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RESEARCH ARTICLE

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Comparison of Oral Misoprostol with Intravenous Oxtocin in the Prevention of Primary Postpartum Haemorrhage in ESUT Teaching Hospital: A Randomized Controlled Trial

Onyekpa IJ*, Odugu BU and Awkadigwe FI

Department of Obstetrics & Gynecology, Enugu State University of Science Technology College of Medicine and ESUT Teaching Hospital, Enugu, Nigeria.

ABSTRACT

Background: Postpartum haemorrhage (PPH) is one of the major causes of maternal mortality globally. About 14 million patients suffer from postpartum haemorrhage annually worldwide, of which about 140,000 die. The active management of third stage of labour with the use of uterotonic drugs has reduced the risk of postpartum haemorrhage significantly. The most common uterotonic drug currently in use is oxytocin but the problem of insufficient skilled manpower for its administration, inadequacy of electric power supply to ensure the stability of the drug at appropriate temperature, and its high cost have made widespread use of oxytocin difficult in the resource-poor countries. This has made the search for an effective, affordable, stable and available alternative necessary. Misoprostol, an analogue of prostaglandin-E1, has a good uterotonic activity, is highly affordable, does not require specialized skill to administer and is very stable at room temperature. It also has multiple routes of administration, which makes its use in resource-poor countries indispensable.

Aim: To determine if there is any difference in the efficacy of intravenous oxytocin over oral misoprostol in the prevention of primary postpartum haemorrhage.

Study Design: This was a prospective, double-blinded, randomized study of uncomplicated pregnant women who had vaginal delivery in ESUT Teaching Hospital, Enugu.

Sample Size: Two hundred (200) pregnant women who satisfied the inclusion criteria were recruited in this study with each arm of the study accommodating 100 participants.

Methodology: The eligible women were recruited on presentation to the labour ward after giving their consent. They were randomly allocated into 2 groups: A and B. Group A received 2 tablets (400mcg) of oral misoprostol and 1mililtre (ml) of sterile water intravenously while group B received 2 tablets of white vitamin c and 1ml (10iu) of intravenous oxytocin immediately after cord clamping and cutting following the delivery of the baby. Pre-weighed delivery mats and vulval pads were used to collect the blood at delivery and for the first 24 hours for weighing and estimation of blood loss. A proforma was used to record the necessary data.

Statistical Analysis: Data collected from the study was analyzed with the Statistical Package for Social Sciences (SPSS) computer software version 20.0 for windows. Statistical analysis was both descriptive and inferential at 95% confidence level. The socio-demographic variables were used to categorize the data and this was subjected to comparative statistical evaluation to yield frequencies, means, and percentages. Test of significance between class differences was by Pearson's Chi-square test for categorical variables and student's t-test for continuous variables. All $P<0.05$ at one degree of freedom (df=1) was considered statistically significant.

Results: Two hundred pregnant women were recruited into the study with 100 women on each arm and all completed the study. The amounts of blood loss (in mililitre) in the misoprostol and oxytocin arms were 339.36 ± 122.28 and 378.52 ± 148.24, respectively. Forty-three women had PPH (blood loss ≥ 500ml) but there was no significant difference in the amount of blood loss and occurrence of PPH on both arms of the study.

Conclusion: There was no difference in the efficacy of oxytocin over misoprostol in the management of the 3rd stage of labour for preventing PPH. We therefore, recommend that misoprostol can be adopted as an alternative/substitute to oxytocin in the management of the third stage of labour especially in the developing countries for prevention of PPH.

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Contact Dr. Onyekpa IJ ✉ Department of Obstetrics & Gynecology, Enugu State University of Science Technology College of Medicine and ESUT Teaching Hospital, Enugu, Nigeria, Phone: +234s8064086359; E-mail: ifeanyi.onyekpa@esut.edu.ng.

Introduction

Background

The most important cause of maternal mortality globally is postpartum haemorrhage (PPH), which is still very common in the developing countries. About 14 million patients suffer from postpartum haemorrhage annually worldwide, of which about 140,000 die [1,2]. Primary PPH can be defined as a loss of 500ml or more of blood from the birth canal within 24 hours of vaginal delivery or more than 1000ml following caesarean delivery [3]. Secondary PPH occurs after 24 hours but within 42 days of delivery. PPH is still common in the developing countries as found in sub-Saharan Africa, which Nigeria happens to be one [4-6]. A significant number of our women still access antenatal care and deliver in the hands of traditional birth attendants and in primary healthcare centers where adequate knowledge, skill and facilities for preservation and administration of oxytocin is in short supply making a search for an adequate alternative imperative.

Uterine atony is the most common cause of postpartum haemorrhage and is responsible for about 80% of all cases of postpartum haemorrhage. Hence, any treatment modality or medication in the third stage of labour that will prevent and treat uterine atony will go a long way to reducing the occurrence of PPH and its attendant complications [6].

The use of uterotonic drugs causes a significant reduction in vaginal haemorrhage after delivery. Oxytocin is the current standard of care but its use in the developing countries is limited by the problems of cost, storage and skill for administration [1]. Therefore, identifying an effective and safe uterotonic drug that is affordable and does not require a high-tech facility for storage or specialized skill for administration like oxytocin, for the management of the third stage of labour, especially in the third world countries will significantly reduce maternal mortality arising from PPH. This is also important in the background of anaemia in pregnancy, which is still prevalent in the developing countries of sub-Saharan Africa.

The third stage of labour is the period between the delivery of the baby and the delivery of the placenta in addition, membranes. The management of the third stage of labour is central to the prevention of primary PPH. There are two methods of managing the third stage of labour namely active and physiological/expectant. The definition of active management of the third stage of labour varies. However, it includes the use of uterotonic drugs immediately following delivery of the fetus, early cord clamping and cutting, and controlled umbilical cord traction. International federation of Gynaecology and Obstetrics and International Conference of Midwives (FIGO-ICM) included fundal massage of the uterus every 15 minutes for 15 seconds in the first two hours after the delivery of the placenta [7]. The active management of the third stage of labour has been found to reduce the risk of primary PPH significantly; however, this modality of management has some challenges in the third world countries where oxytocin may not be readily available [8].

There exists a global disparity in the proportion of deliveries supervised by skilled birth attendants between the high income and the low-income economies. In Nigeria, there is a dearth of skilled manpower to deliver qualitative maternal healthcare especially in our primary health centers. According to the National Demographic Health Survey (NDHS), 2013, only 36% of deliveries in Nigeria were conducted by skilled birth attendants [9,10]. Traditional birth attendants are a part of the socio-cultural fabric of various communities in Nigeria. They have wide socio-cultural acceptance; and many of our women deliver under traditional birth attendants with many complications even in the hands of retrained ones [11-13].

Many studies done on the subject in Nigeria Africa and other parts of the world yielded promising results on the use of misoprostol in the third stage of labour [14-25].

Many of our women still deliver under the supervision of unskilled birth attendants, and in primary healthcare centers where parenteral oxytocin or adequate power supply for its storage or the skill for its administration may not be readily available. The stability of misoprostol at room temperature, the ease of its administration, which could be oral, vaginal, rectal or sublingual, and its widespread availability and affordability make it a convenient tool for the reduction of PPH in resource-poor countries.

Aim

To determine if there is any difference in the efficacy of intravenous oxytocin over oral misoprostol in the prevention of primary postpartum haemorrhage.

Objectives

- To estimate the blood loss on both arms of the study from the third stage to the first 24 hours postpartum
- To determine whether there is any significant difference in:
- Estimated blood loss
- Occurrence of primary postpartum haemorrhage

Following the use of 400mcg of oral misoprostol or 10 IU of intravenous oxytocin in the management of the third stage of labour.

Setting

The study was carried out in ESUT Teaching Hospital, Enugu, a state owned tertiary hospital in the capital of Enugu state, South-East, Nigeria. The health institution evolved from a Nursing Home in 1930 for the colonial masters to a teaching hospital in June 2006. It serves as a training center for undergraduate medical students and postgraduate resident doctors as well as a referral center for both government-owned and private facilities in Enugu and the neighboring states.

The antenatal booking clinics hold every Thursday and routine antenatal clinics, daily, from Monday to Friday, except on public holidays. About 2000 women are delivered per annum in our labour ward. The department is made up of 3 professors and 8 consultants shared into 5 units. It also boasts of 18 senior registrars, 36 registrars, many house officers and different cadres of nurses and midwives.

Materials and Methods

This was a prospective, double-blinded, randomized trial of women who delivered in the labour ward of ESUT Teaching Hospital, Enugu from 1st December, 2019 to 29th February, 2020. The research assistants, which included labour ward registrars, house-officers and midwives working in labour and post-natal wards and an uninvolved party in charge of sampling, were trained on the study design and methodology by the researcher. The eligible women were recruited on admission into the labour ward after review and vaginal delivery was anticipated. Their socio-demographic data, previous obstetric and medical history, and current obstetric history were collated using a structured proforma. The materials used included: vulval pads, requisite drugs (misoclear brand of misoprostol, Juhel brand of oxytocin injection, and Juhel brand of water for injection, white vitamin c), transparent drug envelopes, 2 white envelopes, writing materials, paper tags, 5ml syringes, surgical gloves, water-proof aprons and face masks.

Once a patient was admitted into the labour ward, counseled and her consent obtained she was assigned to either group A or B using block randomization. She was also assigned a number from 1-200. Randomization was done using block randomization on blocks of 4 following determination of all 6 possible combinations of assignment (AABB, ABBA, ABAB, BBAA, BAAB, and BABA). The blocks were randomly chosen based on random numbers generated through an uninvolved party using random number generator on Microsoft "Excel". Recruited patients were then assigned either group A or B based on block combination selected via the random numbers by the uninvolved party. The actual drug combination for each group was concealed in a white envelope known only to the assistant who prepared the drugs. Group-A received 2 tablets (400 µg) of oral misoprostol and 1ml of intravenous sterile water (placebo) and group-B received 2 tablets of white vitamin c orally and10iu of intravenous oxytocin (1ml) immediately after early cord clamping and cutting following the delivery of the baby. The injectable were stored in the refrigerator located in the labour ward and the tablets kept safe in a designated tray.

Once a patient was admitted into the labour ward, counseled and her consent obtained she was assigned to either group A or B using block randomization as described above. Her drug combination was prepared, labeled A or B by a research assistant different from the accoucheur and kept ready for administration immediately after the cord was double-clamped and cut following the delivery of the baby. As soon as the baby was delivered and the cord clamped and cut, an assistant gave the selected injection through intravenous access already in place and provided the oral drug with a sachet of table water for the participant to swallow under supervision. The delivery mat already in use and soaked with liquor was removed immediately and a new, pre-weighed delivery mat replaced under the woman's buttocks. Neither the patient nor the researcher (or accoucheur) was aware of the medication the patient received. Active management of the third stage was conducted. If an episiotomy was given or laceration occurred, it was repaired immediately on the delivery couch. Pre-weighed vulval pads and delivery mats were used to collect all blood at delivery. Then both the pad and the delivery mat were weighed on a weighing scale capable of measuring as low as 10 grams (g), by the researcher to determine the weight of the blood collected. By subtracting the new weight (w2) from the initial weight (w1) the weight of the blood is determined in grams. The difference was equivalent to the amount of blood loss assuming 1g to be equivalent to 1ml of blood. Subsequently, other pre-weighed vulval pads used by the patient were stored in waterproof polyethylene bags by the patients over the next 24 hours [26]. These pads and delivery mats were weighed and the amount of blood collected determined as described above. The sum total of the weight difference in grams will be calculated and the amount of blood loss estimated. The women were usually observed for 1-2 hours in the labour ward before transfer to the postnatal ward where the observation continued for 24 hours. Any vaginal bleeding within the first 24 hours was noted, the quantity estimated, and occurrence of PPH within 24 hours were documented in the proforma. After the data collection and analysis, the two white envelopes containing the combination of the drugs received by each group (A and B respectively) were opened to remove the blinding.

Study Population

The study population was women who delivered their babies vaginally in the labour ward of the ESUT Teaching Hospital during the period of the study (December 2019 to February 2020).

Eligibility Criteria

Eligibility criteria for this study included apparently healthy women with uncomplicated pregnancies in labour at term and who were at least 18 years of age with no obvious risk of postpartum bleeding.

Exclusion Criteria

The exclusion criteria included:

- Multiple gestation
- Ante-partum haemorrhage
- Bleeding disorders
- Trial of vaginal birth after caesarean section
- Presence of significant uterine fibroid
- Grand multiparous women
- Severe preeclampsia
- Women who withheld their consent for the study

Statistical Analysis

Data collected from the study was keyed into the Statistical Package for Social Sciences (SPSS) computer software version 20.0 for windows. Statistical analysis was both descriptive and inferential at 95% confidence level. The socio-demographic variables were used to categorize the data and this was subjected to comparative statistical evaluation to yield frequencies, means, and percentages. Test of significance between class differences was by Pearson's Chi-square test for categorical variables and student's t-test for continuous variables. Odd ratio (OR) at 95% confidence interval (95%CI) was calculated using logistic regression techniques. All $P<0.05$ at one degree of freedom (df=1) was considered statistically significant.

Result

Two hundred pregnant women were recruited into, completed the study, and were randomized into two arms of 100 participants each. From the table 1 below there was no statistical difference in the socio-demographic variables of the two groups.

Table 2 shows the estimated blood loss after 24 hours on both arms of the study. The mean blood loss on the misoprostol arm was **339.36 ± 122.28** while on the oxytocin arm it was **378.52 ± 148.24**, mean difference of **20.84** and p-value of **0.28**. This shows that there was no significant statistical difference for loss on both arms of the study.

Table 3 & figure 1 showed the number of women in the study that had primary postpartum haemorrhage. Of the 200 participants recruited, **43 (21.5%)** had primary postpartum haemorrhage. Of these 43 participants, **24 (12%)** received misoprostol and **19 (9.5%)** received oxytocin. There was no statistical difference in the occurrence of primary postpartum haemorrhage on both arms of the study with a p-value of **0.49** and Odds ratio of **1.35 (1.12-12.0.8).**

Table 1: Distribution of socio-demographic variables.

Variable	Misoprostol N (%)	Oxytocin N (%)	Total N (%)	X^2 (p-value)
Age				
19-25 years	17 (8.5)	19 (9.5)	36 (18)	0.95 (0.81)
26-32 years	58 (29)	54 (27)	112 (56)	
33-39 years	15 (7.5)	19 (9.5)	34 (17)	
>40 years	10 (5)	8 (4)	18 (9)	
Marital status				
Single	6 (3)	5 (2.5)	11 (5.5)	5.28 (0.15)
Married	85 (42.5)	93 (46.5)	178 (89)	
Widow	7 (3.5)	1 (0.5)	8 (4)	
Divorced/Separated	2 (1)	1 (0.5)	3 (1.5)	
Religion				
Christianity	96 (48)	93 (46.5)	189 (94.5)	0.39 (0.54)
Islam	4 (2)	7 (3.5)	11 (5.5)	
Tribe				
Igbo	91 (45.5)	88 (44)	179 (89.5)	1.76 (0.62)
Yoruba	2 (1)	5 (2.5)	7 (3.5)	
Hausa	5 (2.5)	6 (3)	11 (5.5)	
Other tribes	2 (1)	1 (0.5)	3 (1.5)	
Employment status				
Employed	36 (18)	42 (21)	78 (39)	1.18 (0.55)
Self-employed	36 (18)	36 (18)	72 (36)	
Unemployed	28 (14)	22 (11)	50 (25)	
Parity				
0	23 (11.5)	28 (14)	51 (25.5)	6.34 (0.39)
1	22 (11)	12 (6)	34 (17)	
2	23 (11.5)	29 (14.5)	52 (26)	
3	21 (10.5)	20 (10)	41 (20.5)	
4	13 (6.5)	9 (4.5)	22 (11)	
Gestational age				
37-38weeks	33 (16.1)	25 (12.5)	58 (29)	9.96 (0.08)
39-40 weeks	50 (25)	62 (31)	112 (56)	
41-42 weeks	17 (8.5)	13 (6.5)	30 (15)	

Table 2: Comparison of total blood loss in both arms.

Variable	Misoprostol	Oxytocin		
	Mean (SD) (ml)	Mean (SD) (ml)	Mean Diff (ml)	t (p value)
Total blood loss	339.36 ± 122.28	378.52 ± 148.24	20.84	*1.08 (0.28)*

Table 3: Number of women that had primary PPH on both arms.

Variable	N (%)	N (%)	N (%)		
	Misoprostol	Oxytocin	Total	X^2 (p value)	*Odds (RR)*
Post-Partum haemorrhage	24 (12)	19 (9.5)	43 (21.5)	*0.47 (0.49)*	1.35 (1.12-0.8)
Normal	76 (38)	81 (40.5)	157 (78.5)		

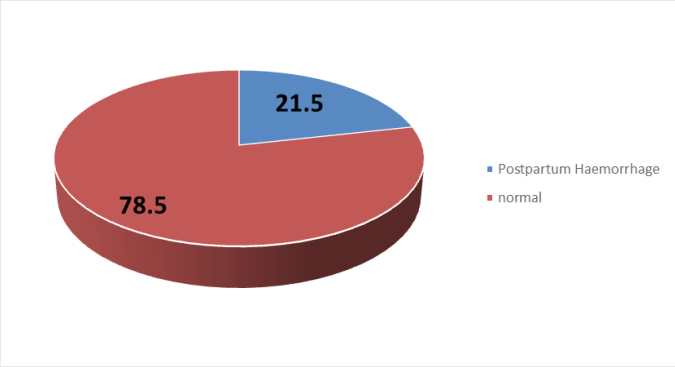

Figure 1

Discussion

The aim of this study was to determine if there was any difference in the efficacy of intravenous oxytocin over oral misoprostol in the prevention of PPH. The use of uterotonic agents is the major component of the active management of the 3rd stage of labour which carries the highest risk of morbidity and mortality for the pregnant woman [27].

The use of misoprostol for the management of the third stage of labour has been found to be as effective as oxytocin from this study. Similar works earlier done in Ilorin, Kwara State, Kwale, Delta State and Ile-Ife, Osun State support this [14-16]. Other studies done in Ghana and the Middle East all showed similar outcomes in the use of misoprostol in the third stage of labour [17-23].

This prospective, double-blinded, randomized trial showed that 400µg oral misoprostol with rapid onset of action was as effective as 10 IU of oxytocin given intravenously in minimizing blood loss and preventing PPH when administered immediately after cord clamping and cutting.

The distribution of the participants based on specific demographic variables such as age, tribe, religion, employment status, marital status, parity and gestational age was similar on both arms of the study as was the case in similar studies done in different centres and at different times [14-16,20].

From the study, the mean blood losses in mililitres, by gravimetric method in the misoprostol and oxytocin arms, were 339 ± 122.28 and 378.52 ± 148.24 respectively. It also showed that 21.5% of the participants had primary postpartum haemorrhage (blood loss≥500ml): of which 12% and 9.5% of the cases occurred in the misoprostol and oxytocin arms respectively. This was similar to what Musa et al. found in Ilorin, Kwara state even though they used 600µg of misoprostol as against 400ug used in our study. However, this was about double the value found by Oboro VO and Tabowei TO in Delta State and Afolabi et al., in Ile-Ife, Osun State [14,15]**.** The study in Delta State involved 496 women given 1ml (10 IU) intramuscular oxytocin or 600µg of misoprostol whereas our study involved 200 women given 10 IU of intravenous oxytocin or 400µg of oral misoprostol [16]. In addition, whereas we used the gravimetric method of blood estimation, the study in Delta used pre, post-delivery packed cell volume (pcv), and the Ile-Ife study used direct visual estimation. All these differences could account for the differences in the estimated blood loss between this and their studies but there was no significant difference in the blood loss on both arms in all the studies. The result is also similar to two other studies done in Ghana by Parson SM et al. using 800µg of misoprostol rectally and orally, and Walley RH et al. using 400µg of oral misoprostol; lending credence to the conclusion that misoprostol at a wide range of doses and different routes of administration can be as effective as oxytocin in the of the third stage of labour for preventing PPH [17-19].

Although the overall blood loss on the misoprostol arm was less suggesting a better efficacy, the difference between the two groups was not statistically significant. This was different from the finding in a similar study in Iran where sublingual misoprostol was found to be more effective than oxytocin in prevention of PPH [21]. However, the study in Iran involved 542 nulliparous women as against 200 low risk women including nulliparous women in our study; they also used sublingual misoprostol as against our oral misoprostol and 20 IU of oxytocin as against our 10 IU of oxytocin. In their study, there was a significant reduction in blood loss in the misoprostol arm using pre and post-delivery haemoglobin concentration as against our gravimetric method, where there was no statistically significant difference. In another study, Nahid R et al. found that the drop in haematocrit following caesarean section was more in the oxytocin group suggesting that misoprostol may be a better uterotonic agent than oxytocin [20]. However, high doses of each drug, 800µg of sublingual misoprostol and 60 IU of intravenous oxytocin, were used for a hundred women. The difference could be because the study was done only on caesarean section patients as against ours done on vaginal deliveries. Furthermore, the small sample size of 100 women in that study as against 200 women used in our study may have contributed to the difference. Other studies by Dabbaghi T et al., Samimi et al., and Shrestha et al. all showed that misoprostol could be as effective as oxytocin or syntometerine, further supporting the outcome of this study [22-24].

Conclusion

The findings from this study demonstrate that oral misoprostol is as efficacious and safe as intravenous oxytocin in the management of the third stage of labour for preventing PPH.

Recommendations

1. Misoprostol should be adopted as a suitable alternative to oxytocin in the third stage of labour for preventing PPH, especially in the rural areas of Nigeria, where electric power supply for the storage of oxytocin may be unreliable and trained medical personnel scarce.
2. The midwives and nurses that man Primary Health Centers and 'trained TBAs' should be instructed on the use of misoprostol in the conduct of the third stage of labour.

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