Original Article

Prophylaxis of Atonic Postpartum Hemorrhage with Misoprostol in Underdeveloped Countries

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Background: In this modern era of 21st century, postpartum hemorrhage is still the leading cause of maternal mortality in poor countries. In 70% cases, the cause is uterine atony. For centuries a therapy was needed which should be effective, cheap, safe, does not need refrigeration and that can be easily administered by untrained staff to control postpartum hemorrhage at primary health care setting in underdeveloped countries where majority of maternal deaths due to PPH occur. Misoprostol is one drug that might fulfill these requirements.

Objectives: The objective of this study is to evaluate the efficacy of rectal misoprostol in the prophylaxis and management of atonic PPH and compare it with conventional I/V syntocinon routinely used in hospitals as part of active management of third stage of labor.

Study Design: Semi experimental.

Materials and Methods: The study was conducted in Services Hospital Lahore, Department of Gynecology unit-2, between Oct 2006 to March 2007.One thousand pregnant females were included in the study and divided into two groups, a control group (500 women who received syntocinon) and a study group (500 women who received rectal misoprostol). Syntocinon (Sandoz Pharmaceuticals) 5u I/V injection and misoprostol (Cytotec, Searle Pharmaceuticals) 600 ug (3 tablets) per rectum were given to women in control and study group respectively, immediately after delivery of the baby. Duration of third stage of labor, blood loss after delivery, and hemoglobin deficit after 24 hours of delivery and frequency of atonic PPH were recorded and compared between the two groups. The side effects of both drugs were also noted.

Results: There was not a significant difference in blood loss after delivery (control group - 252 ml, study group - 304 ml, p-value - 0.18), duration of third stage of labor (control group-14.74 minutes, study group-16.54 minutes, p-value - 0.17) and hemoglobin deficit (control group - 0.375 gm/dl, study group - 0.404 gm/dl, p-value - o.5) between both groups. The frequency of atonic PPH in study and control group was similar ranging between 3 to 4%.Side effects of misoprostol (shivering 25%, fever 15%, vomiting 12% and diarrhea 5%).were significant (p-value <0.05) but all were temporary and not life threatening.

Conclusion: Misoprostol may be used for managing third stage of labor to reduce atonic PPH, especially in poor countries where facilities to deliver in hospitals and storage of oxytocic ampoules or medically trained persons are not readily available. Benefits of misoprostol outweigh its side effects.

Key Words: Prophylaxis, atonic postpartum hemorrhage, rectal, misoprostol, syntocinon, underdeveloped countries.

Introduction

Globally, 500,000[1] woman die each year from complications of pregnancy and childbirth. Obstetric hemorrhage especially the postpartum hemorrhage is the largest single medical cause of maternal mortality, accounting for about 25% of all maternal deaths. Majority of these deaths occurs in poor countries. The United Nations Millennium Development Goals call for all United Nation member states to reduce their maternal mortality ratios by 75% before 2015. Efforts in pursuit of this goal includes prevention and management of obstetric hemorrhage.

Postpartum hemorrhage is excessive bleeding (> 500 ml in vaginal delivery and > 1000 ml in cesarean section) from the genital tract after birth. The condition can result from uterine atony, retained placenta, genital tract trauma and coagulation disorders. It is said to be primary if it occurs within 24 hours of delivery and secondary if it occurs 24 hours after delivery. It complicates 4-10%[2] of deliveries.

The prevention and management of PPH needs a properly coordinated chain of systems from primary to secondary and tertiary health care levels. The developing countries like USA, UK, etc have reduced significantly the frequency of PPH by applying measures e.g. efficient antenatal, intranatal and postnatal services, adequate transport and blood transfusion services. But the situation is different in the developing world where PPH is still the number one killer of mothers.

To prevent and treat PPH, literature strongly supports the use of active management of third stage of labor which includes controlled cord traction, use of syntocinon at deli-

very of anterior shoulder or crowing of fetal head and uterine massage.[2] Studies show that risk of PPH can be reduced to 60% by using active management of third stage of labor.[3]

Uterine contraction and retraction is the first line followed by platelet plug formation as 2nd and clot formation as third line mechanism to control bleeding from placental site after delivery. Different types of drugs (methergine, syntocinone, syntometrine) what we call as uterotonic drugs are used to cause contraction and retraction of uterus after delivery. Ergot alkaloids have been used for decades for this purpose, but they are associated with risk of hypertension and are therefore, contraindicated in patients with hypertension and heart disease.[4]

The drug of first choice in 3rd stage of labor in modern obstetric practice is syntocinon due its excellent efficacy as well as few side effects as compared to ergometrine.[5-7] But syntocinon as well as syntometrine are available as injections only and their use needs sterilized needles and trained staff. Another problem associated with the use of injectable drugs is that they need refrigeration to remain effective. Facilities like trained staff and refrigerators might not be available in poor countries especially at primary health care level. Moreover; some of the studies have shown syntocinon to have cardio toxic effects due to presence of chemical chlorobutanol[8,9] as a preservative in syntocinon ampoules.

Prostaglandins are another group of drugs that have strong uterotonic property. They are not associated with side effects like hypertension.[10] These qualities make prostaglandins a good alternative to syntocinone and methergine that can be routinely used in the management of third stage of labor.

The use of misoprostol brought a revolution in Obstetrics and Gynecology practice. The observation that misoprostol has uterotonic properties was first time documented in literature by El-Refaey et al in 1993.[11] Later on, it was shown to have some side effects like, nausea, vomiting and shivering.

Misoprostol is an E1 prostaglandin analogue that has been used for decades for management of gastric ulcers. It is also used in Gynecology and Obstetrics for various indications e.g. cervical priming, medical TOP and induction of labor although it is not approved by FDA. Recent research shows that misoprostol can also be used for prophylaxis and treatment of atonic post partum hemorrhage.

Misoprostol is a good drug for low resource countries[12, 13] because it is a pill, easy to use (Oral, sublingual, buccal, vaginal,and rectal routes), is stable at ambient temperature and does not require special storage facilities, can be easily delivered at the community level, is cheap and widely available.

So a study was conducted to evaluate the efficacy and safety of rectal misoprostol andcompared them to that of syntocinon for the management of third stage of labor, with special emphasis on PPH prevention.

Materials and Methods

The study was conducted in Services Hospital Lahore between October 2006 to March 2007 on 1000 parturient. An informed consent was taken from all women included in the study.

Inclusion Criteria

Full term living fetus, spontaneous and instrumental vaginal deliveries with or without episiotomy.

Exclusion Criteria

Traumatic PPH, cases with bleeding disorders, Cesarean section deliveries, cases with prolonged difficult labor, placenta previa and abruption placenta, multiple gestation, previous history of PPH.

Cases were randomly selected. Out of 1000 patients, 750 were admitted through emergency and 250 through out door department in labor. Thorough history taking and physical examination was done on all patients.

Investigations

In addition to baseline investigations e.g. urine C/E, blood C/E, blood sugar, blood grouping, clotting profile and screening for Hepatitis B and C, hemoglobin estimation was done before and 24 hours after delivery in both groups. The difference between the two values of hemoglobin was calculated as hemoglobin deficit.

The women in control group were given syntocinon (Sandoz Pharmaceuticals) 5 IU i.v injection which is routinely used in the hospital as part of active management of third stage of labor whereas the study group received 600ug (3 tablets) of misoprostol (Cytotec, Searle Pharmaceutical) per rectum. Both drugs were given immediately after delivery of the baby.

We defined postpartum hemorrhage according to WHO criteria as bleeding > 500 ml after vaginal delivery. Alternatively, we can define PPH as Hemoglobin or hematocrit difference of > 10% between pre delivery and 24 hour post delivery levels. On clinical grounds, we can define PPH as blood loss after delivery sufficient to cause hemodynamic instability. Atonic PPH is the one that results from relaxation of uterine muscles.

Blood loss after delivery was estimated by special drapes put under the parturient andremoved after 1 hour of delivery and blood collected in graduated plastic bags.

Outcome Measures

1. Duration of third stage of labor.
2. Estimation of blood loss,
3. Frequency of primary PPH.
4. Hb deficit 24 hours after delivery.
5. Side effects of misoprostol and syntocinon.
6. Acceptibility of drug by the women via the rectal route.

Placentas were removed by Brand's Andrew method of delivery of placenta. Women`s vital signs were noted and

any excessive bleeding was managed according to WHO recommendations. Side effects of drugs were noted and recorded. Women were asked about any difficulty in tolerating the misoprostol by rectal route.

Calculations

Data were analyzed using SPSS version 13 for windows using student t test. A p-value of < 0.05 was taken as statistically significant.

Table 1: *Comparison of age and parity between study and control group.*

Variables	Control Group	Study Group	P value
Age in years (mean)	26.38	25.04	0.24
Parity(mean)	2.3	2.5	0.372

Results

The age and parity of women in the study and control groups were not statistically different (Table 1).

The duration of third stage of labor (control group-14.74 minutes, study group-16.54 minutes, p-value-0.17) was not significantly different in study and control group (Table 2). Placenta was retained in 11 cases, 4 in control and 7 in study group. They were removed manually under general anesthesia. (Table 2) also shows that mean blood loss after delivery (control group-252 ml, study group-304, p-value-0.17) was not significantly different in the two groups. Also, the mean hemoglobin deficit (control group-0.375, study group-0.404 gm/dl, p-value-0.5) was not statistically different between the two groups.

Table 2: *Comparison between duration of third stage of labor in minutes, blood loss after delivery in ml and Hb deficit in gm/dl in the two groups.*

Variable	Control Group	Study Group	P-value
Duration of 3rd stage of labor in minutes (mean)	14.74	16.54	0.17
Blood loss after delivery in ml (mean)	252	304	0.18
Hb deficit in gm/dl (mean)	0.375	0.404	0.5

The frequency of atonic post partum hemorrhage was the same in control and study group (3 to 4 %) as shown in (Table 3). In the control group, there were 18 cases of atonic PPH, out of which 17 cases had mild to moderate bleeding (550 ml to 800 ml) and there was one case of severe PPH with blood loss of 1800 ml and received one pint of fresh blood. In the study group, there were 20 cases of atonic PPH. of which 18 had blood loss between 600ml to 920 ml, while 2 cases had severe PPH (blood loss > 1000 ml). One received 1 pint and the other received 2 pints of fresh blood.

Table 3: *Frequency of atonic PPH in control* and *study group.*

Groups	No of cases with PPH (no)	%	p-value
Control	18	3.6	
Study	20	4.0	0.2

Table 4 shows side effects of drugs in both groups. It can be seen that the most common side effect is shivering (25%), followed by fever (15%), while vomiting and diarrhea were noted in (12%) and (5%) cases respectively in the study group.

Table 4: *Side effects of drugs.*

Side Effects	Study Group	Control Group	p-value
Shivering	125(25%)	20(4%)	<0.05
Fever	75(15%)	15(3%)	<0.05
Vomiting	60(12%)	10(2%)	<0.05
Diarrhea	25(5%)	8(1.6%)	<0.05

Discussion

For decades, it has been realized to plan strategies to reduce risk of PPH at primary health care level and in rural areas.[14] Misoprostol is cheap, stable at room temperature, is rapidly absorbed after oral, sublingual and rectal routes. It has strong uterotonc activity. It was thought to be ideal for this purpose especially at primary health care level.[15,16]

Literature supports the use of misoprostol in resource poor[12-15] settings. High dose (800) misoprostol can bring results comparable to injectable uterotonics. Multiple controlled trials[17-21] investigating misoprostol for prophylaxis of PPH have been reported.[1].A systemic review of randomized controlled trials of oral or rectal misoprostol to prevent post partum hemorrhage concluded that the traditional injectable uterotonics were more effective than misoprostol as part of active management of 3rd stage labor[21].But many trials have suggested that misoprostol is effective and convenient in poor countries e.g. Guinea Bissau[14], Nigeria,[19] Nepal,[15] India[12] and Indonesia[13] for prophylaxis of PPH.

The blood loss after vaginal delivery should not exceed 500 ml. The results of our study show that third stage blood loss and hemoglobin deficit were not significantly different in the control and study group. This is in accordance with

the results of other studies comparing rectal misoprostol with injectable uterotonics.[21,22]

The incidence of PPH in our study is 3-4% which is comparatively less than the reported incidence in general obstetric population (4 to 10%).[24,25]

This may be due to the fact that study was carried out at a tertiary care hospital with majority of patients studied were low risk for PPH. We also used active management of 3rd stage of labor with syntocinon used as uterotonic in the study and misoprostol in control group. So rectal misoprostol has an excellent potential for prophylaxis andactive management of atonic PPH.

The duration of 3rd stage of labor should not exceed 30 minutes in both primi and multigravidas.It remained within normal limits with little difference between study (16.54 minutes) and control (14.74 minutes) group. This is in agreement with results of all previous studies[25] on misoprostol in PPH.

Postpartum hemorrhage is one of the commonest indications for blood transfusion which is associated with complications like transmission of infections, anaphylactic reactions and clotting disturbances in cases of massive transfusions. We did not note a significant difference in frequency of blood transfusion given between the study (2 cases) and control (1 case) group.

The adverse effects of misoprostol are dose related. One study reported the incidence of shivering and fever decreased to 11% and 4% respectively with 400ug of misoprostol given at cord clamping.[29] One small study showed that 400ug or 200 ug of misoprostol given per rectum in post partum period reported an incidence of shivering in 7% cases.[30]

The incidence of fever and shivering in our study are higher than other studies in literature. But these effects were temporary and caused no serious damage nor require a specific treatment. So mother must be informed that she would have a temporary shivering and fever after delivery.

Limitations

The study had some limitations. We could not do blinding in our study due to some technical problems. The sample included both high and low-risk women. The need is to conduct such studies on high risk cases under controlled conditions.

Conclusion

Overall, this study demonstrated that rectal misoprostol is safe and effective for the prophylaxis and management of postpartum hemorrhage. So it can be safely used in resource poor settings in under developing countries to manage third stage of labor and postpartum hemorrhage. Our study results strongly recommend misoprostol to be included in protocols to manage postpartum hemorrhage in developing world at primary health care level to reduce the risk of postpartum hemorrhage, and maternal mortality and morbidity related with this catastrophic condition.

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