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Comparative Study of Sublingual versus Rectal Route of Misoprostol Administration in Prevention of Primary Post-partum Haemorrhage in Women with Risk Factors in ESUT Teaching Hospital, Enugu, Nigeria

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Abstract:
Background: Post-partum haemorrhage is a major cause of maternal death globally but more in low-income countries. While various studies recognized the efficacy of misoprostol in decreasing intraoperative blood loss, there is no consensus on the most effective route of administration of misoprostol.
Objective: This study compared the effect of sublingual misoprostol with rectal misoprostol in preventing primary post-partum haemorrhage in women with risk factor(s) to PPH.
Methodology: This is a comparative study that involved 200 participants who were randomized to two groups by 1:1 computer-based randomization (group A & group B). Each participant in group A received a 600mcg sublingual misoprostol plus rectal placebo, and participants in group B received a 600mcg rectal misoprostol plus sublingual placebo after delivery. The delivery mat already in use and soaked with liquor was removed once delivery was imminent, a new pre-weighed mat was replaced under the patient's buttocks, and also a pre-weighed sanitary pad was placed in her vulva to collect all the blood loss. The need for additional uterotonics and blood transfusion was assessed, and findings were documented appropriately in the proforma. Blood loss throughout a period of 24 hours after the delivery was measured by the gravimetric method. Weight gain from the sanitary pad/ delivery mat was calculated as 1g = 1 ml. The sanitary pad/mat was weighed in triplicate, and the mean of the three weights was entered into the database. The difference was the amount of blood loss, assuming 1g to be equivalent to 1 ml of blood.
Result: The median 24-hour post-partum blood loss was less in sublingual group when compared with the rectal group (110ml vs 170ml) P=0. 001.The mean post-partum Hb was higher in sublingual group 10.00±1.21 vs 9.00± 0.61 P=0.30. Both sublingual and rectal routes of misoprostol administration were effective in preventing PPH, P-value=1.0 and there was no indication for extra-uterotonic or blood transfusion.
Conclusion: It is concluded that even though sublingually and rectally administered misoprostol showed equal efficacy in preventing PPH, sublingual route is associated with less blood loss.

Keywords: *Misoprostol, sublingual, rectal, post-partum haemorrhage*

1. Introduction

Post-partum haemorrhage has been recognized as a major cause of maternal death globally but more in low-income countries(Aboutzhar,1991). Every minute of every day, a woman dies in pregnancy or childbirth. While primary Post-partum haemorrhage is defined as bleeding from the genital tract in excess of 500ml from vaginal delivery or 1000ml from Caesarian delivery or any blood loss capable of causing haemodynamic instability within 24 hours of childbirth, secondary post-partum haemorrhage occurs after 24 hours but within 42 days of delivery (Baskett, 1999, Sentihes et al, 2016). Post-partum haemorrhage accounts for about 40 maternal deaths per 100,000 births in sub-Saharan Africa against rates of 1 in 100,000 births in the United Kingdom (Fawcus,1995). Blood loss in excess of 1000ml is physiologically significant and capable of causing haemodynamic instability (Bassi et al, 2004). Majority of the deaths occur within 4 hours of delivery, which indicates that Primary PPH may be a consequence of mismanagement of the third stage of labour (Romanathan et al, 2006). It is an obstetric emergency that can largely be prevented. The incidence is increasing worldwide. It affects 1% to 5% of all deliveries, with about 14 million women suffering from primary post-partum

haemorrhage annually and at least 128,000 of them bleeding to death (WHO, 2005). The leading cause of post-partum haemorrhage is uterine atony, which can be prevented by the use of uterotonics like misoprostol. Misoprostol (15-deoxy-16-methyl PG-E1) is a synthetic prostaglandin E1 analogue and a good alternative to oxytocin in preventing post-partum haemorrhage from uterine atony because of its effectiveness, inexpensive nature, sublingual availability, temperature stability, not requiring refrigeration, and its long shelf-life (Blanchard et al, 2002, Bugalho et al, 2001, Doctor et al 2012, Global 2013). Misoprostol is a safe and well-tolerated drug. Pre-clinical toxicological studies indicate a safety margin of at least 500-1000 fold between lethal doses in animals and therapeutic doses in humans. No clinically significant adverse haematological, endocrine, biochemical, immunological, respiratory, ophthalmic, platelets or cardiovascular effects have been found with misoprostol (Kotsonis et al, 1995). Diarrhea is the major adverse reaction that has been reported consistently with misoprostol, but it is usually mild and self-limiting. Nausea and vomiting may also occur and will resolve in 2-6 hours. Some women may complain of an unpleasant taste when it is taken sublingually or orally. A sense of numbness over the mouth and throat has also been reported when it is taken sublingually.

Misoprostol was developed for the prevention and treatment of peptic ulcer disease because of its anti-secretory gastric acid and various mucosal protective properties (Baskett, 1999).

It has become an important drug in obstetrics and gynaecology because of its uterotonic and cervical priming actions. It has shown to be effective in preventing PPH when administered per rectum as prophylaxis following delivery, but with the shortcoming of invasion of women's privacy and risk of faecal matter contamination of surgical wound from this route.

Other routes of misoprostol administration include oral, sublingual, intravaginal, and intracervical. This study determined the efficacy and safety of sublingual route of misoprostol administration in preventing primary PPH and hence, the need to avoid women invasion and possible risk of wound contamination from rectal route of administration.

2. Justification of the Study

Continuous invasion of women's privacy via rectal misoprostol administration in the bid to prevent primary PPH with an associated risk of endometritis, sepsis, infertility, and possible infestation with Ascaris lumbricoides has been a great worry to many women.

The speed of misoprostol administration and the onset of action from the available study are faster with sublingual route. Sublingual route will ensure immediate misoprostol administration after the delivery of the baby during Caesarean section without waiting till the end of the surgery, especially now that regional anesthesia has become the order of the day. Self-administration of misoprostol is possible with sublingual route, and inadvertent insertion into the faeces in case of high fecal matter in the rectum will be averted via sublingual route.

2.1. General Objective

The study compared the efficacy of sublingual misoprostol with rectal misoprostol in preventing primary post-partum haemorrhage (PPH) after childbirth in women with risk factor(s) to PPH in Enugu.

2.2. Specific Objective

- Determination and comparison of blood loss following delivery in the two groups
- Determination and comparison of the number of participants that developed primary PPH in the two groups

3. Study Design

This was a randomized comparative study of sublingual versus rectal misoprostol administration in preventing primary post-partum haemorrhage in high-risk patients in ESUT Teaching Hospital, Parklane, Enugu, South East, Nigeria.

4. Research Participants

The research participants for the study were recruited from pregnant women with identified risk factor(s) for primary post-partum hemorrhage (obstructed labour, grand-multiparity, multiple gestation, polyhydramnios, prolonged labour, caesarean section) who had childbirth in ESUT-TH after getting their written informed consent.

4.1. Eligibility Criteria

- Consent to the study
- Willingness to deliver in ESUT-TH
- No obvious co-morbidity like placental preavia and uterine fibriod

4.2. Exclusion Criteria

- Consent refusal
- No willingness to deliver in ESUT-TH
- Allergy to misoprostol
- Obvious co-morbidity

5. Sample Size Calculation

The minimum sample size (n) for one arm of the study was determined using the formula (Remi *et al, 1993)*

$n = 2[(a+b)^2 s^2]/(u_1 - u_2)^2$

Where,

n= sample size of each group
a= 1.96, i.e., Z score for an error of 5% (95% confidence level)
b= 0.80, i.e., Z score for estimated study power of 80%
s= population variance (standard deviation) of the outcome in the control group
$u_1 - u_2$ = minimum difference between means of study and control group.

In a related randomized controlled study that compared the efficacy of sublingual versus rectal misoprostol in the prevention of post-partum haemorrhage (Screelatha, et al 2017). It was found that the standard deviation of the mean after use was 163.33.

Therefore, s =163.3
Assuming a standard effect of 0.4
$u_1 - u_2 =$ 163.33 x 0.4= 65.32
Therefore, $n=2[(1.96+0.8)^2\ 163.33^2]/(65.32)^2$
$=2[(2.7)^2\ 26676.6889]/4268.270224$
$=2[7.6176x26676.6889]/4268.270224$
$=406424.69072928/268.270224$
$= 95$
Assuming an attrition rate of 5% sample size per group
$=95+ (0.05 \times 95)$
$= 95+5=100$
Therefore, the total sample population for the study =100 x 2 =200

5.1. Procedure

A self-administered proforma was used to obtain information on biodata, obstetrics history/risk factors for PPH, and preferred route of choice for misoprostol administration.

5.2. Randomisation of Research Participants

Each participant was randomized to two groups by 1:1 computer-based randomization (group A & group B). Each participant in group A received a 600mcg sublingual misoprostol plus rectal placebo, and participants in group B received a 600mcg rectal misoprostol plus sublingual placebo.

The pharmacy department provided the study drugs and placebo in the unidentifiable form to the patients but not to the researcher and research assistant.

5.3. Sampling Techniques

Recruitment started in the antenatal clinic at 36 weeks' gestation. The patient was counselled, and her consent was obtained. She was then assigned to either group A or B, as described above. Following the patient's admission into the labour ward, the research assistants received the prepared drug from the pharmacy and other materials and kept them ready at the designated tray, and they were immediately administered at the delivery of the baby. Following the delivery of the baby, the delivery mat already in use and soaked with liquor was removed, and a new pre-weighed mat was replaced under the patient's buttocks, and also, a pre-weighed sanitary pad was placed in her vulva, which collected all the blood loss. The folder of the participant was examined to know the group she belonged to; trained doctors and midwives (research assistants) took the responsibility of patient allocation of appropriate drugs and placebo according to the designed root and randomization table. Both the outcome assessor and patients were blinded to the study medication. Active management of the third stage of labour was done, and the patient was evaluated for any genital tract laceration. Episiotomy, when given, was repaired immediately. The patient was observed for 2 hours in the labour ward before her transfer to the postnatal ward, where further monitoring was continued for the next 24 hours. While on observation post-partum, the need for additional uterotonics, blood transfusion, and any side-effect from the drug was assessed, and findings were documented appropriately in the provided proforma.

5.4. Estimation of Blood Loss

Blood loss throughout a period of 24 hours after the delivery was measured by the gravimetric method. This involved the use of a mettle PB153 weighing scale to weigh the sanitary pads and delivery mat, followed by the application of a known weight (pre-weighed) sanitary pad which was applied to the vulva and delivery mat put under the buttocks, which was used to collect all the blood loss and pads and mats re-weighed to estimate blood loss. Afterward, other pre-weighed vulva pads were used by the patient to collect any other blood loss**.** These pads were collected from the patient whenever she changed the pad and stored in an air-tight transparent polyethylene bag, and all weighed after 24 hours. Weight gain from the sanitary pad/delivery mat was calculated as 1g = 1 ml. The sanitary pad/mat was weighed in triplicate, and the mean of the three weights was entered into the database. The difference was equivalent to the amount of blood loss, assuming 1g to be equivalent to 1 ml of blood.

5.5. ***Outcome Measures***

The outcome measures include 24-hour post-partum blood loss and a history of post-partum hemorrhage after delivery.

6. Data Analysis

Data analysis was done using a statistical package for social science version 23.
The level of significance was set at 0.05.

7. Results

Variables	Sublingual Group (n=100)	Rectal Group (n=100)	Test Stat	p-value
Mean age (years)	27.52 ± 2.08	28.20 ± 3.94	t= -3.77	<0.21
Marital status			χ^2= 3.09	0.38
Single	4(4.0%)	6(6.0%)		
Married	90(90.0%)	92(92.0%)		
Widowed/divorced/separated	6(6.0%)	2(2.0%)		
Educational status			χ^2= 0.59	0.74
Primary	4(4.0%)	6(6.0%)		
Secondary	28(28.0%)	30(30.0%)		
Tertiary	68(68.0%)	64(64.0%)		
Occupation			χ^2= 4.46	0.11
Employed	40(40.0%)	46(46.0%)		
Unemployed	48(48.0%)	50(50.0%)		
Self-employed	12(12.0%)	4(4.0%)		
Ethnicity			χ^2= 2.98	0.40
Igbo	90(90.0%)	88(88.0%)		
Hausa	2(2.0%)	4(4.0%)		
Yoruba	6(6.0%)	8(8.0%)		
Others	2(2.0%)	0(0.0%)		
Religion			χ^2= 0.42	0.52
Christianity	96(96.0%)	94(94.0%)		
Islam	4(4.0%)	6(6.0%)		

Table 1: Socio-Demographic Characteristics of the Study Participants

Variables	Sublingual Group (n=100)	Rectal Group (n=100)	Test Stat	p-value
Median post-delivery blood loss in mls (Range)	100.00 (100-200)	160.00 (120-190)	U=532.00	<0.001*
Median 24 hours blood loss in mls (Range)	110.00 (100-200)	170.00 (120-190)	U=958.00	<0.001*
Median post-delivery Hb in g/dl (Range)	10.00 (8.80-11.80)	9.00(8.70-9.90)	U=4484.00	0.30

Table 2: Comparison of Blood Loss between Sublingual and Rectal Route of Misoprostol Administration Following Childbirth
*U = Mann-Whitney U-test, Hb = Haemoglobin, *=p-value is statistically significant*

Variables	Sublingual GROUP (n=100)	Rectal Group (n=100)	Test Stat	p-value
Occurrence of primary PPH			FT= 0.00	1.00
Yes	0.0(0.0%)	0(0.0%)		
No	100.0(90.0%)	100(92.0%)		
Need for additional uterotonics			FT= 0.00	1.00
Yes	0(0.0%)	0(0.0%)		
No	100(90.0%)	100(92.0%)		
Need for blood transfusion			FT= 0.00	1.00
Yes	0(0.0%)	0(0.0%)		
No	100(90.0%)	100(92.0%)		

Table 3: Comparison of the Proportion of Participants That Developed Primary PPH /Need for Additional Uterotonic and Blood Transfusion in the Two Groups

8. Discussion

About two hundred participants were recruited for this study, and all completed the study, given a completion rate of hundred percent. The mean age of the research participants in the two groups was 27.9 years. There was no statistical difference in the observed socio-demographic characteristics of the research participants in the two groups. The

result of the study showed that the median 24-hour post-partum blood loss in sublingual group was 110ml as against 170ml in rectal group, with a P-value of 0.001. The mean post-partum Hb(g) was higher in sublingual group, 10.00±1.21 vs. 9.00± 0.61 P=0.30. This suggests sublingual misoprostol administration is more efficient in controlling blood loss following delivery when compared with rectal route of misoprostol administration. It was also observed that both sublingually and rectally administered misoprostol in groups A and B, respectively, were effective in preventing PPH with a P-value of 1.00. There was no indication of additional uterotonic or blood transfusion amongst the participants in the two groups, and the P-value was 1.00. These findings are in line with similar observations in a randomized controlled trial of sublingual versus rectal route of misoprostol administration in elective Caesarean delivery conducted in Nigeria, where it was noted that sublingual route of misoprostol administration was more effective in reducing intraoperative blood loss at elective Caesarean than rectal route of administration (Omozuwa, 2018). Similar findings also characterized another comparative study of different routes of administration of misoprostol in the management of the third stage of labour, where it was found that the amount of blood loss and haemoglobin deficit were least in sublingual group, and it was concluded that sublingual misoprostol was more effective in reducing blood loss during the third stage of labour (Screelatha et al, 2017, Awoleke et al, 2020)

9. Conclusion

It is concluded that even though sublingual and rectal administered misoprostol showed equal efficacy in preventing PPH, sublingual route is associated with less blood loss.

10. Recommendations

It is recommended that sublingual route of misoprostol administration following childbirth be adopted based on the observed efficacy and added advantage of avoidance of invasion of women's privacy that is seen with rectal route of administration with a high risk of genital tract infection.

- Data Availability: All the necessary data are included in the manuscript.
- Conflicts of Interest*:* The authors declare that they have no competing interests.
- Funding*:* There was no external funding for this study.
- Ethical considerations*:* Ethical clearance was obtained from the ethical committee of ESUT Teaching Hospital Parklane with reference number ESUTP/C-MAC/RA/034/VOL.2/7.

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