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COMPARISON BETWEEN SUBLINGUAL MISOPROSTOL AND INTRAMYOMETRIAL PROSTAGLANDIN F2α IN ADJUNCT TO ROUTINE MANAGEMENT OF PRIMARY POSTPARTUM HEMMORHAGE

Abstract

Objective: To study the efficacy of sublingual misoprostol as compared with injectable PGF2α in management of primary Post Partum hemorrhage (PPH).
Study Design: Randomized controlled trial
Place and Duration of Study: Combined Military Hospital Risalpur, from January 2006 to September 2008.
Patients and Methods: All patients who reported to CMH Risalpur were included except women with previous cesarean section and those with gestational age less than twenty eight weeks at the time of delivery. They were randomized in two equal groups of thirty patients each. One group received 600mcg sublingual misoprostol (Parke-Davis) combined with standard oxytocic treatment and the other group received intramyometrial PGF2α (Prostin F2alpha, Dinoprost- Parke-Davis) combined with standard oxytocic for treatment of primary PPH.
Results: There was insignificant difference between both groups in terms of blood loss ($p>0.05$), treatment failure ($p=0.640$) and side effects ($p=0.05$). Sublingual misoprostol was found to be equally effective as compared to intramyometrial PGF2α for the treatment of primary PPH but superior when price, availability and storage are taken into account.

Article

INTRODUCTION

Postpartum hemorrhage is one of the leading causes of maternal mortality and morbidity. Blood loss exceeding 500ml at vaginal delivery and 1000ml at caesarean section is considered a primary post partum hemorrhage. However studies have shown that average blood loss at normal delivery is about 600ml1. Blood loss is usually underestimated at uncomplicated delivery, PPH is divided into two categories based on the timing. Primary occurs within 24 hours of delivery and secondary PPH after 24 hours. This distinction has limited usefulness in terms of the differential diagnosis. The patient's response to blood loss varies with initial hemoglobin. A patient with normal hemoglobin may not show any haemodynamic disturbance with blood loss up to 1000ml. An anemic patient, however develops tachycardia, hypotension, faintness and air hunger after loosing only upto 300ml of blood2. So currently suggested definition of primary PPH includes a hemorrhage resulting in a heamatocrit drop of 10% or a hemorrhage that requires immediate transfusion.
Primary PPH is usually due to uterine atony which is failure of the uterus to contract and retract is called uterine atony, and is the most common cause of primary PPH, which accounts for more than 90 % of the cases3. Uterine atony is seen in association with a number of conditions like multiparity; prolonged labor, incoordinate uterine activity, placental causes, uterine over distention, uterine inversion, chorioamnionitis, drugs etc.
Primary PPH is an acute and potentially fatal emergency and every second is important and may prove life saving. The management has two major components i.e. resuscitation of the patient and replacement of blood loss. Both aspects are equally important and must commence simultaneously2. Poor, unhealthy, high parity women delivered away from heath facility are actual victims. Delay in diagnosis, failure to employ sufficient medical and surgical treatment, poor team work, deficiencies in communication and transport, lack of infrastructure impedes transfer of patient to high level of care. Inability to stabilize a patient who is in hemorrhagic shock, rapidly result in death. Guidelines for management of spontaneous onset of labor, induction, and augmentation are needed specifically for low resourced setting4.
The prostaglandins (E1, E2, and F2α) have been successfully used to control PPH. The prostaglandin E1 analogue, misoprostol is available in the form of tablets. The dosage varies widely and the routes of administration include rectal, oral, sublingual, and buccal. Sublingual dose is 600 mcg, and it is an off label use5 which is associated with a significant reduction of blood loss. Prostaglandin E2 is available in 20mg pessary given rectally. It is not heat stable, so if not stored properly, loses its efficacy1. Injectable PGF2α is available in dosage of 250 mcg. Its route of administration include intramuscular, intracervical, or intramyometrial, but can cause (broncho constriction) in asthmatic patients and in cases of reactive airway disease. Local intramyomertrial injection whether transabdominal or transvaginally results in dramatic reduction of rate of bleeding. Therefore, routine clinical application of injectable PGF2α is recommended in the view of its easy performance, excellent haemostatic effect, minimal side effects and good prognosis6.
The aim of the study was to compare the efficacy of the sublingual verses injectable prostaglandins and their side effects, in a smaller setup, where availability and price of the drugs was also important. Storage problems were more in case of injectable as compared to sublingual, although these were not our variable in the study.

PATIENTS AND METHODS

This randomized controlled trial (RCT) was conducted in CMH Risalpur over a period of 2 years and 9 months from Jan 2006- Sep 2008. A total 800 patients were admitted during the study period. In this study we have used 600 mcg sublingual misoprostol, which can be repeated up to two hour interval and compared it with injectable PGF2α injected intramyometrially. In the event of hemorrhage a minimum of 2 hours should lapse after the original dose then second dose was injected. If the initial dose was associated with pyrexia or marked shivering at least 6 hours should lapse before second dose

Inclusion criteria:

1. Women who developed primary PPH (blood loss 500ml or more).
2. Primi as well as multi gravidae.
3. Singleton and twins.

Exclusion criteria:

1. Gestational age<28 weeks.
2. Women with history of caesarean section.
3. Women losing blood less than 500ml.
4. Women with asthmatic problems and reactive airway disease.
5. Women with medical diseases like cardiac, hypertensive, diabetes.

Data collection procedure:

All women underwent routine active management of the 3rd stage of labor with standard uterotonics (syntocinon, ergometrine), controlled cord traction after delivery of the baby and a gentle uterine massage after delivery of placenta. Immediately after the delivery of the baby, blood was collected by placing a clean fracture bed pan directly under the woman's buttocks for a minimum of one hour. The women losing blood more than 500ml were entered into randomized controlled trial (RCT) and randomly divided into two groups. A fresh large perineal pad with plastic backing was positioned just below the bedpan to capture any spattering blood loss. Once the delivery attending person considered active bleeding stopped, the blood was measured in the calibrated jar. All the women who were diagnosed to have PPH due to inadequate uterine contraction as per clinical judgments were randomly divided into two equal groups using random number table. One group of 30 women received 600mcg of sublingual misoprostol (200mgX3). The other group was injected with Intramyometrial prostaglandins F2α per abdominal (in the fundus of the uterus) or through vaginal route into the uterine body. The injection was prepared by diluting one ml of PGF2α in 10 ml of distilled water Simultaneous to the treatment for PPH, blood collection was restarted with a clean bedpan and fresh perineal pad. The additional blood loss was transferred to a calibrated jar and measured. All the gauze and pads were put in a plastic bag and were weighed. So in this study our results were based on the total volume of blood collected.
The main study outcome was to determine if the addition of sublingual misoprostol to standard treatment for primary PPH reduces blood loss when compared with intramyometrial PGF2α. The primary endpoint was to measure blood loss equal to or greater than 500ml to label the patient as a case of PPH. Secondary end point was to measure the change in hemoglobin. Side effects of both the drugs were compared as these were observed, reported and recorded.
Pre-delivery hemoglobin was recorded and post delivery blood loss was estimated. Regular monitoring and training of delivery ward staff

continued throughout the duration of trial. Data was analyzed using SPSS version 15. descriptive statistics were used. Both the treatments were compared using independent samples t-tests p-value<0.05 was considered as significant. Treatment failed in 03 patients in misoprostol group and in 02 patients in PGF2α group with (p>0.05).

RESULTS

The study consisted of sixty selected women randomly divided in two equal groups. Mean age of the women in misoprostol group was 26.8±6.4 years and in PGF2α was 28.5±5.39 years (p>0.05). Most of the women were multipara1-4. However, grandmulti were higher in number in this region (9 in misoprostol group and 8 in PGF2α group), (p>0.05). Placental delivery took place within five mints in majority of patients in both the groups. Manual removal of placenta was done in 2 patients in misoprostol group but 5 women in group of PGF2α (p>0.05). Pre delivery hemoglobin was 10.4±2.5g/dl in sublingual misoprostol group and 9.8±2.1g/dl in PGF2α (p>0.05). Measured blood loss was compared 710±107 ml in sublingual misoprostol group and 740ml ±129ml in PGF2α group (P>0.05). Total blood loss post treatment is 165±113ml in misoprostol group and 157±98ml in PGF2α (p>0.05). Post deliveries mean heamoglobin was 9.1±1.9g/dl in misoprostol cases and 8.4±1.5g/dl in PGF2α group (p>0.05). Drop in hemoglobin was estimated 1.4±0.9 g/dl in sublingual misoprostol group and 1.5±1.1 g/dl in PGF2α group although it was slightly more in PGF2α group but insignificant (p>0.05) as shown in table 1.

Table-1: Pre-treatment and post-treatment study variables between both the treatment.

Pre-treatment Variables	Misoprostol group (n=30)	F2 α group (n=30)	p-value
Age (mean±D)	26.8±6.4	28.5±5.3	0.530
Parity 0 1-4 5-8	 5 16 9	 3 19 8	 0.665
Singleton Twin	57 3	28 2	0.640
Manual removal of placenta	2	5	0.228
Placental delivery within 5 min	23	20	0.390
Pre-delivery Hb level (mean±SD)	10.4±2.5	9.8±2.1	0.10
Measured blood loss at diagnosis (mean±SD)	710±107	740±129	>0.05
Total blood loss post-treatment (mean±SD)	165±113	157±98	>0.05
Post delivery Hb (mean ±SD)	9.1±1.9	8.4±1.5	0.147
Drop in Hb(mean ±SD)	104±0.9	1.5±1.1	0.143
Treatment failure, n (%)	3 (10%)	2(6.7%)	0.640

The side effects were compared in table 2.

Table 2: Comparison of side effects of both the treatments

Variables	Misoprostol group (n=30)	PGF2α group (n=30)	p-value
Nausea			
None	26	28	
Mild to moderate	4	2	0.389
Severe	0	0	
Vomiting			
None	26	29	
Mild to moderate	3	1	0.339
Severe	1	0	
Diarrhea			
None	28	27	
Mild to moderate	1	2	0.228
Severe	1	1	
Headache			
None	25	28	
Mild to moderate	3	2	0.306
Severe	2	0	
Shivering			
None	18	21	
Mild to moderate	9	7	0.711
Severe	3	2	
Fever			
None	11	16	
Mild to moderate	13	12	0.227
Severe	6	2	

Treatment failed in 03 patients in misoprostol group and in 02 patients in PGF2α group (p>0.05).

DISCUSSION

The off-label use of misoprostol, a prostaglandin E1 analogue has entered into clinical practice for management of primary postpartum bleeding, because of its strong uterotonic properties, and its ease in sublingual administration, stability at ambient temperatures, wide availability and low cost. A 600 mcg dose of sublingual misoprostol has been shown safe and effective in primary postpartum hemorrhage. Our study finding are consistent with a hospital based RCT on adjunct use of misoprostol7 for trearment of PPH. However clinical trials have shown that oxytocin prophylaxis is more effective than sublingual misoprostol for active management of third stage of labour8. The pharmacokinetics may explain ourob servation of stronger and more frequent initial uterine contractions with intramyometrial oxytocin than with sublingual misoprostol. The peak of uterine contraction for oxytocin was within the first 10 minutes after administration whereas for sublingual mosoprostol it was only achieved after 30-40 minutes. This mirrors their plasma concentrations. Since misoprostol is less effective than conventional uterotonics, therefore it has been recommended as an adjunct to conventional uterotonics9 for PPH. Injectable PGF2α is also found effective for PPH in our study as shown in table one with blood loss of (740±129ml). Intramyometrial PGF2α whether transabdominal or transvaginal results in dramatic reduction of rate of bleeding in cases of uterine atony as used in previous studies10. When both the drugs were compared for blood loss and post delivery drop in hemoglobin, no statistical difference was found as shown in table-1.

Uterine atony is the most common cause of primary PPH in our study as it is found in previous studies3,12. Our study finding on measurement of postpartum blood loss, high-lighted the clinical importance of management. As it is followed by reduction of blood loss in event of primary PPH. This confers with results from a combined analysis of two placebo-controlled trials on adjunct use of misoprostol and is associated with significant reduction of blood loss12.

A reduction in blood loss reduces need for more invasive procedures. This results in smaller change in post partum hemoglobin, and may prevent more severe maternal morbidity experienced by recently delivered mother13.

Based on trends in blood loss, we see among women in the study, both groups show nearly same potential for reducing postpartum bleeding.

Three patients failed to respond sublingual misoprostol. One responded to balloon tamponad14. One woman's uterus was saved with B lynch brace suture. Life saving hysterectomy was the only treatment option in third case. Two patients failed to respond in injectable PGF2α group. These two developed shock and life saving hysterectomy was mandatory.

In table 2 both the drugs were compared for side effects. The women under trial experienced nausea, vomiting and headach in both cases. It was mild to moderate and treated well with symptomatic treatment. These effects have been reported in many previous studies, and symptomatically cured15.

The most commonly observed side effects were shivering and hyperthermia observed in around half of the women in misoprostol group and in 14 women who received PGF2α. Although there appeared to be clinical differences in the incidence of hyperthermia between two groups, the difference was not statistically significant. Shivering and hyperthermia have been reported in studies using misoprostol for different indication and with variable routes and doses16. In previous studies PGF2α was also associated with significant increase of maternal pyrexia and shivering6. As found in the study both the drugs were associated with maternal pyrexia and shivering .These were however transient and did not result in additional complication. Fortunately we did not experience any serious complication of injection PGF2α17. It was repeated once after two hours in one patient only. Sublingual misoprostol tablets were repeated in three patients. The rate of PPH was 10.5%, as the women who reported to hospital were, booked, unbooked, and dai handled with low socioeconomic status. The objective assessment of postpartum bleeding provided a valuable insight into the diagnosis and management of PPH. The use of the bedpan proved to be a valuable tool for educating delivery ward staff over the course of study on diagnosis and management of postpartum hemorrhage, but the value of its continued use outside a clinical trial is not yet apparent.

CONCLUSION

Due to logistical complexities of postpartum hemorrhage, the obstetrical complication continues to threaten women's lives, especially in facilities short-staffed or lacking uterotonics and protocols to manage PPH safely and effectively. It is concluded that sublingual misoprostol is equally effective as an injectable PGF2α. However misoprostol is an orally active prostaglandin analogue with uterotonic effects, and is a better option for PPH management in low–resource setting because of its thermostability, cost-effectiveness and easy administration.

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