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Research Article,

Comparison of Oral Misoprostol with Intravenous Oxtocin in the In the Management of the Third Stage of Labour: A Randomized Controlled Trial

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Abstract:

Background:
Postpartum haemorrhage (PPH) is defined as the loss of 500ml of blood or more from the vagina following vaginal birth or 1000ml following caesarean delivery. The third stage of labour is the period between the delivery of the baby and the delivery of the placenta and membranes and its management is central to the prevention of postpartum haemorrhage (PPH). There are basically two methods of managing the third stage of labour namely active and physiological/expectant. The active management includes the use of uterotonic drugs immediately following delivery of the fetus, early cord clamping and cutting, and controlled umbilical cord traction. The active management of the third stage of labour with oxytocin has been found to reduce the risk of primary PPH significantly; however, the problem of inadequate supply of electricity, high cost and paucity of skilled manpower to administer it has negatively affected its use in developing countries and has made the search for a more suitable alternative expedient. Misoprostol on the other hand has been found to have good uterotonic activities, affordable and stable at room temperature; making its use in the resource-poor countries a veritable alternative.

Aims:
To determine if there is any difference in the efficacy of intravenous oxytocin over oral misoprostol in the management of the third stage of labour

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

Sample Size:
Two hundred (200) pregnant women who satisfied the inclusion criteria were recruited into the study with each arm 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 (400µg) 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. The patient was observed for significant clinical vaginal bleeding or PPH. For the purposes of this study, any bleeding/PPH accompanied with a greater than 30% rise in baseline pulse rate qualified for transfusion. 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 and Conclusion:

There was no significant difference in the number of women that received blood transfusion, the amount of blood transfused and the need for additional oxytocics on both arms of the study. However, there was a significant difference in the occurrence of side-effects with shivering and vomiting being prominent in the misoprostol and oxytocin arms respectively.

Conclusion:

There was no difference in the efficacy of oxytocin over misoprostol in the management of the 3rd stage of labour. 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 developing countries.

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Keywords: misoprostol, oxytocin, third stage of labour

Introduction:

The most important cause of maternal mortality globally is postpartum haemorrhage (PPH), which is still very common in developing countries.[1,2] Not less than 14 million women suffer from postpartum haemorrhage annually, of which about 140,000 die.[3]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. Secondary PPH occurs after 24 hours but within 42 days of delivery.[4,5,6] PPH with its attendant need for transfusion and its many risks is still common in the developing countries as found in sub-Saharan Africa, which Nigeria happens to be one.

A significant number of our women still access antenatal care and deliver in the hands of traditional birth attendants (TBAs) and in primary healthcare centres 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.[6]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.

The use of uterotonic drugs causes a significant reduction in vaginal haemorrhage after delivery.[1] 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. 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 morbidities and 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. However, the discovery of misoprostol, a prostaglandin E1 analogue, with good uterotonic activities, cheap, stable at room temperature and having multiple routes of administration has offered a more practical alternative in the developing countries.[7]Many researchers within and outside the west-African sub-region have compared intramuscular or intravenous oxytocin with misoprostol administered through various routes and the outcomes have been encouraging: Nigeria,[8-10]Ghana,[11-13]Iran, [14-17]Nepal,[18]and Canada.[19]This study could provide an empirical evidence for the recommendation of the use of misoprostol in the developing countries for the management of the third stage of labour so as to reduce the incidence of PPH and its attendant consequences on the parturient.

Aim:

To determine if there is any difference in the efficacy of intravenous oxytocin over oral misoprostol in the management of the third of labour

Objectives:
The objectives of the study were to determine if there was any significant difference in:

i. The need for blood transfusion
ii. Amount of blood transfused
iii. Need for additional uterotonic agents
iv. Occurrence of side-effects

Following the use of 400µg of oral misoprostol or 10iu 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. Enugu state is one of the five states in the South-East geopolitical zone of Nigeria. It was created in 1991 from the old Anambra state. It shares borders with Abia State to the South, Ebonyi State to the East, Benue State to the North-East, Kogi State to the North-West and Anambra State to the West. It has 17 Local Government Areas most of which are predominantly rural areas except those within Oji-River, Agbani, Enugu metropolis and Nsukka. It has a population of approximately 3.3 million which are predominantly Igbo with pockets of other tribes. The major occupations of its inhabitants range from civil service to trading in the urban areas to subsistent farming and animal husbandry in the rural areas.[20]
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 centre for undergraduate medical students and postgraduate resident doctors as well as a referral centre for both government-owned and private facilities in Enugu and the neighbouring 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.

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 were 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 study population was women who had vaginal delivery in the labour ward of the ESUT Teaching Hospital during the period of the study (December, 2019 to February, 2020).
The eligible women were recruited on admission into the labour ward after review, vaginal delivery was anticipated and a written informed consent given. Their socio-demographic data, previous obstetric and medical history, current obstetric history and periodic vital signs (especially pulse rate) were collated using a structured proforma. Ethical clearance was obtained from the Hospital Ethical Committee. The eligible women were recruited on admission into the labour ward after review and vaginal delivery was anticipated.
The required sample size was calculated to be 200 women with 100 on each arm of the study. Each patient was 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 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. 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. 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. 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. The vulval pad is monitored closely to diagnose significant vaginal bleeding and the pulse rate monitored ¼ hourly. In the case of rise in pulse rate of more than 30% of the baseline, the participant is considered to have lost significant amount of blood to require transfusion.

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.

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 and completed the study and were randomized into two arms of 100 participants each. The **table 1** below showed the distribution of the participants according to the socio-demographic variables of the two groups and there was no difference in their socio-demographic variables.

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	13(6.5)	6(3)	19(9.5)	5.28(0.15)
Married	85(42.5)	93(46.5)	178(89)	
Divorced/Separated	2(1)	1(0.5)	3(1.5)	
Religion				
Christianity	96(48)	93(46.5)	189(94.5)	0.39(0.54)
Others	4(2)	7(3.5)	11(5.5)	
Tribe				
Igbo	91(45.5)	88(44)	179(89.5)	1.76(0.62)
Other tribes	6(3)	12(6)	21(10.5)	
Employment status				
Employed	72(36)	78(39)	150(75)	1.18(0.55)
Unemployed	28(14)	22(11)	50(25)	

Parity				
Nullipara	23(11.5)	28(14)	51(25.5)	6.34(0.39)
Primipara	22(11)	12(6)	34(17)	
Multipara	57(28.5)	58(29)	115(57.5)	
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 shows the association between the use of either misoprostol or oxytocin and the occurrence of specific clinical outcomes considered. It showed that a total of **8(4%)** women in all received blood transfusion in the course of the study**: 4(2%)** on each arm. There was no significant statistical difference in the number of women that received blood transfusion on both arms of the study with a p-value of **0.99**. Three (**1.5%**) and **2(1%)** women each received **1**unit of blood in the misoprostol and oxytocin arms respectively. One (**0.5%**) woman in the misoprostol arm received **2** units whereas **2(1%)** women each received **2** units in the oxytocin arm.

Similarly, **30(15%)** had need for additional oxytocics to prevent excessive blood loss with **15(7.5%)** on each arm of the study. There was no significant statistical difference in the need for additional oxytocics on each arm of the study with a p-value of **0.99**.

In terms of occurrence of side-effects, **155(77.5%)** had no demonstrable side-effects. Four **(2%)** had fever, **2(1%)** on each arm, only **1(0.5)** had diarrhoea in oxytocin arm, **26(13%)** had shivering, **19(9.5%)** and **7(3.5%)** from misoprostol and oxytocin respectively, whereas **14(7%)** had vomiting with **3(1.5%)** and **11(5.5%)** in misoprostol and oxytocin arms respectively. This revealed that there was a significant statistical difference in the occurrence of side-effects in both arms of the study with a p-value of **0.03.**

Table2. Clinical outcomes in the two groups

Variables	N(%)	N(%)	N(%)	
Need for blood transfusion	**misoprostol**	**oxytocin**	**Total**	**X^2 (p-value)**
Yes	4(2)	4(2)	8(4)	0.01(0.99)
No	96(48)	96(48)	192(96)	
Number of units of blood transfusion				
0	96(48)	96(48)	192(96)	0.53(0.77)
1	3(1.5)	2(1)	5(2.5)	
2	1(0.5)	2(1)	3(1.5)	
Need for additional uterotonics				
Yes	15(7.5)	15(7.5)	30(15)	0.01(0.99)
No	85(42.5)	85(42.5)	170(85)	
Side-effects of the drugs				
No side-effects	76(38)	79(39.6)	155(77.5)	11.16(0.03)
Fever	2(1)	2(1)	4(2)	
Diarrhoea	0(0)	1(0.5)	190.5)	
Shivering	19(9.5)	7(3.5)	26(13)	
Vomiting	3(1.5)	11(5.5)	14(7)	

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 management of the third stage of labour. 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.[21] 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. This is supported by similar works earlier done in Ilorin, Kwara State,[8]Kwale, Delta State[9]and Ile-Ife, Osun State.[10]Other studies done in Ghana and the Middle-East all showed a similar outcome in the use of misoprostol in the third stage of labour.[11-19] This prospective, double-blinded randomized trial showed that 400µg oral misoprostol was as effective as 10iu of intravenous oxytocin in the management of the third stage of labour 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. This was in keeping to the findings with similar studies in the past.[8-10]

This study also showed that there was no significant difference in the need for blood transfusion and the number of units transfused on both arms. One of the recipients of blood transfusion in the oxytocin arm had PPH and blood transfusion due to genital tract laceration that was repaired in theatre. This was similar to findings by Oboro VO et al,[9] Afolabi et al,[10] Walley et al,[13] and Sami G et al.[19] The literatures search in the course of the study did not reveal any contrary finding. Similarly, this study further revealed that there was no difference in the need for additional uterotonic agents in both arms of the study. However, Nahid et al[14] and Dabbaghi et al[16] found a significant difference with the need for additional uterotonic agents being more in the oxytocin arm. The difference when compared with the findings of Nahid et al could be accounted for by the differences in sample sizes, sublingual route of administration of misoprostol, population of women who had caesarean delivery and very high doses of the drugs in the former; whereas the difference in the case of Dabbaghi et al could be due to difference in sample size.

This study showed a significant difference in the occurrence of side-effects between the two arms with nausea and vomiting as the major side-effects among the oxytocin group and fever/shivering among the misoprostol group which is in accordance with their side-effect profile.[22,23-26] Our finding was in agreement with the observations of others.[9,10,18]

Many of these previously quoted studies which used different doses and routes of administration of misoprostol and oxytocin suggested that misoprostol can be as effective and as safe as oxytocin in the management of third stage of labour and agree with the findings of this study.

Conclusion:

The findings from this study demonstrated that oral misoprostol is as efficacious and safe as intravenous oxytocin in the management of the third stage of labour and that the side-effects of misoprostol are tolerable and self-limiting.

Recommendations:

1. Misoprostol should be adopted as a suitable alternative to parenteral oxytocin in the management of third stage of labour, especially in the rural areas of developing countries where electric power supply for the storage of oxytocin may be unreliable and trained medical personnel, scarce.
2. That a policy of training and retraining of lower cadre health workers like nurses/midwives and even 'trained traditional birth attendants' on the use of misoprostol in the third stage of labour be initiated

References:

[1] Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J, Barbara L, et al. Obstetric haemorrhage. In: Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J, Barbara L, et al, editors. Williams Obstetrics, 24th ed. UK, Mcgraw-hills; 2014.780-825

[2] Mousa H.A. and Alfirevic Z. Treatment for primary postpartum haemorrhage, Cochrane Database of Systemic Reviews, no.1, Article ID CD003249, 2007

[3] Ronsmanc C., Graham W.J. Lancet Maternal Survival Series Steering Group. Maternal Mortality: who, when, where, and why. Lancet 2006;368(542):1189-200.

[4] Baskett T.F. Complications of the third stage of labour in Essential Management of Obstetrical Emergencies. (3rd ed.), Bristol, Clinical Press, 1999. 196-201.

[5] Sentilhes L., Vayssiere C., Deneux-Tharaux C., et al. Postpartum Haemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anaesthesiology and Intensive Care (SFAR). Eur. J Obstet Gynaecol Reprod Bio. 2016, (198):12-21.

[6] Weeks A. The prevention and treatment of postpartum haemorrhage: what do we know and where do we go next? BJOG. 2015;122(2):201-10.

[7] Watkinson G., Hopkins A., Akbar F.A. The therapeutic efficacy of misoprostol in peptic ulcer disease. Postgrad Med J 1988;64(suppl1):60-77.

[8] Musa A.O., Ijaiya M.A., Saidu R. et al. Double blinded randomized controlled trial comparing misoprostol and oxytocin for management of third stage of labour in a Nigerian hospital. Int J Gynaecol Obstet 2015;129(3):227-30

[9] Oboro VO., Tabowei T. A randomized controlled trial of misoprostol versus oxytocin in active management of the third stage of labour. J Obstet Gynaecol 2003;23(1):13-16

[10] Afolabi EO, Kuti O., Orji E.O., Ogunniyi S.O. Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labour. Singapore Med J.2010;51(3):207-211

[11] Parson S.M., Walley R.L., Orane J.M.G. et al. Rectal misoprostol versus oxytocin in minimizing blood loss in the third stage of labour: a randomized controlled trial. J. Obstet Gynaecol Can. 2007; 29(9):711-8

[12] Parson S.M. et al. Oral misoprostol versus oxycitocin in the management of third stage of labour. J Obstet Gynaecol Can 2006;28(1):20-26qqq

[13] Walley R.L., Wilson J.B., Crane J.M., Sawyer E., Hutchens D.A. double blinded placebo controlled trial of misoprostol and oxytocin in the management of third stage of labour: a randomized controlled trial. BJOG 2000;107(9):1111-5

[14] Nahid R., Neda M., Raheb G. Comparison of sublingual misoprostol and intravenous oxytocin in the management of PPH after caesarean delivery: a randomized controlled trial. Middle East Journal of Reproductive Health Studies. 2018;5(1):e62025

[15] Beigi A., Tabarestani H., Moini A., Zarrinkoub F., Kazerupour M., Amree A.H. Sublingual misoprostol versus intravenous oxytocin in the management of PPH. Tehran Univ. Med. J. 2009;67(8):556-61

[16] Dabbaghi G.T., Elmizadeh K., Moradi S., Rashvand M.E. Comparison of intravenous oxytocin and oral misoprostol in reduction of PPH. Zanjan University of Medical Sciences Journal (ZUMSJ). 2012;20(81):1-8. URL:http://zumsj.ac.ir/journal/article-1-1881-en.html

[17] Samimi S., Abedzadeh K.M., Imani A. Comparison of the effects of rectal misoprostol and Intramuscular syntometrine in the prevention of PPH. Avicema J Clin Med. 2011;18(2):38-44

[18] Shrestha A. et al. Rectal misoprostol versus intramuscular oxytocin for prevention of PPH: a randomized controlled trial. Kathmandu Univ Med J,2011;9(33):8-12

[19] Sami G.K., David C., Mary E.S. et al. Randomized controlled trial of rectal misoprostol versus oxytocin in the third stage management. J Obstet Gynaecol Can. 2002;24(2):149-54.

[20] National Population Commission of Nigeria. Population census 2006 (web)

[21] Ramanathan G., Arulkumaran S. Postpartum haemorrhage. J Obstet Gynaecol Can.2006;28(16):32308-8.

[22] Geller S, Adams MG, Kelly P.J, Kodkany B.S, Derman R.J. Postpartum haemorrhage in resource-poor settings. Int J Gynaecol Obstet 2006;92:202-11

[23] Gulmezoglu A.M., Villar J., Ngoc M.T.N., Piaggio G., Adetoro L. WHO multicentre randomized trial of misoprostol in the management of third stage of labour

[24] Ng P.S., Chan A.S.M., Sin W.K., Tan L.C.H., Cheung K.B., Yuen P.M. A multicentre randomized controlled trial of oral misoprostol and IM syntomethrine in the management of the third stage of labour, Hum Reprod. 2001;16:31-5

[25] Chong YS, Chua S, Arulkuumaran S. Letter to the Editor: Severe hyperthermia following oral misoprostol in the immediate postpartum period. Obstet Gynaecol, 1997;90:703-4. Lancet 2001; 358:689-95

[26] Hofmeyer JG, Singata M M, Jafta Z, et al. Misoprostol for treating postpartum haemorrhage: a randomized controlled trial [ISRCTN2263357] BMC Pregnancy Childbirth. 2004;4:16