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Original Research Article

A comparative study of different route of administration of misoprostol in the management of third stage of labour

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ABSTRACT

Background: Post partum haemorrhage is the most common cause of maternal morbidity and mortality. Misoprostol is a prostaglandin analogue, used for management of post partum haemorrhage. It can be used by various routes with minimal side effects. This study is done to compare the different routes of administration of Misoprostol for the third stage management and their side effects. Objectives of present study were to estimate the amount of blood loss, to assess the maternal side effects of drug, to know the haemoglobin deficit, to know the duration of third stage of labour.
Methods: This was a prospective hospital base study of 150 women delivery at obstetrics and gynaecology department at ESICMC Model Hospital, Rajajinagar. They were randomized into 3 groups of 50 patients each. They received 400 µg of misoprostol either orally or rectally or sublingually immediately after delivery of the fetus. The primary outcomes analysed were amount of blood loss duration of third stage of labour haemoglobin deficit and their side effects
Results: The amount of blood loss and haemoglobin deficit was least in sublingual group which was statistically significant. Need of additional oxytocics was less in sublingual and oral group, though it was not statistically significant.
Conclusions: In the present study, sublingual Misoprostol was found to be more effective in reducing blood loss during third stage of labour.

Keywords: Misoprostol, Post partum haemorrhage, Sublingual, Third stage of labour

INTRODUCTION

Third stage of labour begins after the delivery of the fetus till the expulsion of the placenta and membranes.[1] Though the third stage constitutes short span of time, it is the phase of maximum maternal mortality and morbidity.

One of the major hazards being post partum haemorrhage. PPH complicates approximately 4% of vaginal deliveries and 6% of caesarean deliveries. WHO statistics suggest 30% of maternal deaths worldwide with an estimated 1.25 million cases and morbidity in 20 million women annually are due to PPH.[2,3]

Uterine atony is the most common cause constituting about 80-90% of cases.[4] So, we have to aim at increasing the tone of the uterus by using uterotonic drugs to reduce PPH. Various uterotonic drugs is available like Oxytocin, Ergometrine, Prostaglandins.[5] To prevent and treat PPH, literature strongly suggests the use of active management of 3rd stage[6] which includes use of Oxytocin at the time of delivery of anterior shoulder, controlled cord traction,

early cord clamping. Study shows that risk of PPH can be reduced by 60% using active management of 3rd stage of labour.[6,7]

However, Oxytocin and Syntometrine requires refrigeration because it is unstable when exposed to high ambient temperatures. Furthermore, this drug must be given parenterally, which requires a skilled birth attendant and a continuous supply of sterile syringes and needles which are frequently unavailable in low resource settings.[8]

Misoprostol is synthetic 15 deoxy, 16 hydroxy, 16 methyl analogue of prostaglandin E1 is another drug with strong uterotonic property.[9] It has numerous advantages as it can be administered through various routes orally, rectally, sublingually or Vaginal route.[10,11] It is easy to store and stable at room temperature. Many studies have established the efficacy of the prophylactic use of Misoprostol for reduction of blood loss after delivery when compared to conventional syntocinon, methylergometrine.[1-4]

Although Misoprostol can be used by different routes, still the most effective route with fewer side effects has to be established. So, this comparative study is being undertaken to know the efficacy of Misoprostol in its 3 routes in the management of 3rd stage of labour and their side effects.

Objectives of present study were to compare the different routes of administration of Misoprostol in the management of third stage of labour, to estimate the amount of blood loss, to assess the maternal side effects of drug, to know the haemoglobin deficit, to know the duration of third stage of labour.

METHODS

A comparative prospective Hospital based study of pregnant women at term gestation regularly attending outpatient department at ESIMC-PG IMSR, Bangalore for safe confinement during the period December 2013 to January 2015.

Patients were randomly allocated into three study groups of 50 each.

- Group I (O): Receive 400mcg of Misoprostol Orally.
- Group II (S): Receive 400mcg of Misoprostol Sublingually.
- Group III (R): Receive 400 mcg of Misoprostol Per Rectally.

Inclusion criteria

- Singleton pregnancy
- Cephalic presentation
- Normal vaginal delivery

Exclusion criteria

- Caesarean section
- Anaemia (Hb < 8g%)
- Pregnancy induced Hypertension
- Multiple Pregnancies
- Malpresentations
- Traumatic PPH
- Uterine Fibroids
- Coagulation abnormality
- Presence of Comorbid disease like Cardio respiratory, renal or hepatic disease
- Grand multipara

The study will be carried out on Normal Vaginal delivered patients with singleton pregnancy with Cephalic presentations.

The purpose of study will duly be informed to the patients and a written consent will be obtained from each of them.

- Group O: 2 tablets of 200mcg of T. Misoprostol will be given to the patient orally immediately after the delivery of the baby.
- Group S: 2 tablets of 200mcg T. Misoprostol sublingually
- Group R: 2 tablets of 200mcg T. Misoprostol Rectally

All admitted patients with labour pains will be examined for maternal age, height, weight, parity and significant history.

The basal heart rate, arterial blood pressures will be measured and the agents used before and during the delivery will be noted.

In all the parturient, Placenta will be removed by Brandt-Andrew's method. Blood loss will be measured after the delivery, immediately following clamping and division of the umbilical cord using a drape. Estimation of Hb and PCV will be measured before and 24 hours after delivery.

Apart from blood loss and need for additional oxytocics, the other obstetrical parameters like any incidence of retained placenta and side effects of Misoprostol like shivering, fever, diarrhoea, headache, nausea or Vomiting will be noted.

Data will be recorded as Percentages, Mean and Standard Deviation compared using the chi – square test (x2). Significance is fixed at P <0.05. Multivariate regression was used to analyze effect of multiple variables.

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous

measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made,

- Dependent variables should be normally distributed,
- Samples drawn from the population should be random, cases of the samples should be independent.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. and Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale with in each group. Chi-square/ Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, Med Calc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and microsoft word and excel have been used to generate graphs, tables etc.

RESULTS

Maximum numbers of patients are between 20-30 years-90.7%. 84% in oral group, 92% in rectal group and 96% in sublingual group.

The mean age in Oral group is 24.40±4.84. The mean age in Rectal group is 25.36±3.49. The mean age in Sublingual group is 24.64±2.97. 51.3% of women in study population were primigravida and 48.7% were multigravida.

60% Sublingual group women were primigravida. 54% of women in Oral group were multigravida. 94.7% of patients had full term normal delivery and 5.3% had instrumental delivery. 12% of patients in rectal group had instrumental delivery.

Table 1: Age distribution of three groups of patients studied.

Age in years	Oral	Rectal	Sublingual	Total
<20	5 (10%)	0 (0%)	1 (2%)	6 (4%)
20-30	42 (84%)	46 (92%)	48 (96%)	136 (90.7%)
31-40	3 (6%)	4 (8%)	1 (2%)	8 (5.3%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)
Mean± SD	24.40 ±4.84	25.36 ±3.49	24.64 ±2.97	24.80 ±3.84

Samples are age matched with P=0.432

Table 2: Parity distribution in three groups of patients studied.

Parity	Oral	Rectal	Sublingual	Total
Primi	23 (46%)	24 (48%)	30 (60%)	77 (51.3%)
Multi	27 (54%)	26 (52%)	20 (40%)	73 (48.7%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)

P=0.317, Not significant, chi-square test

Mean amount of blood loss in the study population is 353.13±114.15. In oral group blood loss in 356ml, in Rectal group blood loss in 356ml, in sublingual group blood loss in 356ml. 6% of patients in rectal group had blood loss of more than 500ml. 58% of patients in sublingual group had blood loss of less than 300ml. 12% of patients in sublingual group had blood loss of less than 200ml.

Table 3: Type of delivery three groups of patients studied.

Type of delivery	Oral	Rectal	Sublingual	Total
FTND	49 (98%)	44 (88%)	49 (98%)	142 (94.7%)
Instrumental	1 (2%)	6 (12%)	1 (2%)	8 (5.3%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)

P=0.051+, significant, Fisher exact test

Table 4: Blood loss (ml) distribution three groups of patients studied.

Blood Loss (ml)	Oral	Rectal	Sublingual	Total
<100	0 (0%)	0 (0%)	0 (0%)	0 (0%)
100-200	2 (4%)	0 (0%)	6 (12%)	8 (5.3%)
200-300	16 (32%)	10 (20%)	29 (58%)	55 (36.7%)
300-400	21 (42%)	27 (54%)	10 (20%)	58 (38.7%)
400-500	8 (16%)	5 (10%)	2 (4%)	15 (10%)
>500	3 (6%)	8 (16%)	3 (6%)	14 (9.3%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)
Mean ±SD	356.00±102.79	398.20±119.28	305.20±102.04	353.13±114.15

P<0.001**, Significant, Fisher Exact test

Table 5: Hemoglobin % levels three groups of patients studied.

Hemoglobin %	Oral (n=50)	Rectal (n=50)	Sublingual (n=50)	Total (n=150)	P value
Pre-delivery					
<12	25 (50%)	28 (56%)	30 (60%)	83 (55.3%)	0.630
12-16	25 (50%)	22 (44%)	20 (40%)	67 (44.7%)	
>16	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Post-delivery					
<12	40 (80%)	40 (80%)	42 (84%)	122 (81.3%)	0.898
12-16	10 (20%)	10 (20%)	8 (16%)	28 (18.7%)	
>16	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

Chi-Square test/Fisher Exact test

Table 6: PCV levels three groups of patients studied.

PCV	Oral (n=50)	Rectal (n=50)	Sublingual (n=50)	Total (n=150)	P value
Pre-delivery					
<32	8 (16%)	9 (18%)	12 (24%)	29 (19.3%)	0.736
32-34	27 (54%)	25 (50%)	27 (54%)	79 (52.7%)	
>34	15 (30%)	16 (32%)	11 (22%)	42 (28%)	
Post-delivery					
<32	26 (52%)	27 (54%)	29 (58%)	82 (54.7%)	0.269
32-34	22 (44%)	23 (46%)	17 (34%)	62 (41.3%)	
>34	2 (4%)	0 (0%)	4 (8%)	6 (4%)	

Chi-Square test/Fisher Exact test

Pre-delivery hemoglobin in the study population was <12g/dl in 55.3%, between 12-16 in 44.7% of patients. Post-delivery hemoglobin was less than <12g/dl in 81.3%, between 12-16 in 18.7% of patients. 19% of patients had pre-delivery PCV less than 32. 54% of patients had post-delivery PCV less than 32. 79% population in the study group had PCV in the range of 32-34. Post-delivery 41% of study population were in 32-34 range of PCV.

Table 7: Hemoglobin deficit distribution three groups of patients studied.

Hemoglobin deficit	Oral	Rectal	Sublingual	Total
<1	36 (72%)	31 (62%)	44 (88%)	111 (74%)
1-1.5	13 (26%)	16 (32%)	6 (12%)	35 (23.3%)
>1.5	1 (2%)	3 (6%)	0 (0%)	4 (2.7%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)
Mean±SD	0.87± 0.26	0.90± 0.29	0.70± 0.22	0.82± 0.27

P<0.001**, Significant, ANOVA

Hemoglobin deficit of <1g/dl was found in 74% of patients and >1.5g/dl in 2.7%. It was maximum in rectal group about 0.9g/dl and minimum in sublingual group, about 0.7g/dl and in oral group was 0.87g/dl. The mean hemoglobin deficit in study population is 0.82g/dl, in oral group 72% had <1g/dl deficit, where as in rectal it was 62% and sublingual maximum of 88%.

Table 8: Side effects in three groups of patients studied.

Side effects	Oral (n=50)	Rectal (n=50)	Sublingual (n=50)	Total (n=150)
Nil	34 (68%)	43 (86%)	35 (70%)	112 (74.7%)
Yes	16 (32.0%)	7 (14.0%)	15 (30.0%)	38 (25.3%)
S	6 (12%)	2 (4%)	4 (8%)	12 (8%)
FE	2 (4%)	3 (6%)	6 (12%)	11 (7.3%)
DI	4 (8%)	0 (0%)	4 (8%)	8 (5.3%)
N&V	4 (8%)	2 (4%)	1 (2%)	7 (4.7%)

P=0.076+, Significant, Fisher Exact test

Table 9: Additional dose of oxytocin three groups of patients studied.

Additional dose of oxytocin	Oral	Rectal	Sublingual	Total
No	47 (94%)	42 (84%)	47 (94%)	136 (90.7%)
Yes	3 (6%)	8 (16%)	3 (6%)	14 (9.3%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)

P=0.175, Not Significant, Fisher Exact test

Side effects were seen in 25% of patients, maximum in Oral (32%) followed by sublingual (30%) and least in

rectal group (14%). Shivering was the most common effect seen in 8% of patients and least being nausea and vomiting in 4.7% of patients. In oral group of patients, shivering (12%) was more common, where as in rectal (6%) and sublingual (12%) group fever is more common. 90.7% of patients of the study population did not require additional oxytocics, 9.3% required to reduce blood loss. 16% in rectal group, 6% in oral and sublingual group required additional oxytocics. Mean duration of the third stage of labour in the study population was 9.76 min. In oral group it was 9.24 min, in rectal group it was 10.58min and in sublingual group was 9.46 min. 15.3% of patients had third stagr duration less than 8min, 79.3% of patients had between 8-14min, 5.3% had more than 14 minutes.

Table 10: Duration of 3rd stage (min) in three groups of patients studied.

Duration of 3rd stage(min)	Oral	Rectal	Sublingual	Total
<8	8 (16%)	4 (8%)	11 (22%)	23 (15.3%)
8-14	42 (84%)	41 (82%)	36 (72%)	119 (79.3%)
>14	0 (0%)	5 (10%)	3 (6%)	8 (5.3%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)
Mean± SD	9.24± 1.93	10.58± 2.67	9.46± 2.67	9.76± 2.50

P=0.015*, Significant, ANOVA test

Table 11: Hemoglobin %: a comparative assessment.

Hemoglobin %	Pre-delivery	Post-delivery	difference	t value	P value
Oral	11.71±1.17	10.85±1.22	0.866	23.205	<0.001**
Rectal	11.81±1.16	10.91±1.20	0.904	21.836	<0.001**
Sublingual	11.62±1.22	10.92±1.21	0.700	22.846	<0.001**
P value	0.731	0.947	-	-	-

Student t test (Unpaired) between groups, student t test (Paired) with in group

DISCUSSION

Different drugs and strategies are used to prevent postpartum haemorrhage in different countries.[2] The currently used oxytocics require specific storage conditions to maintain adequate potency, which is practically impossible in developing countries like India, where many deliveries occur in the peripheral sector of the country. Therefore, in these areas, inexpensive drugs, which can be administered by even trained birth attendants are essential. The lack of easily administered and thermostable uterotonic agent is a major hurdle for the prevention of life threatening haemorrhage in developing world. The disadvantages with oxytocin being its instability at room temperature in tropical countries and it should be administered either im or iv. Ergometrine is ineffective orally. PGF2α is highly effective, but it is expensive and needs refrigeration to maintain its potency.[2,3] Misoprostol is a wonderful drug with various therapeutic actions and advantages, which include stability at high temperatures, cost effectiveness, different routes of administrations and minimal side effects.[9,10] The effectiveness of Misoprostol in reducing blood loss and preventing PPH has been proved by various studies.[10,11] But the most effective route has not been established yet.

Table 12: Comparative study of different route of administration of misoprostol.

Name of the study	Route of drug	Blood loss in ml	Duration of 3rd Stage	Hb deficit in g/dl.	Add. use of oxytocics	Side effects
Neeta et al[12]	Rectal	236ml	8.03min	0.69gldl	10%	52%
Hoj et al[13]	Sublingual	443ml	12min	1.1gldl	15%	31%
Nisa et al[14]	Rectal	304ml	16min	0.4gldl	8.3%	57%
Bajwa et al[15]	Oral	206ml	4.94min	N.A	15%	36%
	Sublingual	210ml	3.62min		4.8%	54%
	Rectal	230ml	4.12min		4.6%	12%
Rajaei[16]	Oral	157ml	10.2min	0.7g/dl	7.5%	15%
Present Study	Oral	356ml	9.24min	0.87gldl	6%	32%
	Sublingual	305ml	9.46min	0.7fldl	6%	30%
	Rectal	398ml	10.58min	0.9gldl	16%	14%

So, in present study we are comparing the oral, rectal and sublingual route of administration of misoprostol for the management of third stage of labour.

In present study, the mean duration of third stage was 9.76 min. least in oral route (9.24 min.) which is correlating with Rajaei et al (10.2 min).[16] Mean duration in rectal route was 10.58 min. which is correlating with Neeta et al -8.03min and Nisa et al 16min.[12,14] The mean duration in sublingual route was 9.46 min which was correlating with Hoj et al 12.1 min.[13]

The mean blood loss in present study was 353 ml, it was minimal in sublingual group (305 ml) which is correlating with Bajwa et al 210 ml, Hoj et al, 443ml.[13,15] In oral route it was 356ml which is correlating with Bajwa et al 206ml, in rectal route 398 ml which is correlating with Bajwa [15]et al 236 ml and Neeta et al 230ml.[12,15] The blood loss in sublingual route is significantly less than other routes.

Additional oxytocics were administered when blood loss exceeded 500 ml or in the presence of atonic uterus. Additional dose of oxytocics were required in about 10% of patients, maximum being in rectal group, through it was not statistically significant. This is correlating with Neeta et al 10%, Hoj et al -15%, Nisa et al 8.3%, Three patients required blood transfusion after delivery.[12-14] None of the patients had retained placenta.

The least mean haemoglobin deficit was observed in sublingual group of about 0.7gl/dl, which was statistically significant compared to oral(0.87%g/dl) and rectal routes (0.9g/dl). This is correlating with Neeta et al-0.69g/dl, Rajaei et al 0.7g/dl, Hoj et al 1.1g/dl.[12,13,16]

The misoprostol has minimal side effects, which were self-limited like nausea vomiting, shivering and fever. The incidence was maximum in oral and sublingual routes. The reason behind this is highest peak concentration of misoprostol achieved in these routes. In present study, 25% of study population had side effects, shivering being most common (8%) and nausea, vomiting being least (4.7%). The incidence in oral group is 32%, this is correlating with Bajwa et al =36%.[15] In sublingual group it is 30%, correlating well with Hoj et al-31%.[13] In rectal group, side effects are minimum of 14%, correlating with Bajwa et al-12%.[15]

All the three routes were safe and effective in preventing PPH from the present study. Sublingual route is the best route for administration of misoprostol for the active stage of labour.

CONCLUSION

Misoprostol is a promising drug for the active management of third stage of labour especially in the peripheral and rural health centres because it requires minimal expertise and external medical help for its administration, cost effective and with minimal side effects. Present study concluded that among various routes, sublingual route appears a better route for administration.

More studies on the use of misoprostol and its different routes of administration are required and sublingual misoprostol can be given if injectable uterotonics are not available and parturient should be informed about its side effects.

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