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Research Article

A RANDOMISED CLINICAL TRIAL COMPARING THE EFFICACY OF OXYTOCIN INJECTION AND ORAL MISOPROSTOL TABLET IN THE PREVENTION OF POSTPARTUM HAEMORRHAGE IN MAIDUGURI NIGERIA

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ABSTRACT
To compare the effectiveness of intravenous oxytocin 10 IU and oral misoprostol tablet 600ug in the prevention of PPH. A randomised approach was used to recruit 1800 consenting pregnant women whom were randomly allocated at term to two medication groups of 10 IU oxytocin intravenously at delivery of the anterior shoulder and oral misoprostol group; 600 µg (3 x 200µg) tablets within three minutes of the delivery of baby. Blood loss by each patient was collected using precalibrated kidney dishes. Haemoglobin level was measured at term and 24 h after delivery. The study indicated higher occurrences of PPH (17.9 VS 8.9 %) and higher MBL (388.04 ± 5.910 ml VS 327.68 ± 3.953 ml) in the oxytocin medication group. Drop in the mean haemoglobin levels in the oxytocin group (0.708 ± 0.0340) was significantly ($p < 0.001$) higher than in the misoprostol group (0.549 ± 0.0276). The proportion of enrolees that needed additional oxytocic agents was significantly ($\rho < 0.05$) higher in the oxytocin group (16.4 %) than in the misoprostol group (3.6 %). None of the enrolees in either of the two medication groups had indication for blood transfusion. In Maiduguri metropolis, oral misoprostol tablet 600 µg has demonstrated better prevention of PPH than intravenous oxytocin 10 IU. The two medication approaches are safe and could be inter changed if need arises.
Key Words: Treatment efficacy, Postpartum haemorrhage, Misoprostol, Haemoglobin, Oxytocin.

INTRODUCTION

The commonest cause of maternal mortality is obstetric haemorrhage, usually occurring postpartum, accounting for 25—33% of worldwide maternal mortality[1]. Mortality due to postpartum haemorrhage (PPH) varies widely in the world. The proportions ranged from less than 10 % in developed countries to nearly 60 % in some developing countries[1]. In Nigeria, haemorrhage is the number one cause of maternal death, while it was rated second after hypertension in Maiduguri[2]. PPH is also a major cause of maternal morbidity in both the developed and the developing world[3].

The leading cause of PPH is uterine atony, which is preventable by the use of uterotonics, among which oxytocin is preferred[4,5,6]. However, the use of oxytocin injection is not always possible in low-income countries where births still occur at home with untrained birth attendants[5,7-10]. Ergometrine injection is another uterotonic that is often used but as oxytocin, it requires parenteral administration, which involves the use of sterile needles and syringes. In addition, ergometrine and oxytocin requires refrigeration, and may be inactivated if exposed to high ambient temperatures. Misoprostol have been shown to be effective for the prevention of PPH but it's use was yet to be implemented as standard care[11, 12]. As a stable, orally active and cheap uterotonic, misoprostol could be suited for the prevention of PPH especially in the developing countries. For these reasons the use of oral misoprostol to prevent PPH has attracted considerable attention[13]. A recent guideline on PPH prevention developed by the WHO recommended the use of misoprostol 600 µg orally for prevention of PPH in settings in which use of injectable uterotonics is not feasible.[14] There are conflicting reports on the relative

efficacy of these uterotonic drugs in the prevention of PPH and research on uterotonics are scarce in Nigeria.

The objective of this study is to compare the effectiveness of intra-venous oxytocin 10 IU and oral misoprostol tablet 600ug in the prevention of PPH.

MATERIALS AND METHODS

The study was a prospective, randomised, comparative and multi-centred one, which was started in September 2007 and completed in March 2009. The study was conducted in three health institutions in Maiduguri metropolitan area of Borno state. These were; the University of Maiduguri Teaching Hospital (UMTH), the Maiduguri Specialist Hospital, and Yerwa Maternal and Child Health Care Centre. It was completed with a total sample size of 1865 orally consenting (some written) enrolees. However, 46 of the administered questionnaire were invalidated leaving a total of 1819 valid questionnaires (912 for oxytocin and 907 for misoprostol). The data was further reduced to 1800 through a process of computer randomization so as to have equal study population in the two medication groups: oxytocin group (900 subjects) and misoprostol group (900 subjects).

Women that had uncomplicated vaginal delivery in these facilities during the study period were used for the study. They were randomly allocated to two medication groups of either intravenous oxytocin or oral misoprostol tablets. Randomising was ensured by use of dice box:

The prescriptions of the two uterotonic drugs were separately written on small prescription sheets (900 for oxytocin injection 10 IU and 900 for misoprostol tablets 600 µg). Fifty pieces of these prescription sheets were picked from each of the two groups and placed in a container (dice-box). Prescriptions were allocated to consenting patients randomly from the container after dicing.

The women allocated to the oxytocin group were given 10 IU of oxytocin intravenously (Labtocin; LABORATE Pharm India) at delivery of the anterior shoulder. In the oral misoprostol group, 600 µg (3 x 200µg) misoprostol tablets (Cytotec; Emzor Pharm Limited, Isolo, Lagos) were administered within three minutes of the delivery of baby if there is no any nausea and vomiting. In all patients the uterus was always gently massaged to ensure it was contracted. Each patient was observed for a period of 24 h for blood loss which was quantified using calibrated kidney dishes and measured to the nearest millilitres. Clinical measures such as surgical manipulations, blood transfusion, etc were done by a clinician based on patients needs. The exclusion criteria included Known allergy to either of the drugs, operative delivery, history of co-morbid conditions like diabetes, mal-presentation, anaemia, antepartum haemorrhage, multiple pregnancy, and grandmultiparity (greater than six births).

The bio-data of the consenting enrolees were obtained from their clinical folders. Data specifically recorded included age, tribe, educational qualification, occupation, date of registration for antenatal care, number of children and date of last birth (where applicable) and their expected delivery date (EDD) as computed by the responsible obstetrician at the time of registration. Enrolees were categorised either preterm or post-term if their delivery date fell outside two weeks before their EDD or three weeks after EDD. Where some of these data were missing, oral interview was employed.

Pre-calibrated kidney dishes of various sizes (100 – 1,500 ml) were used to collect any blood loss after delivery of the babies. Each patient was further observed for a period of 24 h for any more blood losses and for any adverse effects of the administered drug (oxytocin or misoprostol). Oral interview and clinical notes were employed in adverse event monitoring. Haemoglobin levels prior to delivery and at 24 h after delivery were recorded. Clinical measures such as prescription of additional oxytocic agent, surgical manipulations, blood transfusion, etc, as done by a clinician were recorded. All relevant data of output measures were recorded promptly using a designed proforma. The primary outcome measure was total blood loss over 24 h in ml and those ≥ 500 ml were classified as PPH (Yes), whereas < 500 ml were PPH (No).

The secondary outcome measures include:

- Haemoglobin level at term and 24 h postpartum;
- Need for additional oxytocics;
- Need for blood transfusion and/or surgical procedures;

Ethical approvals were given by the research and ethical committee of the study hospitals and good clinical practice was adhered to in this study. The minimum sample size for the study was calculated using the Taylors' formula at 95% confidence taking prevalence of PPH to be 50%. This gave a minimal required sample size of 385. However, 1,800 patients (900 in oxytocin and 900 in misoprostol medication groups) were enrolled for the study in order to take care attrition and to increase power.

PPH was defined as blood loss of 500mls and above or any blood loss that results in haemodynamic instability. Heamoglobin concentration was estimated using centrifuge machine and haemoglobin reader. The statistical software SPSS version 16 (SPSS Chi, Ill USA) was used for statistical analysis. Mean values were compared using student *t* test for continuous variables

and chi square χ^2 test for categorical variables. The level of significance was set at $p < 0.05$ and at $p < 0.001$.

RESULTS

Majority (57.7 %) of the participants do not have any form of formal or informal education and they were mainly house wives (90.9 %). The 20 – 24 years of age category formed the bulk (34.2 %) of the study group followed by 25 – 29 years category (27.9 %). The majority of the enrolees had had inadequate birth interval (85.0 %) (less than two years), and also inadequate or late ante-natal care (81.0 %) visits. Most of the participants delivered at term. There was a good distribution of participants between the parity groups; with the 1 – 2 parity groups taking the highest (49.3 %) (Tables 1a and 1b).

Table 2 shows that the occurrence of PPH and the MBL in the oxytocin medication group (17.9 %; 388.04 ml ± 5.910) are significantly ($p < 0.001$) higher than in the misoprostol medication group (8.9 %; 327.68 ml ± 3.953).

Table 3 shows that the drop in mean haemoglobin levels from the values at 39th week to the values at 24th hour after the Childbirth in the two medication groups was significantly ($p < 0.001$) higher in the oxytocin group (0.708 ± 0.0340) than in the misoprostol group (0.549 ± 0.0276).

The proportion of enrolees that needed additional oxytocic agents was higher in the oxytocin group (16.4 %) than in the misoprostol group (3.6 %). The difference was significant ($p < 0.001$).

Of the 144 subjects that were pre-treated with intravenous oxytocin 10IU, 16 (11.1%) had to be administered with additional oral misoprostol (600 μg), and another 16 (11.1%) with intramuscular ergometrine (0.5 mg). None of the enrolees in either of the two medication groups of intravenous Oxytocin (884, subjects) and oral Misoprostol tablet (900 subjects) had indication for blood transfusion.

DISCUSSION

This study indicated higher occurrences of PPH and higher MBL in the oxytocin medication group. Drop in the mean haemoglobin levels from the values at 39th week to the values at 24th hour after the childbirth in the two medication groups was significantly higher in the oxytocin group than in the misoprostol group. And the proportion of enrolees that needed additional oxytocic agents was higher in the oxytocin group than in the misoprostol group. This study is unique in the sense that the trio of: PPH occurrence, MBL, along with change in haemoglobin level was considered in the comparative analysis.

The works of El-Refaey *et al*[15,16] , Hofmeyr *et al* [17] and Surbek *et al*[18] demonstrated an impressive efficacy of oral misoprostol in the prevention of PPH when compared to placebos. The superiority of oral misoprostol over intra-venous oxytocin in the prevention of PPH was not apparently clear in some studies as the outcome indicated only comparable efficacy between the two regimens[19,20].

Certain studies have revealed outcomes that were not in agreement with the present work; In a randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour, Cook *et al* reported a Postpartum blood loss that is significantly greater in the misoprostol group than in the oxytocic group[22]. Haemoglobin level drop from pre- to post-delivery was also greater in the misoprostol group. These two outcomes are in counter agreement with the present work; where both the post partum blood loss and the change in haemoglobin level were higher in the oxytocin group. Pharmacogenetics could explain the apparent opposite outcomes of these researches; in that the earlier mentioned study was mainly conducted in other continents of the world other than Africa, whereas the present work was conducted in Africa. In addition, the study area falls in the tropical zone of the Continent where ambient temperature is always on the high side and power supply for proper storage very erratic, thereby contributing negatively to the pharmaceutical stability of the oxytocin injection. In explaining this phenomenon, Ameenah *et al* (2011) reported that heat increases drug degradation because it increases the rate of drug molecular collision[23].

A handful of other studies have shown that there is no significant difference between oral misoprostol and injectable oxytocin[20,6].

However, in the report of its Technical Consultation of 2005, the WHO recommended the use of oral misoprostol where the use of parenteral oxytocin either as intramuscular injection (5 IU) or intra-venous (10 IU) is not feasible[21].

This work has demonstrated some basic facts that could be used to improve Pharmaceutical services in terms of procurement, distribution and storage of uterotonic drugs. Funds that could have been use in procurement of oxytocin injection and the syringe/needles could be partly used in the procurement of misoprostol tablets because of their efficacy, easy handling and administration. For same reasons PPH would be better managed at hospitals and rural set up where births are mostly under the supervision of traditional birth attendants.

CONCLUSION

It was concluded that oral misoprostol tablet 600 mcg has better prevention of PPH than intravenous oxytocin 10 IU as evidenced by its lower occurrences of PPH, lower estimated blood loss, and lower average reduction in haemoglobin level. This point was further buttressed by a lower need of additional oxytocic agent in the misoprostol group. However, environmental factors were theorized to have contributed to these significant differences. The fact that none of the enrollees in either of the medication group had lost more than 1000 ml of blood and that non had indication for blood transfusion, shows that the two medication approaches could be inter changed if need arises.

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REFERENCES

1. AbouZahr C. Antepartum and postpartum haemorrhage. Health dimensions of sex and reproduction. Cambridge, MA7 Harvard School of Public Health on behalf of the World Health Organization and the World Bank. 1998; p165– 89.
2. Mairiga AG, Kawuwa MB, Kyari O. A fourteen-year review of maternal mortality at the University of Maiduguri Teaching Hospital, Maiduguri, Nigeria. Nigerian Hospital Practice. 2008; 2 (5): 115- 118.
3. Cameron MJ, Robson SC. Vital Statistics; an overview. In: A Textbook of Postpartum Haemorrhage. (eds) Christopher B. *et al,* Sapiens Publishing, Dunccow, UK, 2006.
4. Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, AdetoroL. Trial of misoprostol in the management of the third stage of labour. Lancet, 2001;.358: 689–695.
5. Langenbach, C. Misoprostol in preventing postpartum haemorrhage: A meta-analysis. Int J Gynecol Obstet. 2006; 92:10–18.
6. Ng PS, Chan AS., Sin WK., Tang LC, Cheung KB, Yuen PM. A Multicentre randomized controlled trial of oral misoprostol and i.m. syntometrine in the management of the third stage of labour. Hum Reprod. 2001; 16:31–35.
7. Selo-Ojeme DO. Primary postpartum haemorrhage. J Obstet Gynaecol. 2002; 22:463–469.
8. Kodkany BS, Derman RJ, Goudar SS, Geller SE, Edlavitch SA, Naik VA. Initiating a novel therapy in preventing postpartum haemorrhage in rural India: a joint collaboration between the United States and India. Int J Fert Women's Med. 2004; 49:91–96.
9. Miller S, Lester F, Hensleigh P. Prevention and treatment of postpartum haemorrhage: new advances for low-resource settings. J Midwifery Women's Health. 2004; 49:283–292.
10. Walraven G, Blum J, Dampha Y, Sowe M, Morison L, Winikoff B. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomized controlled trial. BJOG. 2005; 112:1277–1283.
11. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad M. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006; 368:1248–53.
12. JHPIEGO. Program Brief on Maternal and Neonatal Health Program. Preventing Postpartum Haemorrhage. Baltimore. 2004; (http://www.jhpiego.org/resources/pubs/mnh/PPHpgmbrief.pdf). Date of browsing: 15th April 2011.
13. Chong YS, Su LL. Misoprostol for preventing PPH: some lessons learned. Lancet; 2006; 368:1216–7.
14. WHO. Guidelines for the prevention of postpartum haemorrhage. Geneva: World Health Organization. 2007
15. El-Refaey H, O'Brien P, Morafa W. Misoprostol for the third stage of labour. Lancet [letter]; 1996; 347(9010): 1257.
16. El-Refaey H, O'Brien P, Morafa W. Use of misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997; 104(3): 336-9.
17. Hofmeyer GJ, Nikodem VC, De Jager M. A randomized placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynaecol. 1998; 105(9): 971-975.
18. Surbek DV, Fehr PM, Hosli I. Oral misoprostol for third stage of labor; a randomized placebo-controlled trial. Obstet Gynecol. 1999; 94(2): 255-258.
19. Walley RL, Wilson JB, Crane JMG. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. Br J Obstet Gynaecol. 2000; 107: 1111-1115. (J)
20. El-Refaey H, Nooh R, O' Brien P. The misoprostol third stage of labour study. Br J Obstet Gynaecol 2000; 107: 1104-10.
21. WHO. Make every mother and child count. The world health report. Geneva, Switzerland7 WHO Press. 2005
22. Cook CM, Spurrett MM, Murray H. A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. Aust NZ J Obstet Gynaecol; 1999; 39: 4: 414-9.
23. Ameenah, K., Amrita, H., Poonam, P., Carissa, B., Smita, T. and Aimara, P. Drug degredation 2011. Lecture delivered at http://www.slideshare.net/ms_optimisstic/drug-degradation. Date of browsing: 19th/April/2011 .

Table 1a: Maternal Characteristics of Study Population

		Frequency	Percent (%)	Valid percent (%)
Education	Primary	49	2.7	3.1
	Secondary	145	8.0	9.3
	Tertiary	193	10.7	12.4
	Qur'anic	273	15.2	17.5
	None	899	50.0	57.7
	Sub-Total	1559	86.6	100.0
	Missing	241	13.4	
	Total	1800	100.0	
Occupation	Housewives	1607	89.3	90.9
	Civil Servants	111	6.3	6.4
	Self employed	16	0.9	0.9
	Students	33	1.8	1.8
	Sub-Total	1768	98.2	100.0
	Missing	32	1.8	
	Total	1800	100.0	
Age Group	15-19	208	11.6	11.7
	20-24	610	33.9	34.2
	25-29	498	27.7	27.9
	30-34	337	18.8	18.9
	35-39	112	6.3	6.3
	40-44	17	0.9	0.9
	Sub-Total	1784	99.1	100.0
	Missing	18	.9	
	Total	1800	100.0	

Table 1b: Maternal Characteristics of the Study Population

		Frequency	Percent (%)	Valid percent (%)
Birth Interval	Inadequate	273	15.2	85.0
	Adequate	49	2.7	15.0
	Sub-Total	322	17.9	100.0
	Missing	1478	82.1	
Antenatal care	Adequate	193	10.7	19.0
	Inadequate	820	45.5	81.0
	Sub-Total	1013	56.3	100.0
	Missing	787	43.8	
	Total	1800	100.0	
Gestation	Preterm	16	0.9	24.0
	Post term	51	2.8	76.0
	Sub-Total	67	3.6	100.0
	Term/Msn	1733	96.4	
	Total	1800	100.0	
Parity	1 – 2	562	31.3	49.3
	3 – 4	257	14.3	22.5
	5 – 6	321	17.9	28.2
	Sub-Total	1141	63.4	100.0
	Missing	659	36.6	
	Total	1800	100.0	

Table 2: Occurrence of post partum haemorrhage and mean blood loss in the two medication groups of intravenous oxytocin and oral misoprostol tablet.

Medication Group	Occurrence of Post Partum Haemorrhage (PPH) Number (%)			Mean Blood Loss (± SEM) (ml)
	No	Yes	Total	
i.v. Oxytocin	739 (82.1)	161 (17.9)	900 (100)	388.04 ± 5.91^{a}
p.o. Misoprostol	820 (91.1)	80 (8.9)	900 (100)	327.68 ± 3.95^{b}
Total	1559	241	1800	

$P_1 < 0.001$; p value for occurrence of PPH by chi square statistics.
$p_2 < 0.001$; p value for MBL by Student's t-test statistics.
Note that means with non similar superscript implies statistically significant difference.
SEM: Standard error of the mean

Table 3: Mean haemoglobin values at 39th week and at 24h after birth in the oxytocin and misoprostol medication groups

Medication Group	No	At 39th Week (± SEM) (g / dL)	24h After Birth (± SEM) (g / dL)	Mean Change (± SEM) (g / dL)
Oxytocin	418	11.842 ± 0.0562	11.135 ± 0.0469	0.708 ± 0.03[a]
Misoprostol	530	11.997 ± 0.0386	11.449 ± 0.0373	0.549 ± 0.03[b]

$p < 0.001$; p value for mean change in haemoglobin level by Student's t – test statistics.
Note that means with non similar superscript implies statistically significant difference.
SEM: Standard error of the mean.

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