9.7(1.0)	9.8(0.8)	0.727
Estimated blood loss	350(300-400)	300(250-350)	0.152
Mother developed PPH	4(7%)	3(6%)	1.000[f]
Injection to Delivery time (Minutes)	340(223-483)	305(253-475)	0.905
Needed augmentation with Oxytocin	25(42%)	17(31%)	0.205
Injection to delivery time for those who received oxytocin	328(215-466)	309(239-462)	0.229
Rupture of membranes to Delivery (Minutes)	97	119	0.117
Active Management of 3rd Stage of Labor	57(97%)	54(98%)	

Mode of Delivery

Cesarean Section rate was 12% in the 40mg arm and 9% in the 60mg arm (p=0.700) (Table 3).

Table 3: Mode of delivery

Mode of Delivery	40m g(n=59)	60mg(n=55)	P value
Vaginal	52(88%)	50(90%)	0.403
Abdominal (CS)	7(12%)	5(9%)	0.700

Perineal Tears, Episiotomy, Precipitate Labor.

Table 4: Perineal tears, episiotomy, precipitate labor

Variable	40 mg (n=55)	60 mg (n=59)	P Value
Perineal Tears	9(15%)	10(18%)	0.089
Episiotomy	5(8.5%)	7(13%)	0.35
Precipitate Labor	3(0.05%)	3(0.05%)	0.124

Nine (15%) in the 40mg arm and 10(18%) in the 60mg arm sustained perineal tears at birth (Table 4). Majority (62%) of these were 1st degree tears. Only 7(0.06%) were 2nd degree or above. Five patients in the 40mg arm and 7 in the 60mg arm needed episiotomy at delivery giving an overall rate of 11%. Six (0.05%) patients had precipitate labor, 3(0.05%) in the 60mg arm and 3(0.05%) in the 40mg arm.

Adverse Outcomes: There was no mortality or severe morbidity reported in the study population.

Discussion

Overview: This trial compared clinical outcomes between 60mg and 40mg of HBB given in early active phase of labor. Effects of 40mg have been investigated and was therefore used in this study as the control. We had observed that in MTRH, 60mg of HBB is used with the believe that duration of labor is inversely proportional to dose despite the fact that its efficacy is not well documented. This study therefore sought to determine the efficacy of 60mg of HBB on labor outcomes using 40mg as the control.

Socio-demographic characteristics (Age, Occupation, Marital status, Education level) were similar in the two arms. Differences in Socio-demographics can therefore not account for the outcomes.

Injection to Delivery Time: HBB compared to either placebo or nothing has been found to reduce the duration of labor by as high as 72 minutes (Samuels et al. 2007) (Qahtani and Hajeri 2011). The present study did not find a statistical difference in the injection to delivery time between 60mg and 40mg of HBB. Other studies in literature have compared HBB with either nothing or placebo. This could thus be among the first clinical trials to compare two doses of HBB on labor outcomes.

Augmentation with oxytocin and early rupture of membranes are known to shorten labor process. With the need for augmentation with oxytocin and average duration of rupture of membranes to delivery being similar in the two groups, these two parameters did not confound the results.

Mode of Delivery: The cesarean section rate was not significantly different in the two arms. The average CS rate of 11% in the entire group falls within the World Health Organization (WHO) recommended rate of 10 – 15% (Moore 1985). This was either comparable or slightly different from some studies. In a study where rectal suppositories were compared with parenteral HBB on their effect on duration of labor in primigravidas an average CS rate of 8.46% was found. (Makvandi, Tadayon, and Abbaspour 2011). In 2007, WHO did an evaluation of global and regional cesarean section trends (Betrán et al. 2007). The global CS rate was about 15% with the developed countries having higher rates than 15% while most of the developing world had rates below 15%. Africa as a whole had estimated CS rates of 3.5% while East Africa had rates of 2.3%.

Neonatal Apgar Scores: Babies with higher APGAR scores fare better both in the immediate post-delivery and later on in life (Apgar 1952). With no difference in the 1st and 5th minute APGAR scores between the two arms, this compares favorably with other studies that looked at effects of HBB on labor outcomes. Two (0.03%) neonates from the 40mg arm and 3 (0.05%) from the 60mg were admitted to the new-born unit either with Respiratory Distress Syndrome or Transient Tachypnea of the newborn. All eventually improved and were discharged home in good general health. The good APGAR scores and low neonatal admission rates to the new-born unit demonstrates that 60mg of HBB does not have any immediate adverse neonatal effects compared to the 40mg.

Estimated Blood Loss: The median estimated blood loss was similar in the two arms, and so was the rate of PPH. 60mg of HBB is therefore not associated with higher values of blood loss after delivery as compared to 40mg. The fact that 111(97%) of women overall were managed actively in the third stage of labor may account for the few numbers of PPH. A Cochrane review showed that 'active management' is superior to 'expectant management' in terms of blood loss, post-partum hemorrhage and other serious complications of the third stage of labor (Begley et al. 2015).

Perineal Tears, Episiotomy and Precipitate Labor: A team examined medical records of 38,252 women who delivered in one medical center from January 2005 to December 2009. Of these, 96(0.25%) sustained third- or fourth-degree perineal tears (Groutz et al. 2011)**.** With an overall 2nd degree or above perineal tear rate of 0.06%, our study compares favorably with this**.**

Use of episiotomy should be limited and should be based on proper clinical judgement. Its routine use is discouraged. (Carroli and Mignini 2009) (American College of Obstetricians and Gynecologists 2006).

Overall 6 patients had precipitate labor, 3 in each arm. The overall incidence of 0.05% compares favorably with global trends. In 1998, 2% of deliveries in the USA were complicated by precipitate labor (Ventura, S. J., Martin, J. A., Cortin, S. G., Mathews, T. J., & Park 2000).

Conclusion

Head to head, 60mg of parenteral HBB is not superior to 40mg on their effects on duration of labor and feto-maternal outcomes.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement: This research was fully funded by the four authors with no external support.

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How to cite this article: Wanjala A, Kaihura D, Chemwolo B, Muruka K. Comparison of 60mg and 40mg doses of hyoscine butylbromide on labor outcomes at Moi teaching and referral hospital, Eldoret, Kenya. Indian J Obstet Gynecol Res. 2018;5(4):447-453.