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Efficacy and safety of perrectal 400 microgram misoprostol versus intravenous 200 microgram methylergometrine in the management of third stage of labor for prevention of postpartum haemorrhage: A randomized control trial

Dr Anubhuti Jain
Assistant Professor in the department of obstetrics and Gynaecology Geetanjali medical college and hospital Udaipur, Rajasthan
Email: anubhuti80j@gmail.com

Dr Mahendra Kumar Jain
Associate professor in department of neonatology, AIIMS bhopal m.p.
Corresponding author email: drmahendra78@gmail.com

Dr Parul Jain
Assistant professor, Dept of Periodontology, Government College of Dentistry Indore

Dr. Ashish Kumar Jain
Professor, Dept of cardiology, MGM medical College and hospital Indore

***Abstract*---**Background**:** Objective: Postpartum haemorrhage (PPH) is a major cause of mortality and morbidity during childbirth, especially in developing countries. Misoprostol is a cheap, safe, widely available, and stable at room temperature, does not required any intravenous accesses and having few mild side effects. In resource-poor countries with limited facilities, misoprostol may be one of the important interventions to prevent PPH. We aimed to assess the effectiveness of perrectal low dose misoprostol for the prevention of PPH. Method: We designed a prospective randomized control trial, single centre study. 138 indoor low risk pregnant women with gestational age at least 37 weeks who anticipated vaginal delivery were randomly assigned to perrectal 400 microgram misoprostol (n = 71) or intravenous 200 microgram (n = 67) methylergometrine after delivery of baby and placenta. The primary outcome was incidence of PPH (estimated blood loss >500 ml after delivery of baby and placenta). Results: In this

study out of 138 low risk pregnancy, no women developed PPH, no patient required additional dose of oxytocin, no patient required any form of transfusion. Mean blood loss with SD was 242.96±50.50 ml and 239.10± 51.04 ml in misoprostol group and methylergometrine group respectively, in both group median was 230 ml with IQR 90 and 80 in misoprostol group and methylergometrine group respectively,(z score -0.434 p=0.664). There was > 250 ml blood loss found in 22/71 and 20/67 patient in misoprostol group and methylergometrine group respectively, OR with 95% CI was1.055(0.511to 2.18) p=0.885. Conclusion: Misoprostol is an another alternative in prevention of postpartum hemorrhage. It is as effective & safe as other uterotonics in prevention of PPH in low risk patients.

***Keywords*---**postpartum haemorrhage, childbirth, third stage labor.

Introduction

Postpartum haemorrhage (PPH) is a major cause of morbidity and mortality during childbirth, especially in developing countries[1]. Most births and maternal deaths occur in Africa and Asia, where home deliveries are common, infrastructure and transportation are limited, and where birth attendants are scarce or inadequately prepared to prevent and treat PPH[2]. In such settings haemorrhage accounts for 30% of maternal deaths[1]. Sustainable Development Goal 3.1, by 2030, to reduce the global maternal mortality ratio to less than 70 per 100,000 live births cannot be achieved without successful management of PPH[3]. The contribution of PPH to maternal death in developing countries is more marked in domiciliary or rural settings where trained staff are scarce, transport facilities are inadequate and the availability of uterotonic agents and blood are limited. In a community based study in Zimbabwe, PPH was the leading cause of maternal death in rural (40 per 100,000) but not urban (eight per 100,000) women [4].

In Uganda, 97% of those health facilities expected to be able to provide emergency obstetric care had deficiencies in the basic services they could provide [5]. Also, many uterotonic medications have the disadvantage of requiring parenteral administration and specialized storage. Because the majority of deaths due to PPH occur in less developed areas, finding simple methods to lower the risk of developing PPH and to effectively treat the condition is imperative. Active management of the third stage of labor plays a major role in prevention of PPH. The International Federation of Gynecologists and Obstetricians (FIGO) and the International Confederation of Midwives (ICM) issued a joint statement in 2003 stating that active management of the third stage should be routinely offered to women in the third stage of labor. This statement outlined active management as consisting of use of uterotonic medication(preferably oxytocin), controlled cord traction and uterine massage[6].

The effect of misoprostol on uterine contractility was well studied by Gemzell-Danielsson et al.[7] and Aronsson et al.[8] After a single dose of oral misoprostol there is an increase in uterine tonus.[8] To produce regular contractions, however,

a sustained plasma level of misoprostol is required and this requires repeated oral doses. The effect of vaginal administration of a single dose of misoprostol on uterine contractility is initially similar to that of oral administration: an increase in uterine tonus. However, after 1-2 hours, regular uterine contractions appear and they last at least up to 4 hours after the administration of misoprostol[7]. The development of regular contractions after vaginal administration may explain the better clinical efficacy of vaginal administration when compared to oral administration.[9,10]

Parsons et al[11] compared 800 mcg misoproostol administered rectally to 10IU oxytocin administered intramuscularly in a randomized controlled trial conducted in Ghana. They did not detect a difference between the misoprostol and oxytocin groups with respect to blood loss >500mL [3/217(1.4%) vs. 6/227(2.6%), RR 0.58 (95%CI 0.25-3.86)].There was a trend towards a lower need for additional uterotonic in the misoprostol group that was not statistically significant [9/223 (4.0%) vs.19/224(8.5%);RR0.48(95% CI0.22-1.03)].Those in the misoprostol group had a higher incidence of shivering [16/216(7.4%) vs.2/213,(0.9%); RR8.0 (95%CI 1.86-34.36)],while there was no difference in the incidence of fever[8/200 (4.0%)vs.4/209(1.9%);RR2.09(95% CI 0.64-6.83)].

A randomized trial by Derman et al[12] compared oral misoprostol to placebo in1620 subjects in rural India and showed 47% reduction in PPH compared to placebo [52/812(6.4%) vs. 97/808 (12.0%),P<0.0001; RR 0.53 (95%CI 0.39-0.74)]. The subjects who received misoprostol were less likely to require transfer to another medical facility [4/812(0.5%)vs. 12/808(1.5%), P=0.05] or to need blood transfusions [1/812(0.1%)vs.7/808(0.9%), P=0.04]. As with other studies, shivering [419(52.2%)vs.140(17.3%)] and fever [34(4.2%)vs.9(1.1%)] were significantly greater in the Misoprostol group. It appears to be a cost-effective intervention with the potential to significantly impact maternal health in areas of rural births, with an estimated savings of $115,335 per 10,000births with a protocol of administering1000mcg rectal misoprostol after allbirths.[13]In developing countries where there is a high incidence of severe anemia during pregnancy because of nutritional, genetic, or environmental factors, even a relatively small reduction in postpartum blood loss could be clinically relevant. Simple route of administration and use of stable, inexpensive drugs are needed because many deliveries take place away from hospitals or medical facilities and are supervised only by birth attendants (who may not be qualified to administer parenteral oxytocics.[14,15] or most often, not supervised at all.[16]

Re-use of needles for parenteral administration is common practice, thus posing a major risk of the spread of blood-borne infections such as hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection. Further, there is lack of availability of safe blood transfusion services and prior knowledge of blood pressure often is not available.[14]Misoprostol is an inexpensive drug and easily available. It is easy to use and does not require special storage conditions (i.e., can be stored easily at room temperature; is thermostable and light stable; does not require specific conditions for transfer) and has a shelf life of several years.[17,18] These advantages make it a useful drug in reducing the incidence of postpartum hemorrhage in developing countries.[19]

Methodology

This is a prospective randomized control trial, single centre study was done at Department of Obstetrics and Gynaecology, Geetanjali Medical College & hospital, Udaipur, Rajasthan. Patients were enrolled over a total period of 18 months from August 2020 to January 2022. Inclusion criteria were all indoor pregnant women registered or unregistered completed or more then 37 weeks of gestation with spontaneous onset of labor who anticipated vaginal delivery. Exclusion criteria were Cesarean Delivery, Grand Multipara Parity>4, Gestational age <37 weeks, Multiple Gestations, Pregnancy-Induced Hypertension, Patients on Anticoagulant Therapy, Placenta praevia, Antepartum Hemorrhage, Polyhydramnios, Intrauterine Fetal Death, Contraindications of methyl ergometrine - Hypertension / Cardiac diseases, Rh negative mother, Previous history of Postpartum Hemorrhage, Uterine Malformations, Allergy to prostaglandins or alkaloids, Severe Anemia.

Permission was taken from hospital ethical committee to do the study. Written informed consent were taken from eligible patients to participate in the study, when they were admitted in labor anticipating vaginal delivery at Department of Obstetrics and Gynaecology, Geetanjali Medical College & hospital, Udaipur, Rajasthan. A computer programme was used to generate Randomization sequence & it was blocked for a size of 2-4. The Randomization sequence numbers were sealed in sequentially numbered opaque envelopes. Envelops were opened by on duty attending nurses or resident doctors. Participants were assigned to intervention group by on duty resident doctors. Because of nature of intervention blinding could not be done.

Procedure

138 Patients were allocated in two intervention groups; Group A - Tab Misoprostol 400 mcg (n = 71) perrectal given after delivery of baby and placenta. Group B – Inj methylergometrine 200 mcg (n = 67) diluted in 10 ml of distilled water and injected slowly over 5mins intravenously, after delivery of baby and placenta. Blood loss were estimated till 1 hour after delivery by the attending on duty nurses or residents, as is common in other randomized trials on the prevention of postpartum hemorrhage. After delivery of the baby, the amniotic fluid was allowed to drain away, and amniotic fluid-soaked bed linens were changed with dry preweighed 'linen-savers'. A wedge- shaped sterile linen sheet coated bedpan was slipped under the woman's buttock and left in place to collect blood loss till the delivery of placenta and in rest of the time patient was remained on sterile linen sheet. After delivery of placenta or episiotomy (if given), preweighed sterile vulval pad was applied. All swabs used in episiotomy were preserved and weighed. At the end of one hour blood and clots from the bedpan were decanted into a measuring jar and measured in milliliter. Blood soaked swabs and linen-savers and pads are weighed in grams. The known dry weight was subtracted and the calculated volume in millilitre by using the formula –1 gm = 1.06 milliliter (according to the density gradient between blood and water) added to that from the bedpan.

Assessments/outcomes

Primary end points: Amount of blood loss till 1 hour Postpartum.
Secondary end points: Length of 3rd stage of labor, need for additional oxytocics, consistency of the Uterus, side effects including diarrhea, nausea, vomiting, shivering, hypotension &elevated temperature >38^{0}C & haemoglobin and hematocrit values prenatally & 24 hours postpartum.

Other Intervention

If IV oxytocin was used during the 2nd stage of labor, it was stopped immediately after delivery. It was planned that if uterine bleeding was more than normal, and if placental separation did not occur until 30 minutes after delivery, additional oxytocin was administered intravenously 10 IU in 500 ml of RL & repeated as necessary, but it was not needed for any patient. Diagnosis of the Postpartum Hemorrhage had been defined according to the working definition World Health Organization[20], The World Health Organization defines PPH as blood loss 500 ml in the first 24 h after delivery.

Sample size

Sample size for the study was calculated by the formula for hypothesis of two parallel sample means; An observation at our hospital prior to study revealed that average volume of blood loss is 250 ml. .For a allowable difference of 0.1(10%) & expected variance of 0.04 within 0.05 & power of 80% estimated sample size was – 63 in each group.

Statistical analysis

Analysis was performed by using per protocol principle. Baseline characteristics and outcomes of categorical type were analyzed by using chi- square test or Fisher's exact test as appropriate. Baseline characteristics and outcomes on continuous scales were analyzed by using two sample't' test or Mann whitney 'u' test as appropriate. Odds ratios with 95 % confidence intervals & chi-square tests were used to compare proportions between two study groups for outcomes like amount of blood loss. A 'p' value of <0.05 was considered statistically significant. All reported 'p' values were two sided.

Results

We conducted a randomized controlled trial, single centre study to assess *efficacy and safety of perrectal misoprostol 400 mcg* compared with intravenous methylergometrine 200 mcg in the management of third stage of labor for prevention of PPH at Department of Obstetrics and Gynaecology, Geetanjali Medical College & hospital, Udaipur, Rajasthan.

Patient Population

This study was carried out over a total period of 18 months from August 2020 to January 2022. Total 183 patients assessed for eligibility. Of which 26 did not met

inclusion criteria, 8 patients refused to participate. Total 149 women met inclusion criteria in this period. After randomization 11 patients were excluded because cesarean section was performed after randomization (4 in Group A& 7 in Group B). Total 138 women were randomly allocated to receive either perrectal misoprostal (n=71) or methylergometrine (n=67)(fig 1).

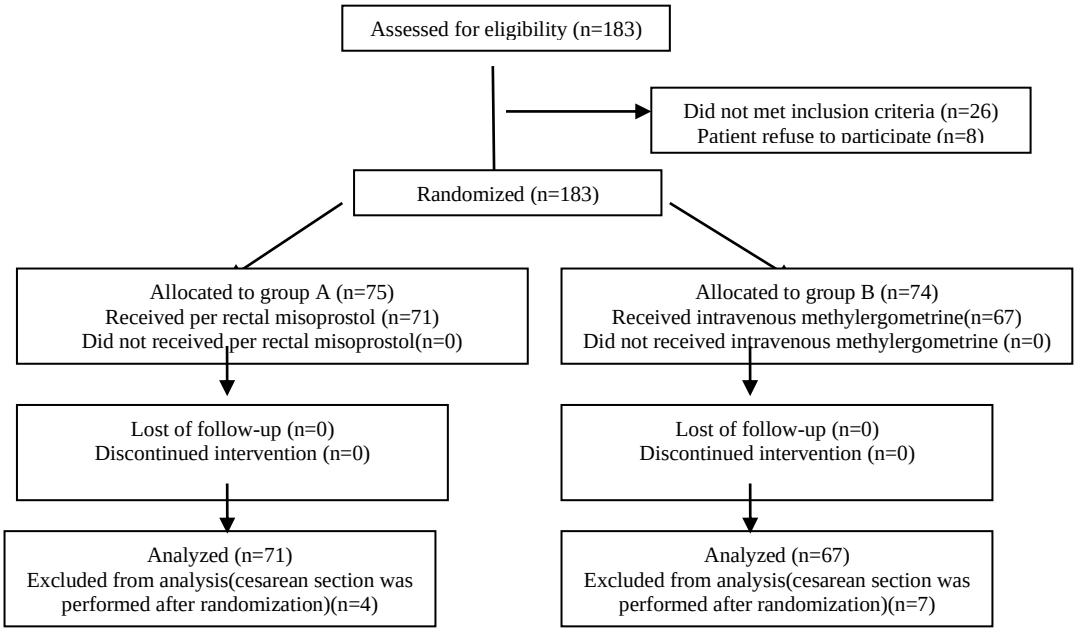

Figure-1. Flow diagram of participants in this trial

In this study all baseline parameters (table 1,2) i.e. age, gravidity, ANC registration, gestational age, antenatal complication, Predelivery Hb/PCV, Total Leukocyte Count, platelet count, induction and augmentation of labor, duration of first stage and second stage of labor, consistency of uterus, method of placenta delivery, placenta weight, neonates weight and neonatal sex (p>0.04 in all parameter) showed study not affected by any kind of confounding factor and bias.

Table 1: Baseline Parameters

		Group A	*Group B*	*P value*
Mean Maternal Age[years]		26.27	26.26	0.827
Ragistered ANC		70/71(98.6%)	66/67(98.5%)	0.967
Unragistered ANC		1/71(1.4%)	1/67(1.5%)	1.00
Gravida	Primigravidas	33/71 (46.5%)	34/67 (50.7%)	0.616
	Multigravidas	38/71 (53.5%)	33/71(49.3%)	0.733
Gestational age(weeks)	Mean gestational age(weeks)	38.8	38.59	0.258

	Term pregnancy	67/71(94.4%)	61/67(91.0%)	0.928
Complications in pregnancy	Postterm	4/71 (5.6%)	6/67(9.0%)	0.740
	IUGR	1/71 (1.4%)	2/67 (3.33%)	0.603
	No cmplication	66/71 (93.01%)	59 /67 (88,1%)	0.390
Predelivery blood indices	Mean Hb(gm)	11.91	11.98	0.655
	Mean PCV(%)	33.28	33.36	0.574
	Mean TLC(Per cubic mm)	9383.1	9480.6	0.705
	Mean Platlets(lakh per cubic mm)	2.15	2.14	0.724
Induction of labor	With PGE2 Gel	4/71(5.6%)	4/67(6.0%)	1
	Labor not induced	67/71(94.4%)	63/71(94.0%)	0.933
Augmentation of labor	By ARM	15/71(21.1%)	15/67(22.4%)	0.521
	By ARM and Oxytocin	45/71()63.4%)	37/67(55.2%)	0.531
	Labor not augmented	11/71(15.5%)	15/67(22.4%)	0.623
Mean duration of first stage of labor(hours)		6.8	7.1	0.221
Mean duration of second stage of labor(minutes)		27.01	27.31	0.979
Mode of Delivery	Vaginal Delivery	14/71(19.7%)	18/67(26.8%)	0.710
	Vaginal Delivery plus Episiotomy	51/71(71.9%)	41(61.2%)	0.579
	Vaginal Delivery plus perineal tear repair	1/71(1.4%)	2/67(3%)	0.721
	Vaccume assisted	4/71(5.6%)	4/67(6.0%)	0.967
	Forceps assisted	1/71(1.4%)	2/67(3%)	0.721
Method of placental delivery	Spontaneous	71/71(100%)	67/67(100%)	1
	MROP	0	0	
Mean weight of placenta	(Gms)	497.39	497.76	0.607
Consistency of uterus	Firm	71/71(100%)	67/67(100%)	1
	Soft (flabby)	0	0	
Sex*	Male	44/71(62%)	37/67(55.2%)	0.421
	Female	27/71(38%)	30/67(44.8%)	O.490
Gestational age*	Term	67/71(94.4%)	61/67(91.0%)	0.928
	Post term	4/71 (5.6%)	6/67(9.0%)	0.740
Mean Birth wt.(Kg)*	2895.07	2923.19	0.510	

*newborn baseline parameter.

Our study showed both drugs effective in prevention in post partum haemorrhage, in this study out of 138 low risk delivery no women developed

postpartum haemorrage, no patient required additional dose of oxytocin, no patient required any form of transfusion. In our study no mother had blood loss > 500ml, so for comparison between two drugs i.e. misoprostol and methylergometrine we had taken mean blood loss with standard deviations and two groups of blood loss i.e. >250ml and ≤ 250ml. In misoprostol group mean blood loss was 242.96 ± 50.50ml , in methylergometrine group mean blood loss was 239.10±51.04 ml misoprostol, in both group median was 230 ml with IQR 90 and 80 in group and methylergometrine group respectively,(z score -0.434 p=0.664). In our study misoprostol Vs methylergometrine for >250 ml(22/71 vs 20/67) blood loss, OR 1.055 , 95% CI in between 0.511to 2.18, (p=0.885).

In our study mean Predelivery Hb/PCV 11.91/33.28 and 11.98/33.36 ; post delivery Hb/PCV 11.25/ 32.18 and 11.30/32.64 in misoprostol group and methylergometrine group respectively, difference was not statistically significant. We did not compare with placebo group. In this study duration of third stage of labor were mean with SD 5.63±0.85mins and 5.63±0.94 days in misoprostol group and methylergometrine group respectively, difference was not statistically significant (p valve = 0.880). Again showed both drugs had same efficacy. Length of hospital stay, mean with SD, were 3.07 ±0.35 days and 3.06±0.49 days in misoprostol group and methylergometrine group respectively, difference were not statistically significant (p valve = 0.352). Again showed both drugs are safe and cost effective.

In misoprostol group two patients had diarrhoea, not required any form of treatment, but did not show any statistically significant difference among the two groups in respect of side effect.(p valve = 0.497). In both group no patient had fever or shivering. This again showed both drugs are safe, not developed any side effect which required any form of treatment. In our study all mothers remained healthy, no mother developed any type of complication in both group. All neonates were healthy, only one neonate required NICU admission in misoprostol group for low birth weight care but statistically and clinically insignificant difference in both group.(p value= 0.486), showed both drugs are effective, did not have any adverse effect on mother and baby .

Table 2: Outcome

		Group A	*Group B*	*P value*	*Z value*
Postpartum Haemorrhage		0	0		
Additional oxytocics		0	0		
Need of Blood/ Blood Products Transfusion		0	0		
Amount of Blood loss(ml)	Mean with SD	242.96 SD 50.50	239.10SD-51.04	0.664	-0.434
	Median with IQR	230.00 SD 90.0	230.00 SD-80.0	0.998	
Amount of Blood loss	>250 ml	22/71(31%)	20/69(29.9%)	0.885	
	<250 ml	49/71(69%)	47/67(70.1%)	1.000	
Post delivery Hb	Hb	11.25	11.20	0.685	

and PCV	PCV	32.64	33.0	0.706	
Duration of third stage of labor (mins)					
Hospital stay(days)	Mean with SD	3.07 SD 0.35	3.06 SD 0.49	0.352	-0.932
	Median with IQR	3.00 IQR0.00	3.00 IQR 0.00	1	
Maternal outcome	Healthy	71/71(100%)	69/69(100%)	1	
	Complication	0	0		
Neonatal outcome	Healthy	71/71(100%)	69/69(100%)		
	NICU Admission	0	0		
Diarrhea not required treatment		2/71(2.8%)	0/69(0%)		
Fever		0	0		
Shivering		0	0		

Discussion

Our single-centre study indicated that both drugs, perrectal misoprostol 400 mcg and intravenous methylergometrine 200 mcg are equally effective in prevention in post partum hemorrhage in low risk delivery ,no women developed postpartum hemorrhage, no patient required additional dose of oxytocin, no patient required any form of transfusion in both group. In our study misoprostol vs methylergometrine for >250 ml(22/71 vs 20/67) blood loss, OR 1.055 , 95% CI in between 0.511to 2.18, (p=0.885). Similar findings by Vimala et al[21], they randomized 120 subjects to 200mcg sublingual misoprostol or 200mcg intravenous methylergometrine. The misoprostol group demonstrated a trend towards increased incidence of PPH [2/60(3.3%) vs. 0/60(0%), P>0.05] and need for additional uterotonics [5/60(8.3%) vs.3/60(5.0%), P>0.05] but these results were not statistically significant.139 But Vimla et al used sublingual misoprostal whereas we used per rectal misoprostol. In this study two patient had blood loss >500ml, but in our study no patient developed bleeding >500ml, suggest perrectal route is more effective than sublingual route.

Amant et al[22] evaluated even higher dose of misoprostol, 600mcg, administered orally in comparison to 200mcg methylergometrine. The misoprostol-treated group experienced PPH more frequently, but the difference Was not statistically significant [7/96 (7.3%) vs. 4/93(4.3%), P=0.57; calculated RR 1.65 (95%CI 0.50-5.45)]. Shivering was nearly four times more Common in the subjects in the misoprostol Group 36/86(41.9%) vs. 8/94(8.5%), P<0.001; calculated RR 3.76(95%CI1.83-7.73)].140 In contrast to Amant et. al. we use 400mcg misoprostol, this explained why not our patient developed statistically significant shivering like side effect, in our study only two patient had diarrhea which not required any treatment. In our study also misoprostol group has more patient of blood loss > 250 ml 22/71 (32%) vs 20/67(28%) but difference was not statistically significant [OR 1.055 , 95% CI in between 0.511to 2.18, (p=0.885)] . Nasr et al[23] and Derman et al[12] used 800 mcg and 1000 mcg perrectal misoprostol respectively shown statistically significant higher incidence of fever and shivering.

Conclusions

Misoprostol is another alternative in prevention of postpartum hemorrhage. It is as effective & safe as other uterotonics in prevention of PPH in low risk patients. Lower dosage of Misoprostol e.g. 400 Mcgm is having same efficacy and better tolerability. Perrecral route of misoprostol is easy to administer, efficacious and has less side effects.

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