SUBLINGUAL MISOPROSTOL VS INTRAVENOUS METHYL ERGOTAMINE IN REDUCING BLOOD LOSS AFTER DELIVERY – A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background Postpartum hemorrhage is a very important cause of maternal mortality worldwide. According to WHO, 20 million of morbidities and 33 % of maternal mortality can be attributed to PPH world wide. WHO states that misoprostol can also be used to prevent PPH, due to its beneficial effects in low income settings.

Objective: The objective of the study was to compare the effectiveness of sublingual misoprostol in reducing blood loss with that of methyl ergotamine in first two hours after delivery.

Methods: It was a randomized controlled, single center, double blind trial of sublingual misoprostol versus intravenous methyl ergotamine for control of blood loss in 82 women with singleton pregnancies at term who underwent delivery at Lady Willingdon hospital. Participants were divided randomly into two groups (A and B). Randomization was done by Microsoft Excel 5.0 random number generator. The participants were given either misoprostol 600 micrograms sublingually immediately or injection methyl ergotamine 0.2 mg at time of delivery of anterior shoulder of baby. The outcome measures studied were blood loss, blood transfusions, drop in hemoglobin and side effects of both drugs.

Results: Mean age of women in Misoprostol group was 25.76±3.48years. Mean age of methyl ergotamine was 26.0 3.67 years Mean gestational age of women in Misoprostol group was 39.73±1.32 and mean gestational age of women in methyl ergotamine group was 40.09±1.22 weeks. Before delivery mean Hb level was statistically same in both group but post-delivery mean Hb level was significantly dropped in other group. I.e. p-value=0.000165.In Misoprostol group none had blood transfusion while in methyl ergotamine group 4(9.76%) women had blood transfusion but this difference was not statistically significant. Nausea, vomiting and hypertension were significantly higher in methyl ergotamine group. However for pyrexia and shivering an opposite trend was seen for Misoprostol when compared with methyl ergotamine.

Conclusion: Results of this trial showed that sublingual misoprostol is more effective as compared to intravenous methyl ergotamine. It has many advantages including easy transport, storage and oral route which make it a good uterotonic agent in low-resource areas. It was also associated with lesser side effects.

Key words: Intravenous methyl ergotamine, Blood loss, Sublingual misoprostol, Complications, Blood transfusion

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INTRODUCTION

One of the leading cause of maternal death is Postpartum Hemorrhage. Its incidence is around 5-10% in developed and 100 times more in developing countries like ours.

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Atony of uterus is implicated in 70% of cases of PPH and sometimes extensive surgical measures are required for its remedial.[1, 2]

Most tested treatment for atonic postpartum hemorrhage starts with methyl ergotamine, oxytocin and prostaglandins. Though many clinicians use IV Oxytocin to decrease blood loss during third stage but it was seen around half of females required other uterotonic drugs like Ergot Alkaloids or Prostaglandins. Compression Sutures, Arterial Embolization, Aortic Compression, Intrauterine packing, & recombinant factor 7 may be required in many cases. [3, 4, 5]

Methyl ergotamine has been used in management of third stage of labor for a very long time. It is an ergot alkaloid and is given by oral, intramuscular or

intravenous route and causes intense and sustained uterine contraction .It has been related with vomiting, hypertension and severe pain especially for weeks. Misoprostol is an analogue of Prostagladin 1, binds with prostanoid receptors selectively. Multiple routes including sublingual route can be used to deliver it but has shivering and pyrexia as its side effects. [6, 7, 8]

Oxytocin and methyl ergotamine are very useful in reducing blood loss but they have to be stored at a specific temperature and need to be given by medical staff. Misoprostol use is free from these formalities. These qualities of Misoprostol have drawn attention towards as it as an active alternative for post-partum hemorrhage prevention and management**.** [9]

However uterotonic effects of methergin versus misoprostol in reduction of blood loss have been found inconsistent in published studies. In a study done by Rajeshwari, methyl ergotamine was found to be more effective in controlling blood loss but the side effects were more as well. **.** In another study conducted by Humera in India misoprostol and methyl ergotamine were found to be equally effective.[1, 2]

The rationale was to conduct a study in our study due to conflicting evidence for determining whether this cheap & widely used misoprostol is better to prevent PPH than Methyl ergotamine which is also one of the favored drug in reduction of blood loss in the third stage of labour.

METHODS

It was a single center, double blind, randomized controlled trial, conducted at Lady Willingdon hospital over a period of one year. The sample size was calculated by Sample size determination in health studies. Sample size of 82 patients, 41 patients in each group with 99% power of test, 3% level of significance, and taking expected mean value of misoprostol 58.2 and methyl ergotamine as 80.516 respectively. Non probability purposive sampling technique was used. All pregnant women who were primigravidas, second and third gravida with no risk factors were considered candidate after 37 completed weeks. Women with antepartum hemorrhage, hypertensive disorders of pregnancy, over distended uterus due to obstetric causes ,women with history of previous major obstetric hemorrhage (>1000 mL) , those receiving anticoagulant treatment and having known history of medical disorders , grand multipara, women with two or more caesarean sections and those history of ruptured uterus were excluded from the study.

DATA COLLECTION PROCEDURE

Participants were randomly divided into two groups A and B).Randomization was done by the help of Microsoft Excel 5.0 random number generator. The participants were randomly assigned to receive either misoprostol 400 micrograms sublingually immediately at birth or methyl ergotamine at the delivery of anterior shoulder. Placenta was delivered by cord traction in a controlled method. When obstetrician noted poor uterine contraction additional oxytocin was injected .The blood loss after the delivery and the immediate postpartum period was calculated by placing a plastic sheet under woman s buttock and on the floor and keeping a sterile tray at the vulva.After the delivery of the fetus **,** blood loss is estimated by calculating the blood in kidney tray, secondary blood spread on the plastic sheets and the collected blood and the blood clots and the volume measured by a measuring jar. All these figures were noted on preforma , which was filled by researcher who calculated mean estimated blood loss.

DATA ANALYSIS PRODECURE

Data was tabulated and analyzed by SPSS version 17. The quantitative data (age, gestational age at time of delivery, calculated estimated blood loss, pre delivery hemoglobin, post-delivery hemoglobin on third day was presented in the form of mean ± SD. Independent sample t-test was used to estimate mean blood loss in all treatment groups. If normality assumption is not fulfilled then Mann-Whitney U test was applied. P-value 50.05 was considered significant. Side effects of both treatment groups were compared by using chi-square test.

RESULTS

Mean age of women in Misoprostol group was 25.76±3.48 years. Minimum and maximum age of women in this group was 18 and 35 years Mean age of women in Misoprostol group was 25.76±3.48 years. Minimum and maximum age of women in this group was 18 and 35 years. Mean age of women in Methyl ergotamine group was 26.0±3.67 years. Minimum and maximum age of women in this group was 20 years and 34 years.(Table 1)

Mean gestational age of women in Misoprostol group was 39.73±1.32 and mean gestational age of women in Methyl ergotamine was 40.09±1.22 weeks (Table 2).

Mean blood loss was significantly higher in methyl ergotamine group as that of Misoprostol. i.e. p-value<0.00I) (Table 3).In Misoprostol group the mean blood loss in kidney tray was 255.36±18.18 ml. Minimum blood loss in kidney tray was 220 ml and maximum was 300 ml. On the other hand in Methyl ergotamine group the mean blood loss in kidney tray

was 304.±28.99 ml. Minimum blood loss in kidney tray was 250 ml and maximum blood loss was 400 ml. Mean blood loss was significantly higher in methyl ergotamine group as compared to Misoprostol group. I.e. p-value<0.001.

Post-delivery Weight of plastic sheet contaminated with blood: (1gm=1ml) In Misoprostol group the mean post-delivery weight of plastic sheet was 170±26.17 ml. Minimum and maximum weight of plastic sheets was 100 and 210 ml. whereas in Methyl ergotamine group mean weight of plastic sheet was 180±28.08 ml. Minimum and maximum weight of plastic sheets was 110 and 250 ml respectively**.** In Misoprostol group mean volume of clots retrieved from vagina was 114.63±31.47. Minimum volume of clots retrieved from vagina was 60 and maximum was 160. In methyl ergotamine group mean volume of clots retrieved from vagina was 106.09±16.71. Minimum volume of clots retrieved from vagina was 70 and maximum was 150. Mean weight of clots retrieved from Vagina was statistically same in both treatment groups. Although women who were given Misoprostol among them weight of clots was higher but it was not statistically significant. I.e. p-value=0.130

Pre operatively mean Hb level was statistically same in both group but post operatively mean Hb level was significantly dropped in Methyl ergotamine group. I.e. p-value=0.000165 (Table 4**)**

In Misoprostol group none (0%) of the women had blood transfusion while in Methyl ergotamine group 4(9.76%) women had blood transfusion. (Table 5).

In Misoprostol group only 5(12%) patients and in methyl ergotamine group 20(49%) patients had nausea. Vomiting was not seen in any of the patients in Misoprostol group while 12 patients in methyl ergotamine group had vomiting. Similarly none of the patients in Misoprostol group suffered from hypertension whereas in Methyl ergotamine group 20(49%) of the patients suffered from Hypertension. Nausea, vomiting and hypertension was significantly higher in methyl ergotamine group as compared to that of Misoprostol group. (Table 6).

Table-1: Descriptive Statistics for Age

	Sublingual Misoprostol	Intravenous methyl ergotamine
N	41	41
Mean	25.76	26.0
Std. Deviation	3.48	3.67
Minimum	18.0	20.0
Maximum	35.0	34.0

Table-2: Descriptive Statistics for Gestational Age

	Sublingual Misoprostol	IV Methyl ergotamine
N	41	41
Mean	39.73	40.09
Std. Deviation	1.34	1.22
Minimum	35.0	37.0
Maximum	41.0	42.0

Table-3: Descriptive Statistics f for Estimated Calculated Blood Loss

	Sublingual Misoprostol	IV Methyl ergotamine
N	41	41
Mean	612.68	691.71
Std. Deviation	20.97	39.50
Minimum	560.0	630.0
Maximum	650.0	870.0

Table-4: Descriptive Statistics for Pre Operative and Postoperative Hemoglobin

	Before After		Before After	
	Sublingual Misoprostol	Methyl ergotamine	Sublingual Misoprostol	Methyl ergotamine
Mean	10.92	11.03	10.38	10.00
Std. Deviation	0.39	0.34	0.42	0.45
Minimum	10.0	10.2	9.2	9.0
Maximum	11.7	11.6	11.0	10.9
t-test	1.36		3.952	
p-value	0.177		0.000165	

Table-5: Need for Blood Transfusion

Blood Transfusion	Sublingual Misoprostol	IV methyl ergotamine	Total
Yes	0(0%)	4(9.76%)	8
No	41(100%)	37(90.24%)	78
Total	41	41	82

Chi-square=3.40
P-value= 0.065

Table-6: Side Effects in Both Treatment Groups

		Sublingual Misoprostol		Intravenous methyl ergotamine		p-value
		N	%	n	%	
Nausea	Yes	5	12%	20	49%	0.00032
	No	36	88%	21	51%	
Vomiting	Yes	0	0%	12	29%	0.00029
	No	41	100%	29	71%	
Hypotension	Yes	0	0%	20	49%	<0.0001
	No	41	100%	21	51%	
Pyrexia	Yes	15	37%	3	7%	0.00136
	No	26	63%	38	93%	
Shivering	Yes	22	54%	2	5%	<0.001
	No	19	46%	39	95%	

DISCUSSION

Death due to pregnancy stays to be an important cause of premature death of women globally, claiming that 500,000 women die per annum and 25% of them occurs because of hemorrhage following delivery. In developed and as well as under developing countries 3-5 % of the deliveries can end up into post-partum hemorrhage, which is commonest cause of maternal morbidity and mortality.' ACOG defines early PPH as an at least a loss of 1000 ml of blood or loss coinciding with signs and symptoms of hypovolemia within 24 hours of delivery**.** [10]

500 ml of blood loss after delivery is considered to be normal and loss above this is counted to be Post-partum hernorrhage. To be more specific, loss of blood more than 500 ml in birth via vaginal route, and more than 1000 ml during C-section is another definition.**[11]**

Another way of defining post-partum hemorrhage is the loss of blood sufficiently enough that can lead to hypovolemia, or drop in hematocrit of 10%, or the loss of blood that requires blood transfusions (irrespective of the delivery mode). Death percentage due to PPH in Pakistan is around 34%.**[12]**

Uterine Atony is one of the commonest causes. The first line drug for its management is Oxytocin followed by methyl ergotamine and misoprostol. Third stage of labor is very tricky making it the most difficult stage to manage.[13, 14]

In a study done by Aisha Humera in India, Intravenous methyl ergotamine was found as effective as oral misoprostol in high risk patients. This study is in contrast to our study. This may be due to high risk patients employed in the study**.** [1]

In a study done by Amant, a randomized controlled trial, both intravenous methergin and misoprostol were equally effective. The side effects associated with methyl ergotamine were more. More side effects were seen in methyl ergotamine group in our study as well [15]

In a study conducted by Rajeshweri, intravenous methergin was associated with less blood loss and more side effects. On the contrary per rectal misoprostol was associated with more blood loss and less side effects. This difference could be due to different route of administration used for misoprostol**.** [2]

In a study conducted in India oral misoprostol and intravenous methyl ergotamine were used. No difference in reduction of blood loss was found between the two**.** In a study done by Alexander and colleagues methyl ergotamine was found to be more effective in reducing the blood loss. In another study misoprostol was found to be more effective in comparison with methyl ergotamine and oxytocin. Adding misoprostol to the other two does not confer any additional benefit**.** In a similar study methyl ergotamine was found to be more effective but had more side effects as well. [8, 16, 17]

In a study done by Megha and colleagues misoprostol was found to be more effective in reducing blood loss as compared to Oxytocin and Meth

ergotamine .[18] Various studies performed across the globe point towards difference in results.

Limitations: This study has been carried out on a small sample size.
Strength: The study has been done on something which is very pertinent and can be easily related to our topic.

CONCLUSION

Misoprostol has proven to be an effective modality for reducing blood loss in third stage of labor and is associated with lesser side effects as compared to methyl ergotamine. It is a suitable drug for low resource settings like ours. There remains a need to conduct this study on a larger sample size.

Conflict of interest: None
Sources of funding: None

ETHICAL APPROVAL:

The study was approved from Ethical Review Committee of Lady Willingdon Hospital, Lahore, Pakistan.

AUTHORS' CONTRIBUTION:

MI: Writing manuscript, data collection, editing
RW: Writing manuscript, data collection
MJ: Data collection, result analysis

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