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DETERMINATION OF THE EFFICACY OF 600MCG ORAL MISOPROSTOL IN THE PREVENTION OF POSTPARTUM HAEMORRHAGE

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Abstract- Postpartum haemorrhage (PPH) is a fatal complication of the third stage of labour. PPH accounts for 25% maternal mortality worldwide. Fortunately most PPH cases are preventable and thus can significantly reduce maternal mortality and morbidity. Misoprostol, a PGE1 analogue, an uterotonic, is inexpensive, easily available with simple route of administration. The study group was given 600mcg of misoprostol within 5 min of clamping of cord and blood loss was measured with help of BRASS-V delivery drape. The parameters ascertained were total blood loss in third stage of labour, length of third stage, time taken for retraction of uterus, need of any additional uterotonic drug or surgical intervention, need for blood transfusion, adverse effect of 600mcg of oral misoprostol. Oral administration of 600mcg misoprostol is an effective method of preventing PPH, though it may not be as effective as potent uterotonics like ergometrine or PGF2alpha. Nevertheless, it scores over them in low resource settings due to its cost effectiveness, and ease of availability, transport, storage and administration to the patient.

Keywords- Misoprostol, Postpartum haemorrhage, BRASS-V drape.

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Introduction

The third stage of labour is potentially the most dangerous one for the mother. Fatal complications include postpartum haemorrhage, retention of placenta, shock, pulmonary embolism and uterine inversion. PPH is defined as blood loss in excess of 500 millilitres, after the delivery of baby. But any amount of blood loss, even if <500ml, which leads to deterioration of maternal hemodynamics, also constitutes postpartum haemorrhage [1]. PPH complicates 3.9% of vaginal deliveries and 6.4% of caesarean section. PPH is of two types. Primary PPH is defined as blood loss of more than 500ml within 24 hours after delivery, this is the common form. Secondary PPH is defined as blood loss of more than 500ml beyond 24 hours after the birth of baby to one month of delivery. There are 5.29 lakh maternal deaths per year from the complications of pregnancy and childbirth [2]. Of these, PPH accounts for 25% maternal mortality worldwide, 30.8% maternal mortality in Asia and 27.6% maternal mortality in India [1]. It causes 1.5 lakh maternal deaths and 20 million cases of maternal morbidity per year [3]. Fortunately most PPH cases are preventable and prevention of PPH can significantly reduce maternal mortality and morbidity. This in turn shall help in reaching the Millennium Development Goal of reducing mortality ratio by 75% by 2015 [1].

Active management of third stage of labour (AMTSL) includes the following components:

- Administration of prophylactic uterotonic within 5mins of clamping the cord.
- Delivery of placenta by controlled cord traction (Brandt-Andrews technique)
- Uterine massage after delivery of the placenta as appropriate.

A 2003 Cochrane review found that AMTSL was associated with a 60% reduction in PPH [4]. Uterotonics used include oxytocin, ergot alkaloids and prostaglandins such as PGF2 alpha. These uterotonics require skilled birth attendants, who can identify patients in whom these drugs are specifically contraindicated, and who can administer these drugs parenterally. The World Health Organisation (WHO) estimates that 60% of births in the low income countries occur outside a health facility. Thus these births take place in the absence of trained birth attendants who can administer the above drugs in order to prevent PPH. Also the uterotonics remains unavailable at a proper room temperature. These women are thus at a great risk of developing PPH [5]. Misoprostol, PGE1 analogue, is an inexpensive and easily available uterotonic. Due to its simple route of administration and lack of need for special storage conditions, it is especially useful in developing countries. The aim of this study is thus to determine the efficacy of 600mcg oral misoprostol in preventing postpartum haemorrhage and to ascertain its side effects and to assess need of additional uterotonics or surgical

methods for control of PPH.

Material and Methods

This study was a prospective randomised controlled study, conducted in department of Obstetrics and Gynaecology at Pad. Dr. D.Y. Patil Medical College, Hospital and Research Centre.

A total of 100 cases falling under inclusion criteria cited below and not coming under any exclusion criteria were randomly recruited in the study, after obtaining a written and informed consent from them.

Inclusion Criteria

- Women with gestational age more than 28 weeks and at low risk of PPH, undergoing vaginal delivery.
- Patients having the ability and willingness to provide an informed consent.

Exclusion Criteria

- Previous pregnancy associated with PPH
- Patients with traumatic PPH
- Antepartum haemorrhage
- Multiple pregnancies
- Noncephalic presentation
- Multipara,big baby, fibroid uterus,polyhydraminos
- Previous LSCS or LSCS in present pregnancy
- Medical disorders complicating pregnancy e.g. anemia, diabetes, hypertension, seizures.
- Induced labour with Oxytocin.
- IUD
- Epidural anaesthesia
- Bronchial asthma or respiratory disorders.

Method

Women delivering vaginally, who fall into the inclusion criteria, were selected for the study after a written and informed consent. They were randomly put in either Group-1 or Group-2. Women in Group-1 were given 600 mcg of oral misoprostol within 5 mins of clamping the cord. This was followed by controlled cord traction. Uterine massage was done after the delivery of placenta as appropriate. If the uterus failed to contract in 10 minutes, or if there was a blood loss >100ml between 3 and 5 minutes postpartum, then additional uterotonic intramuscular (I/M)250 mcg PGF2 alpha was administered. If bleeding was not controlled, another dose of 250 mcg (I/M) PGF2 alpha was repeated. Other medical or surgical measures were to be used if bleeding continued inspite these measures. Blood transfusion and treatment of shock were to be done if required.

Women in Group-2 were given intravenous (I/V) ergometrine 0.2 mg upon birth of anterior shoulder. The other steps were the same as in Group-1.

The blood loss in the third stage of labour and postpartum period was measured with the help of BRASS-V Delivery drape [Fig-1], which was placed under patient's buttock after the delivery of the baby. This bag is calibrated and thus gives an objective and reliable measure of the blood lost.

The efficacy of 600mcg oral misoprostol in preventing PPH was ascertained by measuring the following parameters:

- Total blood loss in the third stage of labour and postpartum period.
- Time taken for the retraction of uterus.
- Need of any additional uterotonic drug to control bleeding after giving 600mcg oral misoprostol.
- Need of surgical intervention to control bleeding after giving 600mcg oral misoprostol.
- Need of blood transfusion.
- Need of manual removal of placenta.
- Any associated maternal mortality.
- Adverse effects of 600mcg oral misoprostol.

The data, in view of the above observations for each patient was recorded on a proforma, tabulated and compared to obtain the efficacy and side-effects of the uterotonic used in the two groups.

Results

In our study, we divided the efficacy of oral misoprostol 600 mcg, as the uterotonic, in preventing PPH. This was compared with a control group, in which 0.2 mg I/V ergometrine was administered upon the birth of the anterior shoulder.

Table 1- Group of patients

Groups	Uterotonic used	Number of patients
Group-1 (Cases)	Misoprostol (600mcg orally)	50
Group-2 (Controls)	Ergometrine (0.2mgI/V)	50
Total		100

Table 2- Distribution of parity

Sr. No.	Parity	Group-1		Group-2	
		Number of patients	Percentage	Number of patients	Percentage
1	Primipara	30	60%	28	56%
2	Multipara	20	40%	22	44%

Table 3- Duration of first and second stage of labour

Sr. No.	Average duration of a stage of labour	Group-1		Group-2	
		Primipara	Multipara	Primipara	Multipara
1	First stage	10.60 hrs.	6.97 hrs.	11.40 hrs.	6.63 hrs.
2	Second stage	33.50 min	20.05 min	32.70 min	21.62 min

Table 4- Duration of third Stage of labour

Sr. No.	Mean duration	Group-1 (minutes)		Group-2 (minutes)	
		Primipara	Multipara	Primipara	Multipara
1	Third stage	5	5.82	4.66	5.22
2	Mean	5.41		4.94	

Table 5- Time taken for retraction of uterus after administration of a uterotonics.

Group-1 (minutes)		Group-2 (minutes)	
Time range	Jun-20	Time range	04-Oct
Mean	12.41	Mean	6.91

Table 6- Mean blood loss at frequent intervals after administration of a uterotonic drug

Sr.No.	Time	Group-1			Group-2		
		Mean blood loss in primipara (ml)	Mean blood loss in multipara (ml)	Total mean blood loss (ml)	Mean blood loss in primipara (ml)	Mean blood loss in multipara (ml)	Total mean blood loss (ml)
1	3 min	257.5	262.8	260.15	235.8	218.2	227
2	5 min	80.6	82.5	81.55	77.1	80.5	78.8
3	15min	86.1	89	87.55	80.2	84.4	82.3
4	Total after 2 hrs	407.83	447.25	427.54	392.14	371.81	381.97

Table 7- Group-1 - Observations which prompt action to prevent development of PPH and the efficacy of such action

Sr.no.	Time taken for retraction of uterus (mins)	Blood loss between 5 mins and 15 min after giving oral misoprostol	Additional uterotonic (250mcg carboprost I/M) given based on previous two observations	Total blood loss 2 hrs. after administration of oral misoprostol and after additional uterotonic	Additional measure required to control bleeding in patients with PPH
1	15.5 mins	120ml	Yes	480 ml	None
2	18 min	145 ml	Yes	580 ml	250mcg I/M carboprost
3	17 min	115 ml	Yes	360 ml	None
4	16.5 min	150 ml	Yes	560 ml	250 mcg I/M carboprost

Table 8- Group-2 - Observations which prompt action to prevent development of PPH and the efficacy of such action

Sr.No.	Time taken for retraction of uterus (min)	Blood loss between 5 min and 15 min after giving oral misoprostol	Additional uterotonic(250 mcg carboprost I/M) given based on previous two observations	Total blood loss 2 hrs. after administration of oral misoprostol and after additional uterotonics	Additional measure required to control bleeding in patients with PPH
1	15.5 min	120ml	Yes	450 ml	None
2	16 min	150 ml	Yes	550 ml	250 mcg i/m carboprost

Table 9- Percentage of patients who needed an additional uterotonic (Before development of PPH).

	Group-1	Group-2
Number of patients	4	2
Percentage of patients	8%	4%

Table 10- Percentage of patients who developed PPH with blood loss >500ml

	Group-1	Group-2
Number of patients with blood loss >500ml in 2 hrs.	2	1
Percentage of patients	4%	2%

Table 11- Side Effects

Sr. No.	Side effect	Group-1		Group-2	
1	Nausea, vomiting	3	6%	0	0%
2	Diarrhoea	1	2%	0	0%
3	Shivering	31	62%	16	32%
4	Pyrexia	4	8%	6	12%

Discussion

PPH is thought to be the single largest medical cause of maternal death, accounting for 25% maternal lives annually, which amounts to 1.5 lakhs maternal deaths annually. Out of these, 30.8% occur in Asia and 27.6% occur in India [1,3]. A woman suffering from PPH can die quickly, often within 2 hours, unless she gets immediate and appropriate medical care [6]. The average blood loss after vaginal and caesarean birth is 500ml and 1000ml respectively. It has been observed that nearly half of all women who deliver vaginally shed 500ml or more blood when it is measured quantitatively. However observations have shown that estimated blood loss is commonly only about half of the actual loss [7]. Visual assessment of blood loss underestimated postpartum blood loss by 33 to 50%, compared to photospectrometry. BRASS V drape estimates blood loss more accurately than visual estimation and is of great value in the developing world [8]. In 2009, WHO recommended that in the absence of personnel to offer AMSTL, the trained health worker should offer misoprostol 600mcg orally, immediately after the birth of the baby [9]. In our study we have randomly divided a total of 100 patients in 2 groups. Group-1 consists of 50 cases that were given 600mcg oral misoprostol and Group-2 consists of 50 controls that were given 0.2 mg (I/V) ergometrine [Table-1]. The parity in both the groups was comparable [Table-2]. In our study we found that labour was not prolonged in any of the patients, which if present could predispose to uterine inertia and thereby PPH [Table-3]. The mean duration of the third stage of labour in was 5.41 minutes in Group-1 as compared to 4.94 minutes in Group-2 [Table-4]. In study by Amant F., Spitz B., Timmerman D., et al in 1999, the median length of labour was similar in both misoprostol and ergometrine group [10] as was in our study. However, an opposite observation was made by Chandhiok N., Dhillon B.S., Datey S., Mathur A., Saxena N.C. in their study in 2006. They found that there was a significant reduction in duration of the third stage of labour in the misoprostol group. Duration was 7.9 +/- 4.2 minutes in the misoprostol group versus 10.9 +/- 4.3 minutes in the ergometrine group [11]. However a larger randomised controlled trial is required to definitely establish the efficacy of oral misoprostol in reducing the length of the third stage of labour. The time taken for retraction of uterus after administration of any of the available uterotonics is about 12-15 minutes. Thus in our study, oral misoprostol proved as efficacious as I/V ergometrine in retraction of uterus [Table-5]. Oral misoprostol is absorbed slowly and peak action is at 20 minutes wherein the third stage for most women is over. Thus more prolonged the bleeding (PPH), the more effective misoprostol is [5]. The mean of the total blood loss after 2hrs in both groups was <500ml [Table-6]. The BRASS-V drape used in our study is calibrated and is more accurate, reliable, cost effective method of estimating blood loss in low resource settings to identify woman at risk [8]. Similar result was found in the study by Hoj L., Cardoso P., Nielsen B.B., Hvidman L., Nielson J., Aaby P. in 2005, mean blood loss in misoprostol group was 443ml, as compared to 496ml in the placebo group [12]. In a study by Derman R.J., Kodkany B.S., Gou-

dar S.S., Geller S.E., Naik V., Bellad M.B., et al in 2006, conducted in Belgaum, India, the mean blood loss was 214.3ml in the misoprostol group, while it was 262.3ml in the placebo group [5]. In Group-1, four patients were observed to have blood loss of >100ml between 5-15 mins of administration of oral misoprostol [Table-7]. This accurate measurement of blood loss was possible because of BRASS- V drape which provides quantitative estimation of blood loss and thus allows early recognition of women who are at potential risk of developing PPH. In Group-2, two patients had blood loss >100ml between 5-15 mins of administration of I/V ergometrine [Table-8]. These patients [Table-7] and [Table-8] were given additional 250mcg I/M PGF2 alpha at the end of 5mins. However, in Group-1, inspite of having given additional PGF2 alpha at the end of 5mins, two patients had blood loss of >500ml at the end of 2 hours and in Group-2, one patient had blood loss of >500ml at the end of 2 hours and were given additional uterotonic. However, patients in both the groups did not require any further medical or surgical management or blood transfusion. Thus an additional uterotonic, in the form of I/M PGF2 alpha was required in 8% patients in Group-1 and 4% patients in Group-2 [Table-9]. Walraven, et al in 2005 showed in their study that blood loss >500ml occurred in 11% patients of misoprostol group, as compared to 12% patients in oral ergometrine group. They also stated that a blood loss >1000ml occurred in 0.3% patients of misoprostol group, versus 0.7% patients in oral ergometrine group [Table-10] [13]. In a large RCT by Derman R.J., Kodkany B.S., Goudar S.S., Geller S.E., Naik V., Bellad M.B., et al in 2006, conducted in rural areas of Belgaum, India, it was found that oral misoprostol 600 mcg reduced PPH by 47% [5]. Side effects produced by oral misoprostol include shivering, nausea, vomiting, diarrhea and pyrexia. All of these were preventable and treatable. None of the patients had a major reaction to the drug or serious side effects. In the misoprostol group, nausea and vomiting is produced in 6% of patients and diarrhea in 3% [Table-11]. None of them developed dehydration due to these. None of these side effects was seen in the ergometrine group. In the study to investigate the side effects of 600mcg oral misoprostol, Patted S., Goudar S., Naik V., Bellad M.B., Eldavich S., Kodkany B., Patel A., et al in 2009 found that there were no differences in nausea, vomiting or diarrhea between the misoprostol and placebo group [14]. Walraven, et al in 2005 reported that shivering occurred in 32% patients of misoprostol group, versus 11.7% patients of oral ergometrine group [13]. Chandhiok N., Dhillon B.S., Datey S., Mathur A., Saxena N.C. in their study in 2006, observed a temperature >38 C in 9.7% patients of the misoprostol group, versus the 4.3% patients in the ergometrine group [11]. In a study by Hofmeyr G.J., Gulmezoglu A.N., Novikova N., Linder N., Ferreira S., Piaggio G. worked on a systematic review and meta-analysis of maternal deaths, published in a bulletein of WHO in 2009.they found that in 46 RCT they reviewed, their were 11 maternal deaths. These occurred in 5 trails conducted by Durman, et al 2006 [5], Gulmezoglu AN 2001 [15], Walraven, et al in 2005 [13], Hogg, et al 2005 [12], Hofmeyr, et al 2004 [16]. Of these, 8 occurred in women receiving misoprostol, 6 being associated with PPH [17]. Since the utility of oral misoprostol is mostly in rural areas, to be administered by skilled birth attendants, it is important to know how well the drug can be used by them. Since our study was conducted in a tertiary health care centre, we could not assess this. But Chandhiok N., Dhillon B.S., Datey S., Mathur A., Saxena N.C. conducted a study in 2006, to see whether paramedical workers from rural primary health centers in India are able to administer oral misoprostol. They concluded that paramedical workers followed instructions in almost all deliveries (99%) in the intervention group [11]. Thus we conclude, when compared with ergometrine or PGF2 alpha, oral misoprostol has the advantage of being stable inspite of room temperature and light exposure, thereby avoiding storage and transport problems and is safe in patients with hypertension, anaemia and heart disease.

The utility of oral misoprostol in prevention of PPH is of great value in the low resource rural set ups which lack the adequate infrastructure and lack skilled birth attendants. The advantage offered by oral misoprostol outweighs its side effects like shivering, pyrexia, nausea, vomiting and diarrhoea. The use of calibrated BRASS V Drape provides accurate quantitative estimation of the amount of blood loss, thereby allowing close vigilance of efficacy of the uterotonic in prevention of PPH. Thus calibrated estimation versus visual estimation allows timely recognition and intervention in prevention of PPH.

References

[1] UN Millennium Development Goals (2000) *www.un.org/milleniumgoals*.

[2] Rogers J., Wood J., McCandlish R., Ayers S., Truesdale A., Elbourne D. (1998) *Lancet,* 351, 693-699.

[3] AbouZahr C., Murray C.J.L., Lopez A.D. (1998) *Health Dimension of Sex and Reproduction Burden of Disease and Injury Series*, 3*rd edition*., 111-164.

[4] Prendiville W.J., Elbourne D., Mcdonald S. (2000) *Cochrane Database of Systematic Reviews, John Wiley and Sons Ltd*. 3, CD000007.

[5] Derman R.J., Kodkany B.S., Goudar S.S., Geller S.E., Naik V., Bellad M.B., et al. (2006) *Lancet*, 368, 1248-53.

[6] Ronsman C., Graham W.J. (2006) *Lancet,* 368, 1189-2000.

[7] Pritchard J.A., Baldwin R.M., Dickey J.C., et al. (1962) *Am. J. Obstet. Gynecol.*, 84, 1271.

[8] Patel A., Goudar S.S., Geller S.E., Kodkany B.S., Edlavitch S.A., Wagh K., et al. (2008) *Int. J. Gyne. Obstet.*, 93(3), 220-4.

[9] Gulmezoglu M.A., Souza J.P., Chou D., Methai M., Hill S., Abalos E. (2008) WHO Guidelines for Management of PPH., 18-21.

[10] Amant F., Spitz B., Timmerman D., et al. (1999) *BJOG*, 106, 1066-70.

[11] Chandhiok N., Dhillon B.S., Datey S., Mathur A., Saxena N.C. (2006) *Int. J. Gynecol. Obstet.,* 92(2), 170-5.

[12] Hoj L., Cardoso P., Nielsen B.B., Hvidman L., Nielson J., Aaby P. (2005) *BMJ,* 331, 723.

[13] Walraven G., Blum J., Dampha Y., Sowe M., Morison L., Winikoff B., et al. (2005) *BJOG*, 112, 1277-83.

[14] Patted S., Goudar S., Naik V., Bellad M.B., Eldavich S., Kodkany B., Patel A., et al. (2009) *Journal of Maternal-Fetal and Neonatal Medicine*, 22(1), 24-28.

[15] Gulmezoglu A.M., Villar J., Ngoc N.T.N., Piaggio G., Carolli G.,

Adetoro L., et al (2001) *Lancet,* 358, 689-95.

[16]Hofmeyr G.J., Ferreira S., Nikodem V.C., Mangesi L., Singata M., Jafta Z., et al. (2004) *BMC Pregnancy Childbirth,* 4, 16.

[17]Hofmeyr G.J., Gulmezoglu A.M., Novikova N., Linder N., Ferreira S., Piaggio G. (2009) *Bulletin of the World Health Organization,* 87, 666-677.