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Original Research Article

Comparison of oral misoprostol versus intramuscular oxytocin for active management of third stage of labour: a single centre randomised controlled study

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ABSTRACT

Background: This study was conducted to compare the efficacy and safety of oral misoprostol against intramuscular oxytocin in the active management of the third stage of labour, so that it can be widely used in the areas of limited resources to contribute in preventing post-partum haemorrhage and thus decreasing maternal mortality ratio.
Methods: This was a prospective randomised controlled clinical study. Two hundred patients fulfilling inclusion criteria were randomized to receive either oral misoprostol (600 mcg) or intramuscular oxytocin (10 IU) in the active management of third stage of labour. Primary outcome measured was mean blood loss and incidence of primary PPH.
Results: The mean blood loss during third stage of labour in oral misoprostol group and oxytocin group was 239.16±22.78 ml and 240.19±19.70 ml respectively with p value-0.7331 which was insignificant. Similarly mean fall in haemoglobin was also not significant. There was no significant differences between the two groups with regard to the incidence of PPH (3% vs. 2% respectively; p=0.651). Women experiencing side effects like shivering and fever were significantly higher among misoprostol group than in oxytocin group.
Conclusions: In this study, oral misoprostol was found to be comparable to intramuscular oxytocin regimen, in terms of amount of blood loss, occurrence of postpartum hemorrhage, duration of third stage of labour, fall in hemoglobin and fall in blood pressure. However, shivering and fever were more common with misoprostol, but no other serious side effects were noted.

Keywords: Misoprostol, Oxytocin, Post-partum haemorrhage, Active management of third stage labour

INTRODUCTION

The maternal mortality ratio (MMR) is defined as the number of maternal deaths during a given time period per 100,000 live births during the same time period. Management of postpartum haemorrhage (PPH) is a necessary step towards the achievement of health targets of the third sustainable development Goal (SDG3): i.e. to reduce the global maternal mortality ratio to less than 70 per 100,000 live births by 2030.[1] Around 830 women die from direct pregnancy or childbirth related complications all over the world every day.[2] In 2014, WHO reported 8% of all maternal deaths are caused by PPH in developed regions, while in the developing part of the world the maternal mortality ratio is very high, 20% in Eastern Asia to 32% in Northern Africa.[3] MMR of India for the period 2016-18 is 113/100,000 live births, declining by 17 points, from 130/ 100,000 live births in 2014-16.[4] PPH accounts for 1/4th of maternal deaths worldwide.[5] According to the recent Confidential Enquiries into Maternal and Child Health (CEMACH) Report, Postpartum haemorrhage occurs in around 3.7 per 1000 births with uterine atony being the commonest cause.[6] PPH is commonly defined as blood loss of 500 ml or more from or into the genital tract following the birth of the baby up to the end of puerperium which adversely affects the general condition of the patient

as evidenced by rise in pulse rate and fall in blood pressure.[7] In early 2012, the World Health Organization (WHO) held a technical consultation and issued new recommendations regarding active management of third stage of labour (AMTSL), which can be used to strengthen and focus the implementation of this lifesaving intervention.[8] AMTSL as a prophylactic intervention is composed of a package of three components or steps: administration of uterotonic, preferably oxytocin, immediately after the birth of the baby; Controlled cord traction (CCT) to deliver the placenta; Massage of the uterine fundus after the placenta is delivered.[9] The uterotonic agents stimulate uterine contractions which cause compression of the maternal blood vessels at the placental site after delivery of the placenta thus controlling bleeding and ultimately preventing PPH. The most ideal uterotonic agent for the AMTSL has been the subject of research. However, intramuscular 10 IU of oxytocin remains the standard of care by the world health organization (WHO) recommendation. The disadvantages of oxytocin are its short half-life, instability at room temperature. Hence, there is a need for refrigeration (2-8 degrees centigrade) for storage and transport, a need for a clean needle, syringe and a trained person for administration. These requirements are difficult to meet in primary health care settings and in non-institutional deliveries, therefore alternative measures are required. Prostaglandins are increasingly being employed as an alternative therapy to treat PPH resulting from uterine atony and also to overcome the drawbacks of oxytocin. Misoprostol is a prostaglandin E1 analogue, a methyl ester of prostaglandin E, additionally methylated at C-16, which selectively binds to myometrial EP2/EP3 prostanoid receptors.[10] It is a potent uterine stimulant when administered orally and vaginally in the induction of abortion, cervical ripening and induction of labour. It is effectively absorbed from the mucosa following oral, vaginal and rectal administration.[11] It is also useful in the treatment of PPH unresponsive to oxytocin and ergometrine, and its use has been suggested for the management of the third stage of labour. Oral and sublingual misoprostol has the quickest onset of action and high peak plasma concentration as compared to the vaginal and rectal routes.[12] Vaginal route is not suitable in cases of PPH and for the management of the third stage of labour as the drug is washed away before adequate absorption so the rectal route has been advocated for the management of PPH as it has a longer half- life and thus prolongs uterine contraction which controls bleeding.[13] An oral dose of misoprostol has an 8 minute onset of action and a duration of action of approximately 2 hours and rectal dose has a 100 minute onset of action and a duration of action of approximately 4 hours.[13,14] Thus, the oral route is potentially advantageous. Shivering and fever are the main side effects of misoprostol. Its other side effects are nausea, vomiting and diarrhoea, which are managed easily by conservative methods.[15] The Use of misoprostol as a uterotonic agent in the management of the third stage of labour has been recommended by international federation of gynaecology and obstetrics (FIGO) and the international confederate of midwives (ICM), in situations where safe administration of injectable oxytocin and ergometrine is not feasible. Oral misoprostol because of its cost effectiveness, thermostability, easy administration by oral route, long shelf life without special storage conditions is a promising drug for such situations. Hence this study was conducted to compare the efficacy and safety of oral misoprostol against intramuscular oxytocin in the active management of the third stage of labour, so that it can be widely used in areas of limited resources to contribute in preventing PPH and thus decreasing MMR.

METHODS

This was a randomized controlled study which was carried out at the department of obstetrics and gynaecology, government multi-speciality hospital, Sector 16, Chandigarh, India. A written and informed consent was taken from all the participants. The study protocol was approved by the hospital based ethical committee. The defined guidelines of the central ethics committee for biomedical research on human subjects by ICMR and guidelines as per the Helsinki Declaration were strictly adhered to.

Inclusion criteria

Inclusion criteria for current study were; age group (20-35 years), gestational age (37-42 weeks), vertex presentation**,** parity (0-4), spontaneous vaginal delivery of a single live neonate and TOLAC (trial of labor after cesarean) cases.

Exclusion criteria

Exclusion criteria for current study were; Women were excluded from study if they had known risk factors of PPH like grand multiparity >5, multiple gestation, polyhydramnios, fetal macrosomia, fibroid uterus, Antepartum hemorrhage, pregnancy induced hypertension, premature rupture of memberane/ chorioamnionitis, intrauterine death, prolonged labour, h/o PPH in previous pregnancies, postdated pregnancy and instrumental deliveries. Women with medical disorders like anemia, cardiovascular, respiratory, liver or hematological diseases were excluded. Scar rupture in second stage of labour. Women with known fever and contraindication to either oxytocin or misoprostol.

A total of 200 women undergoing spontaneous vaginal deliveries were randomized either to receive oral misoprostol (600 mcg) or intramuscular oxytocin (10 IU) in the AMTSL. A block randomization, using computer-generated random numbers, was used to allocate study participants; Group A: Inj. Oxytocin 10 units IM given at the time of delivery of anterior shoulder. Group B: 600 mcg Oral misoprostol given at the time of delivery of anterior shoulder. The Estimated blood loss (A= B+C) during the third stage of labour was calculated keeping a sterile kidney tray at the vulva after delivery of the fetus and blood volume measured by measuring jar (B). The

difference in the weight of drapes and gauzes was also estimated by weighing the drapes before and after delivery (C). Measurement of blood loss (ml) = Weight of soaked gauze (gm) - weight of unsoaked gauze (gm) x 1.06. (Density of blood =1060 kg/m³; 1ml of blood = 1.06 gm of blood)

The interval between injection and expulsion of placenta, amount of blood loss, length of the third stage, third stage complications, side effects like nausea, vomiting, diarrhea, shivering, retained placenta and need for the additional drug was noted. Blood pressure was recorded before onset of labour and 30 minutes after delivery. Hemoglobin (Hb) was estimated at the time of admission and 24 hours after delivery and the difference was noted. All quantitative variables were estimated using measures of central location (mean and median) and measures of dispersion (standard deviation). Mean was compared with respect to independent t-test (for two groups). All statistical tests were seen at two-tailed level of significance ($p \leq 0.01$ and $p \leq 0.05$).

RESULTS

Demographic and baseline characteristics of the two groups were comparable (Table 1).

Table 1: Maternal baseline characteristics (n=100).

Parameters		Oxytocin group N (%)	Misoprostol group N (%)	P value
Age (years)	20-25	60 (60)	55 (55)	0.243
	26-30	31 (31)	28 (28)	
	31-35	9 (9)	17 (17)	
	Mean ± SD	25.37 ±3.37	25.67±4.21	
Parity	Primigravida	29 (29)	35 (35)	0.363
	Multigravida	71 (71)	65 (65)	
Gestational age (Weeks)	37-38	11 (11)	13 (13)	0.744
	38.1-39	32 (32)	25 (25)	
	39.1 -40	35 (35)	38 (38)	
	>40	22 (22)	24 (24)	
	Mean	39.24	39.28	
Mode of delivery	NVD	18 (18)	16 (16)	0.973
	NVD + 1st degree tear	14 (14)	13 (13)	
	NVD + 2nd degree tear	6 (6)	6 (6)	
	NVD +RMLE	62 (62)	65 (65)	

NVD-Normal vaginal delivery, RMLE-Right medio-lateral episiotomy

Table 2: Primary outcomes between the two groups.

Parameters		Oxytocin group (Mean±SD)	Misoprostol (Mean±SD)	P value
Blood loss (ml)	In third stage	240.19±19.70	239.16±22.78	0.733
	After 1 hr. of delivery (ml)	84.54±9.82	84.61±7.48	0.955
Fall in hemoglobin (gm/dl)		1.42±0.71	1.40±0.74	0.899
Blood pressure (mmHg)	Systolic BP before delivery	116.72±5.31	115.90±5.87	0.302
	Systolic BP after delivery	114.00±5.64	113.34±4.88	0.378
	Fall in systolic BP	2.72±5.05	2.56±5.09	0.824
	Diastolic BP before delivery	73.52±3.98	74.06±5.08	0.404
	Diastolic BP after delivery	72.10±4.66	72.90±4.38	0.602
	Fall in diastolic BP	1.42±5.09	1.16±4.79	0.680
Atonic PPH	N (%)	2 (2%)	3 (3%)	0.651

The mean blood loss during third stage of labour in oral misoprostol group and oxytocin group was 239.16±22.78 ml and 240.19±19.70 ml respectively with p=0.733 which was insignificant (Table 2). Similarly mean fall in haemoglobin was also not significant. The mean reduction of systolic blood pressure was 2.72 mmHg as observed in the oxytocin group against 2.56 mmHg in the misoprostol group (p=0.824). There was also no significant difference in the average reduction of diastolic blood pressure for both groups: 1.42 mmHg in the oxytocin group against 1.16 mmHg in the misoprostol group (p=0.680). There was no significant differences between the two groups with regard to the incidence of PPH (3% vs. 2% respectively; p=0.651). Women experiencing side effects like shivering

and fever were significantly higher among misoprostol group than in oxytocin group (p=0.0001) (Table 3). Mean duration of third stage of labour was 5.2 minutes in oxytocin group as compared to 4.98 minutes in misoprostol group (p=0.153).

Table 3: Secondary outcomes.

Parameters		Oxytocin group	Misoprostol group	P value
Use of additional oxytocics, N (%)		4 (4)	3 (3)	0.7
Side effects, N	Fever	0	18	0.0001
	Shivering	0	22	0.0001
	Nausea	2	3	0.65
Duration of third stage (Minutes)	Mean±SD	5.20 ±1.51	4.98±0.25	0.153

DISCUSSION

Postpartum hemorrhage is the leading cause of morbidity and mortality in childbirth with an incidence of 1-6% and still remains a major obstetrical challenge. AMTSL is evidence based intervention which is useful in preventing PPH. Oral misoprostol because of its cost effectiveness, oral administration and long shelf life is a promising drug which can be widely used in areas of limited resources and contributes significantly in decreasing MMR. The present study was done to compare the safety and efficacy of oral misoprostol (600 mcg) and intramuscular oxytocin (10 IU) in the AMTSL and to measure secondary outcomes like duration of the third stage, amount of blood loss and incidence of PPH, use of additional oxytocic drugs, drop in haemoglobin and occurrence of side effects in both groups.As per the present study, the incidence of PPH (blood loss >500 ml) was 2% in participants who received oxytocin and it was 3% in those who received misoprostol 600mcg orally. In the study conducted by Subedi et al, the incidence of PPH was 4% (2 out of 50) in patients receiving oxytocin and 0% (0 out of 50) in women who received oral misoprostol.[16] Similar results were observed in studies conducted by Oboro et al and Afolabi et al[18] with an incidence of PPH 0% vs 1% and 0% vs 0% respectively. In the present study, the mean duration of 3rd stage of labour in both the groups was <6 min. The mean duration of 3rd stage of labour was longer in the oxytocin group as compared to the misoprostol group but the difference between the 2 groups was not statistically significant (p value =0.153). Similar results were observed in studies conducted by Subedi et al and Walley et al and all studies showed a longer duration of 3rd stage of labour in patients receiving oxytocin. In the present study, in both the groups the majority of women had blood loss of upto 250 ml. Blood loss > 500 ml was observed in only 2 women in the oxytocin group and 3 in the misoprostol group. The average blood loss in the oxytocin group was more when compared to the misoprostol group and the average blood loss at the time of delivery between the 2 groups was not statistically significant (p value=0.733). The studies conducted by Walley et al, Alam et al and S Kaudel et al showed an average blood loss of less than 200 ml in both groups.[19-21] In the present study, shivering was observed in 22% of the patients in the misoprostol group (n=22) compared to 0% in the oxytocin group (n=0). Fever was observed in 18% of the patients in the misoprostol group (n=18) and no fever was reported in the oxytocin group (n=0). Shivering and fever were the most common side effects noted in the misoprostol group and this difference was found to be statistically significant (p value= 0.0001). Subedi et al[1]observed similar results in their study and shivering was found to be statistically significant, more in the misoprostol group than in the oxytocin group (19 and 1 respectively, p≤0.001). The Study conducted by Kaudel et al and observed that 9 women in the misoprostol group had side effects whereas none in the oxytocin group experienced side effects and it was statistically significant (p value=0.002). All the adverse effects were mild and they subsided spontaneously. None of them required any intervention and were managed with close monitoring.[22]

CONCLUSION

In conclusion, the effectiveness of oral 600 mcg misoprostol was comparable to intramuscular oxytocin regimen, in terms of volume of blood loss, occurrence of postpartum haemorrhage, duration of the third stage of labour, requirement of additional oxytocics, postpartum complications, fall in haemoglobin and blood pressure. There was no case of retained placenta in either of the groups. However, a comparison between the two groups showed that shivering and fever were the more common side effects with misoprostol, but no serious side effects were noted. In developing countries, postpartum haemorrhage is a major cause of maternal death and most preventable. Attempts to reduce deaths from postpartum haemorrhage have been complicated by the fact that many deaths occur in out of hospital settings or too quickly for the patient to be transferred to a health facility. Furthermore, prevention and treatment have depended primarily on injectable uterotonics, which are seldom available for births out of the hospital and peripheral health centres. Oral misoprostol 600mcg can be a miraculous drug at the level of peripheral health centres, home deliveries due to its ease and widely accepted route of administration with the feasibility of self-administration, compliance, ease of availability, usefulness in busy obstetric settings, self-limiting and less severe side effects, thermo stability, shelf life, low cost and less need of skilled personnel. For these reasons, the use of misoprostol to prevent or treat postpartum haemorrhage has attracted

considerable attention. Administration of this drug on a wide scale at the community level to prevent and treat postpartum haemorrhage is of major public health importance.

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