Comparison between Misoprostol and Ergometrine in Routine Prophylaxis of Postpartum Haemorrhage

Prof. Mohammed Khalid Mustafa[1], Dr. Mohammed Mohammed Al-Kholy[2] and Tarek Abd El-Latif Mohamed Abd El-Ghani[3]

*Professor of Gynecology & Obstetrics, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
[2]Lecturer of Gynecology & Obstetrics, Faculty of Medicine Al-Azhar University, Cairo, Egypt.
[3]M.B.B. CH, Department of Gynecology & Obstetrics, Sohag Teaching Hospital, Egypt.
Dr.tarekabdo.gyn@gmail.com

Abstract: Objectives: To compare the effects of misoprostol versus ergometrine for PPH prevention, and provide important evidence to choose optimal agents for preventing PPH in developing countries. **Methods:** A prospective non-randomized controlled clinical trial carried out in the Department of Obstetrics and Gynecology, Sohag Teaching Hospital. Total 300 women enrolled in the study. Women allotted to one of the 3 groups. Active management of 3rd stage of labor in Group A with tablet misoprostol 400 µg rectally, Group B with injection methyl ergometrine 0.2 mg intramuscularly and Group C with saline injection (placebo). **Results:** Data was analyzed using SPSS computer program version 22.0. Quantitative data was expressed as means ± standard deviation, median and range. Qualitative data was expressed as number and percentage. The data were tested for normality using Shapiro-Wilk test. The nonparametric Mann–Whitney test and Kruskal–Wallis test were used for data which wasn't normally distributed. One-way analysis of variance test and Tukey's multiple-comparison test were used for normally distributed data. Chi-Square test was used for comparison between qualitative variables. A 5% level was chosen as a level of significance in all statistical tests used in the study. **Conclusion:** Conclusion of our study is that rectal misoprostol appears to be more effective than intramuscular methylergometrine in the prevention of PPH. Because of its affordability, low price, can be administered conveniently through oral, rectal, sublingual, and vaginal ways, stability at room temperature and longer shelf life it could be considered a good alternative in our country, although pyraexia and shivering are self-limiting side effects.
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1. Introduction

Postpartum hemorrhage (PPH) is commonly defined as blood loss exceeding 500 mL following vaginal birth and 1000 mL following cesarean ***(Rath et al., 2011).*** Definitions vary, however, and are often based on inaccurate estimates of blood loss ***(Kavle et al., 2006; Stafford, 2008).*** Moreover, average blood loss at birth frequently exceeds 500 or 1000 mL ***(Schorn et al., 2010).***

PPH is one of the leading causes of maternal mortality and morbidity worldwide and accounts for nearly one-quarter of all maternal deaths ***(WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage 2012).*** PPH also results in long-term disabilities and severe maternal morbidities ***(Khan et al., 2006; Campbell et al., 2006).*** About 14 million women around the world suffer from PPH every year (26 women every minute) ***(Miller et al., 2004).*** The vast majority of these cases occur in low and middle-income countries (LMICs). Yet, recent studies have shown increasing incidence of PPH in developed countries as well ***(Callaghan et al., 2010; Knight et al., 2009; Lutomski et al., 2012).*** The United Nations aimed to reduce maternal mortality by 75% by 2015. So far, the progress is slow in developing countries ***(WHO guidelines, 2014).***

Postpartum haemorrhage (PPH) can be classified as primary (early) or secondary (late). Primary PPH, the most common and severe, occurs within the first 24 hours after delivery. Secondary PPH occurs 24 hours to 12 weeks after delivery. Most cases of morbidity and mortality due to PPH are the result of primary PPH.

Bleeding during and after the third stage of labor may result from uterine atony, trauma (cervical, vaginal, or perineal lacerations), retained or adherent placental tissue, clotting disorders, and inverted or ruptured uterus ***(Haeri et al., 2012).***

Uterine atony is a main cause of PPH in pregnant women. ***The World Health Organization (WHO) (2012)*** and International Federation of Gynecology and Obstetrics (FIGO)2012 guidelines have recommended that routine administration of uterotonics-including oxytocin,

ergometrine/methylergometrine, the fixed-dose combination of oxytocin and ergometrine (ergometrine-oxytocin), misoprostol, and other prostaglandins should be administered in the third stage of labor for preventing PPH. Oxytocin is consistently recommended as the first management option to prevent PPH. The other drugs are often recommended as the second-line drugs.

According to WHO recommendations, in the case of treatment failure or unavailability of oxytocin, the second line treatment of choice are ergometrine. Ergometrine and methylergometrine are more unstable at room temperature compared to oxytocin. It is also photosensitive and thus requires special temperature and light storage conditions to remain effective ***(De Groot et al., 2012).*** A skilled personnel is required to administer ergometrine. However, compared to oxytocin ergometrine has more severe side effects, which includes hypertension, coronary vasospasms, increased systemic vascular resistance, pulmonary edema, intracranial haemorrhage and seizures, and retinal detachment ***(Haeri et al., 2012).***

Misoprostol has a competitive low price and can be administered conveniently through oral, rectal, sublingual, and vaginal ways ***(Zieman et al., 1997; Khan et al., 2003).*** It is often considered an affordable option for preventing PPH in settings where economics is less developed ***(El-Rafaey et al., 1996).*** The randomized evidence has proved effects of misoprostol over placebo ***(Chong et al., 2004; Høj et al., 2005)*** but the effects of misoprostol relative to other uterotonics were inconsistent ***(Caliskan et al., 2003; Gülmezoglu et al., 2001; Walraven et al., 2005).*** An alternative to misoprostol that can be used in less developed setting is ergometrine-oxytocin, which has lower price relative to other second-line uterotonics, but is characterized with rapid onset due to oxytocin and sustainable effect given ergometrine.

Adequate evidence is lacking to assess the comparative effectiveness of misoprostol and ergometrine for preventing PPH, including the considerations about their doses and administration route. That's why; further randomized studied is needed to compare efficacy and safety between misoprostol and ergometrine-oxytocin for preventing PPH.

Aim of The Work

To compare the effects of misoprostol versus ergometrine for PPH prevention, and provide important evidence to choose optimal agents for preventing PPH in developing countries.

2. Patients and Methods

Methods:

A prospective non-randomized controlled clinical trial carried out in the Department of Obstetrics and Gynecology, Sohag Teaching Hospital. Total 300 women enrolled in the study. Women allotted to one of the 3 groups. Active management of 3rd stage of labor in Group A with tablet misoprostol 400 µg rectally, Group B with injection methyl ergometrine 0.2 mg intramuscularly and Group C with saline injection (placebo).

Inclusion criteria:

Women with singleton pregnancy, between 32 and 42 week of gestation, no high risk factors and give a written and informed consent enrolled in the study.

Exclusion criteria:

Women with hemoglobin ≤ 7 gm%, pregnancy induced hypertension, Abruptioplacentae, placenta Previa, low-lying placenta,, grandmultipara, malpresentation, polyhydramnios, previous uterine scar, chorioamnionitis, instrumental delivery, intra uterine fetal death, coagulation abnormalities. History of medical disorder such as: Asthma, epilepsy, heart or renal disease will be excluded from the study. On admission to labor room, hemoglobin and blood grouping was done. All the women were followed up through the 1st and 2nd stage of labor.

3. Results

Table 1 showing non-significant difference between the three groups regarding occurrence of major hemorrhage. Major hemorrhage occurs in two cases in group (A), occurs in six cases in group (B), and occurs in ten cases in group (C).

Table (2) showing significant difference between the three groups regarding need for additional ecbolic. Group (A) 4 cases needed additional ecbolic, Group (B) 8 cases needed additional ecbolic, Group (C) 14 cases needed additional ecbolic.

Table (3) showing significant difference between the three groups in compering pre and post treatment hemoglobin level (g/dl).

Table (4) showing non-significant difference in hematocrit volume (%) with misoprostol, and significant difference with methergine and placebo.

Table (5) showing that shivering and fever occur in 32 cases with misoprostol, although pyraexia and shivering are self-limiting side effects. While there is no pyraexia and shivering with methergine.

Table (1): Comparison between the three studied groups regarding major hemorrhage

Parameter	Group A (Misoprostol) (N= 100)	Group B (Methergine) (N= 100)	Group C (Placebo) (N= 100)	P-value
Major hemorrhage **Yes (%)** **No (%)**	 2 (2%) 98 (98%)	 6 (6%) 94 (94%)	 10 (10%) 90 (90%)	 0.0.59 (NS)

P- value was calculated by Chi squared test. NS= Non Significant

Table (2): Comparison between the three studied groups regarding usage of additional ecbolic

Parameter	Group A (Misoprostol) (N= 100)	Group B (Methergine) (N= 100)	Group C (Placebo) (N= 100)	P-value
Additional ecbolic **Yes (%)** **No (%)**	 4 (4%) 96 (96%)	 8 (8%) 92 (92%)	 14 (14%) 86 (86%)	 0.041*

P- value was calculated by Chi squared test. *Statistically significant

Table (3): Comparison of pre and post treatment hemoglobin level (g/dl) in the study groups

Group	Pre-treatment (N= 100)	Post-treatment (N= 100)	P-value
Group A (Misoprostol) **Mean± S.D.** **Median (Range)**	 11.2 ± 1.1 11.3 (8.5 – 13.4)	 10.6 ± 1.2 10.7 (8.2 – 12.8)	 0. 000**
Group B (Methergine) **Mean± S.D.** **Median (Range)**	 11.4 ± 1.4 11.5 (8.5-14)	 10.8 ± 1.4 10.9 (7.8 -13.4)	 0.000**
Group C (Placebo) **Mean± S.D.** **Median (Range)**	 11.5 ± 1.2 11.6 (8.5 – 14)	 10.6 ± 1.3 10.9 (7 – 12.4)	 0.000**

*P- value was calculated by Wilcoxon test **Statistically highly significant

Table (4): Comparison of pre and post treatment Hematocrit volume (%) in the study groups

Group	Pre-treatment (N= 100)	Post-treatment (N= 100)	P-value
Group A (Misoprostol) **Mean± S.D.** **Median (Range)**	 33.1 ± 3.4 33.7 (22.5 – 38)	 33.1 ± 3.2 33.8 (24 – 38.3)	 0.861 (NS)
Group B (Methergine) **Mean± S.D.** **Median (Range)**	 35.2 ± 3.8 35.4 (28.7-41.1)	 33.3 ± 4.02 32.9 (25 -40.2)	 0.000**
Group C (Placebo) **Mean± S.D.** **Median (Range)**	 38.1 ± 1.3 38 (34.5 – 41.1)	 36.3 ± 2.8 36.5 (30 – 41.2)	 0.000**

*P- value was calculated by Wilcoxon test **Statistically Highly significant
NS= Non Significant

Table (5): Comparison between group A and group B regarding shivering and fever

Parameter	Group A (Misoprostol) (N= 100)	Group B (Methergine) (N= 100)	P-value
Fever **Yes (%)** **No (%)**	 32 (32%) 68 (68%)	 0 (0%) 100 (100%)	 0.000**

P- value was calculated by Chi squared test. **Statistically highly significant

4. Discussion

Postpartum haemorrhage is one of the top five causes of maternal mortality in both developed and developing countries.

The first cause of haemorrhage at the time of delivery after is uterine atony, therefore there is general agreement that active management of the labour rather than expectant management is recommended.

Advocates of active management argue that administering prophylactic uterotonic agents promotes strong uterine contractions and leads to faster retraction, placental separation and delivery. This has the effect of decreasing the amount of maternal blood loss at delivery and the rate of PPH. They also argue that the more effective uterine activity leads to a reduction in the incidence of retained placenta ***(Prendiville et al., 2002).*** The three uterotonic drugs used most frequently are the oxytocins, prostaglandins, and ergot alkaloids. Uterotonic drugs may be given intramuscularly (IM), intravenously (IV), suppository and as a gel.

We conducted a study to compare the effectiveness of rectal Misoprostol (600 ug) with that of intramuscular Methylergometrine (0.2mg) administered immediately after delivery of the foetus in reducing blood loss. We also compared the incidence and severity of post-partum haemorrhage, need for additional ecbolics, need for additional manouvers. We also compared the incidence of drug specific side effects.

We have chosen the rectal route of misoprostol-because of its promising pharmacokinetic property. Simultaneously, we kept blood loss as primary outcome. We have used an objective method of measuring blood loss, rather than a subjective or clinical one (methods used in other studies). The amount of blood loss is a more meaningful and direct parameter to define post-partum haemorrhage rather than Haemoglobin level estimation.

The results of the study demonstrated that misoprostol is more effective than methergin in the management of third stage of labour. Significantly fewer woman under methergine treatment needed extra-uterotonics or uterine massage to decrease the amount of post-partum bleeding. Misoprostol was associated with lower blood loss and haemoglobin drop.

A systematic review of randomized controlled trials of oral or rectal misoprostol to prevent postpartum haemorrhage concluded that rectal misoprostol in a dose of 400µg was significantly better than the injectable methylergometrine in reducing third stage blood loss and haemoglobin deficit. Therefore, it is possible that the effect of misoprostol is a dose related one ***(Hofmeyr et al., 1998).***

Ng et al. (2001), evaluated the use of 600 mcg oral misoprostol versus syntometrine IM in the management of the third stage of labor in 2058 patients. Their primary outcomes were also estimated blood loss and PPH > 500ml. There was significant difference in the amount of estimated blood loss and the incidence of PPH > 500 or 1000 ml or in the mean fall in haemoglobin concentration after delivery, both modes vaginal and caesarian section deliveries were included in this study. However, the need for an additional oxytocic injection was significantly higher (232/1026 versus 144/l032) in the misoprostol group (P<0.05) with a RR of 1.62 (95% CI 1.34-1.96).

Unlike our study that showed significant statistical difference concerning need for blood transfusion ($p < 0.05$), which was needed in 10 cases from methergine group (10%) in comparison with 2 case from misoprostol group (2%), similar results were reported in a double-blind randomized trial comparing 600 mcg oral misoprostol with IV methylergometrine ***(Amant et al., 1999).***

Bamigboye et al. (1998) conducted a study to compare the effectiveness of rectal misoprostol with syntometrine in the management of third stage of labour, 491 women were randomized to receive either 400 µg rectal misoprostol or syntometrine, one ampoule intramuscularly. Duration of the third stage, blood loss and haemoglobin estimation postpartum were similar in both groups. Postpartum diastolic hypertension was more common in the syntometrine group ***(Bamigboye et al., 1998),*** comparing with our study in no change in the blood pressure measurements.

Since 1997, ***EI-Refaey et al***. identified shivering as a side effect of misoprostol. The severity of shivering was dose-related and consistent across trials. In his study, shivering occurred in 62 % of patients and was described as self-limiting, starting approximately 20minutes after administration of the tablets and lasting10-15minutes while in our study shivering occurs in 32 patients have fever 37.5-37.8 which resolved with paracetamol. Gastrointestinal side effects were infrequent in his study with vomiting occurring in 8% of women and loose stool in 3%. Unlike our study vomiting 10%, diarrhea 12%.

Several observational and randomized studies ***(Amant et al., 1999),*** compared oral misoprostol with placebo or with other uterotonics. Most of these trials have found misoprostol to be better than placebo with respect to blood loss. Also a systematic review ***(Joy et al., 2003)*** and the recent update of Cochrane meta-analysis ***(Gulmezoglu et al., 2007)*** also found that misoprostol is better compared to placebo in reducing blood loss in third stage of labor, but it is less

effective compared to conventional uterotonics used as a part of active management of third stage of labor. ***Garg et al.*** found 600g oral misoprostol as effective as 0.2 mg intravenous methyl-ergometrine in active management of third stage of labour ***(Garg et al., 2005).***

Enakpene et al. reported oral misoprostol to be more effective in reducing blood loss during the third stage of labor than intramuscular methyl-ergometrine. Till nowadays there is no accepted standard dose or route of administration of misoprostol for prevention of PPH.

There are various studies ***(Chhabra et al., 2008)*** comparing sublingual misoprostol with injectable uterotonics in active management of third stage of labor. ***Vimala et al.*** found equal efficacy of sublingual misoprostol and intravenous methylergometrine in active management of third stage of labour.

Chhabra and Tickoo reported that a low dose of sublingual misoprostol (100 and 200g) appears to be as effective as a low dose of i.v. methyl-ergometrine (200mg) in the prevention of PPH ***(Chhabra et al., 2008).***

In a another study**,** ***Lam et al.***, found similar efficacy of 600 mg sublingual misoprostol and 1 ml intravenous syntometrine in the third stage of labour, for prevention of PPH ***(Lam et al., 2004).***

Conclusion

Conclusion of our study is that rectal misoprostol appears to be more effective than intramuscular methylergometrine in the prevention of PPH. Because of its affordability, low price, can be administered conveniently through oral, rectal, sublingual, and vaginal ways, stability at room temperature and longer shelf life it could be considered a good alternative in our country, although pyraexia and shivering are self-limiting side effects.

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