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Original Article

400 µg oral Misoprostol versus 0.2mg intravenous Methyl ergometrine for the active management of third stage of labor.

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Abstract

Objectives: The present study was conducted with the aim to assess and comparatively evaluate the safety and efficacy of oral misoprostol 400 µg and I/V methylergometrine 0.2mg in the active management of third stage of labor. *Methods:* The study was conducted in the department of Obstetrics & Gynaecology Pt. J.N.M. Medical College, Raipur (C.G.) and associated Dr. B.R.A.M. Hospital from January 2006 to July 2006. The 200 cases selected for the study were divided in two groups of 100 cases each. In the study group misoprostol 400 µg was given orally and in the control group 0.2mg methylergometrine was given intravenously at the time of the delivery of anterior shoulder of the fetus. The duration of the third stage, amount of blood loss, side effect and complications if any were noted down. The results were analyzed. *Results:* The mean duration of the third stage of labor in the study group was 10.17±6.87 minutes as compared to 5.68±1.91 minutes in the control group (P=<0.001).The mean blood loss in the study group was 117.28±99.77 ml as against 124.58±64.19 ml in the control group (P=>0.05). The side effects observed in the misoprostol group were shivering, fever and in methylergometrine group were nausea, vomiting & headache. *Conclusions:* Oral misoprostol is an effective alternative to conventional uterotonics for the active management of third stage of labor.

Key words: active management of third stage, misoprostol, methylergometrine maleate, post partum hemorrhage

Introduction

Postpartum hemorrhage (PPH) is an important cause of morbidity and mortality especially in developing countries where up to 28% of the maternal deaths are attributed to this cause. Although risk factors may increase a woman's chances of developing post partum hemorrhage, 2/3rd of the cases of PPH occur without any predisposing factors, hence all pregnant woman remain at a risk of developing PPH. The prophylactic use of oxytocic in the third stage of labor has shown to significantly reduce the risk of postpartum hemorrhage by about 40%, implying that for every 22 women who are given such an oxytocic, one post partum hemorrhage is prevented[1] and its use is generally advocated in the management of third stage of labor.

Most of the oxytocic require parenteral administration and ergometrine is one of the most widely used oxytocic. However, the administration and storage of ergometrine may not always be possible in some

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hospitals or rural communities due to the nonavailability of sterile needles, syringes or refrigeration equipment. The efficacy of syntometrine has been shown to be significantly reduced when it is stored in suboptimal environment. The rapidity with which a woman dies once massive hemorrhage starts, presents a major problem in a setting where delay in reaching and receiving effective interventions are common. The WHO estimates that 60% of the births in the group of low income countries occur outside a health facility. The International Federation of Gynecologists and Obstetricians recommended that all women receive active management of third stage of labor. Therefore there is a need for alternative to parenteral oxytocic.

Oral administration of ergometrine has been shown to be ineffective in reducing postpartum blood loss[2] and the oral preparation is not stable under simulated tropical conditions, making it unsuitable for use in tropical countries. Misoprostol is an orally active uterotonic agent; it is a prostaglandin El analogue and was first marketed as an antipeptic ulcer drug. Recently it has been found to be effective in medial evacuation of the uterus in spontaneous abortion, cervical ripening and induction of labor first and second trimester termination of pregnancy. After oral administration it is absorbed rapidly into the blood stream and when taken in early pregnancy, it has been reported to cause an increase in uterine tonus within 7 minutes. It is stable at high temperature and has a long self life.

The use of ergometrine is contraindicated in hypertensive cases as ergometrine stimulate vasoconstriction, causes hypertension, and may cause headache, convulsions and even death in preeclamptic cases. Misoprostol on the other hand has shown to decrease the mean arterial pressure and systemic vascular resistance, hence, may be used as an oxytocic in hypertensive or preeclamptic women undergoing vaginal delivery[3]. WHO has also recently recommended the use of misoprostol for active management of third stage of labor, especially by trained birth attendant in rural areas.

Objective

The study had been undertaken with the aim to comparatively evaluate the safety and efficacy of oral misoprostol and intravenously administered methyl ergometrine in the active management of 3rd stage of labor.

Methods and Material

The present study of 400µg oral misoprostol vs 0.2mg intravenous methylergometrine for the active management of third stage of labor was conducted in the Department of Obstetrics and Gynaecology Pt. J.N.M. Medical College, Raipur (C.G.) and associated Dr. B.R.A.M. Hospital from January 2006 to July 2006.

The comparative study evaluated 200 selected cases admitted during the above mentioned period for delivery. A control group of 100 cases being administered methylergometrine maleate was compared with a study group of 100 cases administered oral misoprostol.

Each case was enquired of present pregnancy, duration of amenorrhea, antenatal care received, and onset of labor pain. A detailed obstetric history regarding gravidity parity and previous pregnancy outcome, and complication if any in previous pregnancies, family and personal history was noted down. Detailed medical history was obtained to rule out the medical disease if any.

General and systemic examination was done. A thorough obstetric examination including per abdomen examination for the duration of pregnancy, presentation, amount of liquor, singleton or multiple pregnancy, fetal well being, per vaginal examination for dilatation, effacement of the cervix, presentation and assessment of pelvis was done. Two hundred cases with singleton vertex presentation delivering normally were selected for the study. Cases with the severe hypertension, pregnancy induced hypertension, antepartum hemorrhage, bronchial asthma, cardiac disease, epilepsy, renal disease and a history of drug sensitivity in the past were excluded from the study. Patients with instrumental deliveries were also excluded from the study.

All aseptic precautions were taken during the delivery. Duration of the first stage and second stage of labor were noted. The study group received 400 µg oral misoprostol, and the control group received 0.2 mg of intra-venous methylergometrine maleate at the time of delivery of the anterior shoulder and time noted. After delivery of the baby, the cord was clamped and baby was separated. All the socked linen were removed and fresh pre weighed linen and a

kidney tray was kept beneath the buttock of patient for collecting and evaluating blood loss. As soon as signs of placental separation were evident, placenta was removed by Brandt's Andrew method. The drapes and kidney tray were reweighed after the third stage of labor i.e. complete expulsion of the placenta and membrane; the blood loss was measured as difference in grams and then converted into ml by using the formula: Amount of blood in ml = blood amount in gram x by 1000/1060, as the density of blood is 1060. The duration of third stage is noted as the time taken for the complete expulsion of the placenta and membranes. Placenta and membranes were examined for any abnormality and its completeness. During the entire period a close watch was kept over the tendency of the uterus. If atonic postpartum hemorrhage occurred, injection methylergometrine / oxytocin was given intravenously. Third stage complication if any like retained placenta, inversion of the uterus, PPH & side effect if any were observed, and managed symptomatically. Data were analyzed using various methods like mean, t-test, and chi-square test.

Observations

In the present study there were 100 cases in each of the two groups. Majority of the cases were from urban area (Table No.1). The mean parity was 0.58±0.62 and 0.61±0.60 in Misoprostol and methylergometrine maleate group respectively (P=>0.05) (Table No.1).

The mean duration of 1st stage of labor was 10.41±1.94 hrs and 9.48±1.49 hrs and of second stage was 23.39±8.58 hrs and 23.92±7.79 hrs in misoprostol and methylergometrine maleate group respectively (Table No.1).

The mean duration third stage of labor in misoprostol group was 10.17±6.87 as against 5.68±1.91 in Methylergometrine maleate group. Majority of the patients in the misoprostol group had third stage of labor of 10-12 minutes duration while in the methylergometrine maleate group, for majority of the patients the duration of third stage of labor was 5-6 minutes (Table No.2).

The mean amount of blood loss was 117.28±99.77 and 124.58±64.19 ml in misoprostol and methylergometrine maleate group respectively (P=>0.005) (Table No.3).

In the present study, in both groups pre delivery and post delivery Hb% levels were in comparable range with mean fall in Hb% being 0.63±0.89 and 0.64±0.96 in misoprostol and methylergometrine maleate group respectively (P=>0.005) (Table No.4)

In none of the cases PPH, inversion of uterus, retained placenta was noted in either of the groups. The additional doses of oxytocic were required in 12 and 8 cases, in misoprostol and methylergometrine maleate group respectively.

In Misoprostol group side effects noted were shivering in 26% of the cases and fever in 9% cases, while in methylergometrine maleate group, nausea was observed in 10% of the cases and vomiting in 2% cases only (Table no. 5).

Table 1.

S.No.	Factors	Misoprostol n=100	Methylergometrine maleate n=100	P Value	
1	Urban	77	66	>0.05	NS
2	Mean parity	0.56±0.61	0.58±0.62	>0.05	NS
3	Mean age in years	23.10±4.42	23.81±3.76	>0.05	NS
4	Mean duration of 1st stage of labor (in hrs)	10.41±1.94	9.48±1.49	>0.05	NS
5.	Mean duration of 2nd stage of labor (in min)	23.39±8.58	23.92±7.79	<0.05	S

Table 2. Distribution of cases according to duration of 3rd stage of labor in the two groups.

S.No.	Duration in (min)	Misoprostol n=100		Methylergometrine maleate n=100		P Value
		N	%	N	%	
1	1-2	2	2	4	11	<0.001
2	3-4	11	11	26	40	<0.001
3	5-6	12	12	40	41	<0.001
4	7-9	28	28	30	8	<0.001
5	10-12	47	47	0	0	
	Total	100	100	100	100	
	Mean ± SD (In minutes)	10.17 ± 6.87		5.68 ± 1.91		<0.001

Table 3. Distribution of cases according to amount of blood loss in the third stage of labor in the two groups.

S.No.	Amount of blood loss	Misoprostol group		Methylergometrine maleate group		P value
		N	%	N	%	
1	<50 ml	8	8	6	6	>0.01
2	51-100	45	45	48	48	>0.05
3	101-200	38	38	36	36	>0.01
4	201-300	9	9	10	10	-
5	301-500	0	0	0	0	-
6	>500	0	0	0	0	-
	Mean±SD	117.28±99.77 ml	124.58±64.19ml	>0.001		

Table 4. Comparison of changes in Hb% level between the two groups.

	Misoprostol	Methylergometrine maleate	P value
Pre delivery	10.49±0.59	10.24±0.68	>0.05
Post delivery	9.86±0.61	9.74±0.66	>0.05
Fall in Hb %	0.63±0.89	0.64±0.96	>0.05

Table 5. Distribution of cases according to side effects.

Symptoms	Misoprostol		Methylergometrine maleate		P Value
	N	%	N	%	
Nausea	-	-	10	10%	-
Vomiting	-	-	2	2%	-
Shivering	26	26%	-		
Fever	9	9%	-		

Table 6. Comparative evaluation of different Studies.

S. No.	Author	Year	Drug used	Doses/Route	Duration of 3rd stage of labor	Amount of blood loss in 3rd stage of labor	Side effects	Complications
1	Deniel V. Surbek et al[4]	1997-98	Misoprostol Placebo N=32	600µgm/Oral Oral	8±0.9 9 + 1	345±19.5 ml 417+25.9 ml	Shivering 60%	PPH – 2 cases 7% PPH- 5 Cases 15%
2.	WK Sin, LCH Tang, KB Cheung [3]	1998-99	Misprosstorl N=1026 N=1026	600µgm/Oral	<10mts-816 cases 11-30mts-190cases >39 mts - 14 cases	296 ml+160	Nausea-20, Vomiting-14 Headache-81, Shivering 130, Fever-87	>500ml - 60 cases >100ml - 5 cases >MRP - 4 cases > Delayed Hemorrhage - 5 cases
			Syntormetrine N=1032	Synto 5 u IM + 0.5 mg Ergometrine	< 10 mts - 890 cases 11-30 mts - 123 > 30 mts - 16	254 ml + 157	Nausea - 27, Vomiting Headache - 83, Shivering- 120, Fever - 30	>500 ml - 44 cases >1000 ml - 4 cases > MRP-14 cases > Delayed Hemorrhage - 6 cases
3.	Devi P.K. et al[5]	1988	Prostodin Methergine	125µgm/IM 0.2 µgm/IV	4.8 + 0 mts 10.9+108 ml	99.8 + 155 ml 283 + 108 ml		
4.	Bhattacharya et al[6]	1989	Prostodin Methergine	125µgm/IM 0.2 µgm/IV	4.8 + 0.8 mts 4.06 + 06 mts	73.09 + 44ml 145 + 15.1 ml		
5.	Present Study	2006	Misoprostrol N=100	400 µgm/Oral	10.17 + 6.87 mts	117.28+99.77ml	Nausea-0, Vomiting-0 Shivering-26, Headache-0, Fever-9,	
			Methergin N = 100	0.2 mg/IV	5.68 + 1.91 mts	124.58+64.91ml	Nausea-2, Vomiting-1	

Discussion

The third stage is considered from the delivery of fetus to delivery of placenta. Separation of placenta and membrane is brought about by uterine contraction. Methylergometrine maleate when given intravenously acts directly on the myometrium, producing tetanic uterine contractions and hastens the separation of placenta and minimizes blood loss.

Misoprostol acts by bringing about the contraction of uterus and promoting vasoconstriction at the target site (placental site) produced by a well contracted and retracted myometrium, ultimately leading to hemostasis, hence, minimizing blood loss.

The onset of the action methylergometrine maleate when given by intravenous route is within 30-45 seconds while the action of misoprostol when given orally starts in few minutes, reaches a peak within 12-3 minutes and persist for 20-40 minutes. This is also evident in the present study when the mean duration of third stage of labor was 5.68±1.91 minutes in methylergometrine maleate group as against 10.17±6.87 minutes in misoprostol group.

Nearly half of the cases had separation of placenta in 10-12 minutes after the delivery of fetus in misoprostol group while in methylergometrine maleate group all had expelled the placenta within 9 minutes.

Similar duration of third stage of labor was observed by Surbek et al[4] and Ng et al[3], who used oral misoprostol and syntometrine in third stage of labor. However, longer duration was observed by Devi et al[5] and Bhattacharya et al[6] while using methylergometrine maleate 0.2 mg intravenously (Table no. 6).

Walraven et al compared 600 µg misoprostol vs 2.0 mg methylergometrine orally and found no significant difference in no. of cases having blood loss =500 ml (11 vs 12%) in the two groups respectively with the mean blood loss being 281 ml [7].

The ultimate aim of active management of the third stage of labor is to reduce the amount of blood loss. In the present study though there was a significant difference in the duration of the third stage of labor in both the groups, mean blood loss was in comparable range being 117.28±99.77ml and 124.58±64.19 ml in misoprostol and methergin group respectively (Table No.3). None of the cases in either group had PPH. Hoj et al in 2005 comparing 600 µg sublingual misoprostol with placebo, observed that mean blood loss is 10.5% less in misoprostol group than in the control group.

Significantly fewer patients in misoprostol group had severe PPH =1000 ml, 11% vs 17% and =1500 ml 2% vs 8% in the misoprostol and the methylergometrine maleate group respectively [8].

Amant et al observed PPH in 8.3% of the cases as against 4.3% in the misoprostol 600 µg group and methylergometrine IV 0.2 mg group respectively [9].

The amount of blood loss with intravenous methylergometrine as observed by other authors was 283±108 ml and 145±15.1 ml [5,6]. Comparatively higher amount of blood loss has been observed by other authors, who used methergin 0.2 mg intravenously (Table No. 6).

In the WHO multicenter randomized trial of misoprostol in the management of the third stage of labor, using 600 µg misoprostol orally or 10 IU oxytocin IV/IM, it was observed that 4% of the misoprostol group as against 3% of the oxytocin group had blood loss =1000 ml (p=<0.0001), while 15% in the misoprostol group as against 12% in the oxytocin group required additional oxytocic[10].

As a result of expanded blood volume, parturient may tolerate a significant amount of blood loss, therefore, clinical parameter evaluation before development of hypovolemic shock such as BP and pulse are not so reliable. Measurement of change in Hb% concentration before and after delivery is a more objective method in assessing amount of blood loss and subsequent decision for blood transfusion or iron replacement and fall of =10% of hematocrit or need for blood transfusion has already been defined as PPH.

Measuring the blood loss in percentage reduction in Hb level before and within 12-24 hours after delivery in the present study, it was 0.63±0.89 and 0.64±0.96 in misoprostol and methergin group respectively (Table no.4). This is particularly important in our country where majority of the women are anemic. There was no difference in the mean fall in Hb concentration (1.34 vs 1.34) in misoprostol and syntometrine group respectively. In both the groups a decrease in Hb concentration of 10-20% occurred in 32.7% and 32.9% of the patients and by >20% in 18.6% and 17.6% of the case respectively. The incidence of blood transfusion was 1.5% and 1.6% respectively [3].

Hoj et al. observed a decrease in Hb of 0.16 mmol lower in the misoprostol group than in the placebo group[8]. Amant et al observed no difference in fall in Hb level in the two groups [9].

The side effects observed were shivering and pyrexia in misoprostol group. Shivering was observed in 26% of the cases and pyrexia in 9% of the cases. Shivering and pyrexia are likely to be a prostaglandin E effect on central thermoregulatory centers and are undesirable though it was self limiting and respond to chlorpheniramine or tramadol. In methylergometrine maleate group the side effects were nausea in 10% and vomiting in 2% of the cases. These are because of its gastrointestinal effect. Similar observation had been made in other studies as shown in (Table no 6.)

Lumbinganon et al observed shivering in 19% and pyrexia in 7.5% of the cases in 400 µg oral misoprostol vs 19% and 7.5% in 600 µg misoprostol group. Thus most of the side effects are dose related[11]. Ng et al observed shivering in 30% of the misoprostol group, pyrexia in 8.5%, headache in 7.9% and chest pain in 7.1%[3]. Walraven et al observed shivering in 32.1% of the cases in the misoprostol group as against 11.7% in methylergometrine group[7]. Amant et al also observed shivering more commonly with misoprostol group (42%) as against only 8.5% in the methylergometrine maleate group[9]. Hofmeyr et al noted shivering in 19% of the cases in misoprostol group as against only 5% in the placebo group[12].

Conclusion

The use of oral misoprostol (400 µg) following delivery of anterior shoulder of baby reduced postpartum blood loss as estimated by reduction in the fall of hemoglobin level. Oral misoprostol administration proves to be simple, non-invasive, easy to administer, safe and an acceptable alternative to existing available other uterotonics in use for the third stage management of labor. It is also useful in patients at high risk for post partum hemorrhage and where intravenous access is limited or difficult to achieve. It is the simplest route desirable in developing countries where many of the deliveries are still being conducted at home especially in the rural areas, not attended by medically trained staff.

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