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Comparative Study of Methylergometrine and Oxytocin in the PREVENTION of Primary Postpartum Haemorrhage

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Authors' contributions

This work was carried out in collaboration among all authors. Author BJF designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors ABA and JAO managed the analyses of the study. Author TAI managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Primary postpartum haemorrhage (PPPH) is a major cause of maternal mortality especially in low income countries. Reducing the likelihood of PPPH by routine active management of third stage of labour (AMSTL) can help reduce the maternal mortality associated with it.
Aim: To compare the efficacy and safety of intramuscular methyl-ergometrine with intramuscular oxytocin in the third stage of labour.
Study Design: Randomized comparative study.
Place And Duration Of Study: Department of Obstetrics and Gynaecology, University of Benin Teaching Hospital Benin between 9th June, 2016 and 9th September,2016
Methodology: Four hundred and ninety two women undergoing normal vaginal delivery were

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recruited and randomized to group A and B with two hundred and forty six in each group. Group A received 0.2mg methyl-ergomertine intramuscularly and Group B received 10 i.u. oxytocin intramuscularly immediately after delivery of the baby. The efficacy and safety of these two drugs were analyzed based on percentage fall in haemoglobin (Hb) level, need for additional uterotonic agents, need for exploration and uterine evacuation, need for blood transfusion, duration of the third stage of labour, elevation of blood pressure, number of patients with retained placenta and the need for manual removal of placenta (MRP). All data were analyzed using the Statistical Package for Social Sciences (SSPS) version 16.

Results: Fall in haemoglobin, mean blood loss, duration of third stage of labour, need for additional uterotonics, and blood transfusion were significantly less in group A. There was significant difference (p 0.003) in the mean intra-partum blood loss between the methyl-ergometrine (166.4±92.0ml) and oxytocin (207.4±196.9ml) groups. However side effects like nausea, vomiting and rise in systolic and diastolic blood pressure were higher in women in group A. However, only the diastolic blood pressure elevation was statistically significant ($p < 0.0001$).

Conclusion: Methyl-ergometrine is superior to intramuscular oxytocin in controlling primary post-partum haemorrhage. Its use should be encouraged for the active management of the third stage of labour, especially in those without any contra-indication to its use.

Keywords: Methyl-ergometrine; oxytocin; comparison; primary postpartum haemorrhage.

1. INTRODUCTION

Postpartum haemorrhage (PPH) remains a major contributor to maternal mortality and morbidity especially in developing countries [1,2]. The report from WHO suggests that 25% of maternal deaths are due to PPPH [3]. Several international health and developmental agencies have suggested that a low technology and evidence based intervention in reducing the incidence of PPPH is by the active management of the third stage of labour (AMTSL) [4,5]. Such interventions include prophylactic administration of uterotonic drug within one minute of delivery of the baby, early clamping and cutting of the umbilical cord and delivery of the placenta by controlled cord traction [6].

Most uterotonic agents used in preventing atony are divided into three groups; ergot alkaloids, oxytocin and prostaglandins [7,8]. The commonly used ergot alkaloids for controlling PPPH are ergometrine and its derivative methyl-ergometrine particularly when atonic uterus is the suspected cause [9,10,11,12]. WHO recommended the administration of ergometrine and methyl-ergometrine for AMTSL when oxytocin is not available especially in women without high blood pressure and in women with atonic uterus and secondary PPH [12]. The WHO recommendation of the use of oxytocin in low resource setting is as a result of paucity of health workers and the increased incidence of retained placenta and the other side effects associated with ergometrine, especially where AMTSL is not being practised [13,14,15].

Some studies have shown that methyl-ergometrine is more effective in controlling PPPH than oxytocin [16]. Similarly, in some observations there have been increase in the incidence of PPPH in multiparous women. In the Nigeria context, there are few studies that compared the efficacy and side effects of the aforementioned drugs. Also, considering the cost and efficacy of the use of ergometrine compared to oxytocin, it becomes necessary to revisit the use of ergometrine for preventing PPPH. Hence, a randomized comparative study was conducted and the efficacy and safety of intramuscular methyl-ergometrine were compared with intramuscular oxytocin in the third state of labour.

2. METHODOLOGY

The study was a randomized comparative study that was conducted at the Obstetrics and Gynaecology Department of the University of Benin Teaching Hospital, Benin City from 9th June 2016 to 9th September 2016. A total of four hundred and ninety two (492) patients who had spontaneous vaginal deliveries were randomized into intramuscular methyl-ergometrine and oxytocin groups with two hundred and forty six parturients in each group. All women with singleton live pregnancy at term in cephalic presentation undergoing spontaneous onset of labour without any high risk factor and who were ready to give consent were enrolled in the study. However, women with anaemia (Hb <9g/dl), sickle cell disease, hypertensive disorder in pregnancy, patients who had Caesarean

section/previous operative delivery, multiple pregnancy, disorders of blood coagulation, heart disease, previous PPPH and Uterine fibroids were excluded.

All women who met the inclusion criteria were enrolled after obtaining their informed consent on admission to labour room. Patients were selected at random using a computer generated random table and group assignment done using a sequential numbered opaque sealed envelopes to eliminate bias. Five millilitres of venous blood was drawn from each patient and sample was sent for haemoglobin (Hb), blood group and cross matching. All the women were followed through the 1st and 2nd stage of labour. Active management of third stage of labour was done in Group A with 0.2mg intramuscular methyl-ergometrine and Group B with 10 I.U of intramuscular oxytocin. After this, a flat pan was kept under the buttocks of the parturient and blood collected in it. Cord was clamped, cut and controlled cord traction was done without waiting for the signs of placenta separation. The allocated drug was administered intramuscularly within 1 minute of delivery of the baby. The collected blood was poured into a standard measuring jar and the volume was measured. For the placenta that failed to deliver after 30 minutes following birth of the baby, retained placenta was diagnosed and manual removal of the placenta (MRP) was done. In case of marked bleeding and uterus remaining flabby, it was massaged and additional uterotonic drugs given. Blood transfusion given if required. Patient was kept in labour ward under observation for a period of 2 hours for any drug side effects.

A repeat Hb estimation was done after 48 hours, the incidence of PPPH was measured as blood loss greater than 500ml and this was compared in both groups as the primary outcome measure. The secondary outcome measures were the need for additional uterotonics, blood transfusion, side effects such as nausea, vomiting and high blood pressure, and duration of third stage of labour. The data analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 16 and the categorical variables (outcome measures) were compared using the Chi – square test or Fisher exact test. The level of significance was set at $P < 0.05$.

3. RESULTS

The mean age of the parturients were 31 ± 4.7 years and 30.7 ± 5.3 years for the methyl-ergometrine and oxytocin group respectively. There was a reduction in postpartum haemoglobin in both groups, the difference in the value was statistically significant p = 0.001 [Table 1].

When the mean intra-partum blood loss measurements were compared, oxytocin group (207.4 ± 196.9) was 41 ± 10.4 higher than the methyl-ergometrine group (166.4 ± 92.0). Of the 246 parturients in the methyl-ergometrine group, 6 (2.4%) had PPPH (blood loss ≥ 500ml) compared to 16 (6.5%) of the oxytocin group this was statistically significant p value = 0.029. The relative risk of a patient having PPPH in the oxytocin group was 1.8 (0.94 – 3.72 at 95% CI), [Table 2].

Additional uterotonics was administered in 15 (6.1%) women who received methyl-ergometrine compared to 35 (14.2%) women who received oxytocin and it was statistically significant (p value = 0.003) [Table 3].

Methyl-ergometrine had higher frequency of side effects such as nausea, vomiting, headache, retained placenta and manual removal of placenta when compared to oxytocin. Methyl-ergometrine showed statistically significant difference for nausea and headache (p values 0.01, and 0.02) respectively compared to oxytocin. The other side effects were not statistically significant [Table 4].

The mean systolic blood pressure before delivery for methyl-ergometrine was 112.2 ± 9.2 compared to 114.3 ± 9.7 in the oxytocin group. The mean systolic blood pressure 1 hour after delivery in the methyl-ergometrine group was 122.6 ± 9.2 compared to 116.1 ± 10.8 in the oxytocin group. The systolic blood pressure was higher in the methyl-ergometrine group 1 hour after delivery (10.4 ± 00) compared to 1.8 ± 1.1 in the oxytocin group. This was statistically significant ($p < 0.0001$). Twenty one (8.5%) developed systolic blood pressure rise up to 140mmHg compared to 20 (8.1%) women in the oxytocin group. This was however not statistically significant (p value = 0.87). The mean diastolic blood pressure before delivery for methyl-ergometrine was 72.9 ±4.6 compared to 73.5 ± 4.8 in the oxytocin group. The mean diastolic blood pressure 1 hour after delivery in the methyl-ergometrine group was 83.2 ± 4.7 and 75.0 ± 6.6 in the oxytocin group. The diastolic blood pressure was higher in the methyl-ergometrine group 1 hour after delivery (10.3 ± 0.1) compared to 1.5 ±

1.8 in the oxytocin group (p < 0.0001). Eighty one (32.9%) women had diastolic blood pressure rise of 90mmHg in the methyl-ergometrine group compared to 22 (8.9%) women in the oxytocin group. The difference in both groups was statistically significant (p < 0.0001) [Table 5].

The mean blood loss was highest in grandmultiparous women in both groups; 197.3 in methyl-ergometrine group and 387.5 inoxytocin group respectively. However, the difference was not statistically significant (p value 0.218) [Table 6].

Table 1. Comparison of haemoglobin concentration

Haemoglobin (g/dl)	Group A Methyl-ergometrine		Group B Oxytocin		P. value
	Mean	±SD	Mean	±SD	
Before delivery	11.2	0.9	11.1	1.0	0.438
Range	10.0 – 16.0		10.0 -14.0		
After delivery (48 hours)	10.3	0.9	10.1	1.0	0.007
Range	7.3 – 15.3		6.0 – 12.7		
Difference	0.9	0.4	1.0	0.7	0.001
Reduction (%)	7.5	3.4	9.1	6.1	<0.0001

Table 2. Comparison of mean intra-partum blood loss and duration of the third stage of labour

	Group A Methyl-ergometrine n =246	Group B Oxytocin n =246	P. value	CI	RR
	Mean ± SD	Mean			
Mean Blood loss (ml)	166.4 ± 92.0	207.4 ± 196.9	0.003		
Range (ml)	100 – 1000	100 - 1500			
≥500mL	600.0 ± 200.0	818.8 ± 388.5	0.208		
≥500mL [n(%)]	6 (2.4)	16 (6.5)	0.029	0.941 – 3.726	1.872
Duration of third stage of labour (mins)	4.3 ± 2.8	5.1 ± 3.2	0.049		
Range (min)	1 – 30	1 – 23			

RR = Relative risk, CI = Confidence interval

Table 3. Comparison of efficacy using other parameters

Variable	Group A Methyl-ergometrine N (%)	Group B Oxytocin N (%)	P. value	RR	CI
Additional uterotonics	15 (6.1)	35 (14.2)	0.003	0.574	0.372 – 0.885
Exploration and uterine evacuation	4 (1.6)	2 (0.8)	0.681	1.339	0.755 – 2.374
Blood transfusion	2 (0.8)	5 (2.0)	0.446	0.568	0.175 – 1.838

RR = Relative risk, CI = Confidence interval

Table 4. Side effects of methyl-ergometrine and oxytocin

Variable	Group A Methyl-ergometrine	Group B Oxytocin	P. value
Nausea	21 (8.5)	7 (2.8)	0.006
Vomiting	8 (3.3)	2 (0.8)	0.055
Headache	16 (6.5)	6 (2.4)	0.029
Retained placenta	4 (1.6)	2 (0.8)	0.681
Manual removal of placenta	4 (1.6)	0 (0.0)	0.132

Table 5. Comparison of Blood Pressure before Delivery, and 1 Hour after delivery

Time Interval	Group A Methyl-ergometrine	Group B Oxytocin	P. value	RR	CI
	Mean ± SD	Mean ± SD			
Systolic Blood Pressure (mmHg)					
Before delivery	112.2 ± 9.2	114.3 ± 9.7	0.015		
Range	100 – 130	100 – 130			
1 hr after delivery	122.6 ± 9.2	116.1 ± 10.8	<0.0001		
Range	110 – 140	100 – 140			
≥140 [n(%)]	21 (8.5)	20 (8.1)	0.870	0.974	0.712– 1.332
Diastolic Blood Pressure (mmHg)					
Before delivery	72.9 ± 4.6	73.5 ± 4.8	0.149		
Range	70 – 80	70 – 80			
1 hr after delivery	83.2 ± 4.7	75.0 ± 6.6	<0.0001		
Range	80 – 90	70 – 90			
≥90 [n(%)]	81 (32.9)	22 (8.9)	<0.0001	0.539	0.463– 0.629

Table 6. Comparison of Mean Blood Loss/PPPH and Parity

	Group A Methyl-ergometrine		Group B Oxytocin		P. value
	Mean	±SD	Mean	±SD	
Primipara	169.1	75.8	209.0	189.6	0.084
Multipara	163.1	95.7	193.5	169.7	0.059
Grandmultipara	197.3	134.1	387.5	472.6	0.218

4. DISCUSSION

Maternal mortality is largely caused by PPPH and uterine atony is implicated in over 80% of cases of PPPH. The prophylactic use of oxytocin is the most essential component in active management of third stage of labour (AMTSL). It is a cheap, veritable tool in the prevention of PPPH and is now well established. The commonly used drugs are ergometrine and oxytocin however differences in the selection of the drugs remain despite WHO advocacy for oxytocin [17].

A more objective method of assessing postpartum blood loss is haemoglobin concentration by comparing the pre-delivery and postpartum delivery state and this was used in this study. In this study the fall in haemoglobin concentration in both groups is similar to the finding of Suman and colleagues in Kolkata [18], this is not unexpected because following delivery there is some degree of blood loss but it must not be excessive to cause haemodynamic instability in the parturient.

There was considerable reduction in the blood loss in favour of methyl-ergometrine, this finding is similar to the findings from other researchers elsewhere [16,19,20]. Similar study by Boopathil and colleagues [16] showed blood loss of more than 500ml was found in 6.7% and 2.7% in the oxytocin and methylergometrine groups respectively. This study showed that intramuscular methyl-ergometrine is superior to intramuscular oxytocin in preventing PPH during the third stage of labour. In our environment of practice where PPH is a major cause of maternal mortality, ergometrine might therefore be preferred because its benefit might outweigh the risks.

In the present study, the safety and efficacy of both drugs were compared using other parameters. The oxytocin group reported increased requirement of additional oxytocic drug (14.2%) compared with the methyl-ergometrine group (6.1%). This finding is in consonance with a previous study in Nigeria [19].

The difference in diastolic blood pressure between both groups was stastistically significant ($P< 0.001$), this finding is similar to that by Chukwuemeka and colleagues [19]. The side effects with higher frequency particularly in the methyl-ergometrine group were similar to those observed by Gohil and co-workers [20], this is less life threatening compared to mortality that could arise from uncontrolled bleeding. Also, other side effects noticed in the methyl-ergometrine group were not serious to warrant other forms of treatment and most of them subsided spontaneously within 24 hours postpartum.

Blood loss was better controlled with methyl-ergometrine compared with oxytocin in all parities which further showed it will be very effective in grand multiparous women who are more prone to PPPH due to uterine atony.

5. CONCLUSION

It can be concluded from this study that methyl-ergometrine, a derivative of ergometrine is superior to oxytocin in the prevention of primary PPH in routine AMTSL. The unpleasant side effects associated with methyl-ergometrine are minimal and often self-limiting. The side effects are likely to be acceptable and prefered to excessive bleeding after delivery.

6. RECOMMENDATION

Methyl-ergmoetrine should be encouraged in the active management of third stage of labour for prevention of primary post-partum haemorrhage, especially in high risk patients if there are no contraindications.

7. LIMITATIONS OF THE STUDY

1. Inability to blind both the patient and the investigator.
2. Larger randomised controlled studies are needed to confirm our findings.

CONSENT

Written consent was obtained from the women at presentation in labour ward.

ETHICAL APPROVAL

The ethical approval for this study was obtained from the Research Ethics Committee of the University of Benin Teaching Hospital, Benin City, Edo State.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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