ORIGINAL ARTICLE

A COMPARISON OF THE EFFECTIVENESS OF SUBLINGUAL MISOPROSTOL VERSUS INTRAVENOUS OXYTOCIN INFUSION IN REDUCING BLOOD LOSS IN FIRST TWO HOURS AT CAESAREAN SECTION

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ABSTRACT

Objective: To compare the effectiveness of sublingual misoprostol in reducing intraoperative and postoperative blood loss with that of intravenous (IV) oxytocin infusion in first two hours at caesarean delivery.

Methods: It was randomized controlled trial. Study was conducted in Lady Aitchison Hospital, Lahore unit IV-King Edward Medical University and duration of study was one year. Eighty-two women with term singleton pregnancy undergone elective cesarean section under spinal anesthesia were randomly allocated to receive either misoprostol 400 µg sublingually or IV infusion of 20 units oxytocin in 1000ml of normal saline soon after delivery of the baby. Estimated blood loss at surgery and within the first 2 h post-operation was measured in both groups. Side effects in both groups were also recorded.

Results: Mean blood loss with misoprostol was significantly less as compared to that of oxytocin. Post-operative hemoglobin was decreased by -4.95% in sublingual misoprostol and in oxytocin group it was decreased by -9.33%. Blood transfusion and additional uterotonic therapy was significantly higher in oxytocin group as compared to that of misoprostol. Nausea, vomiting and hypotension was significantly higher in oxytocin group as compared to that of misoprostol group. On the other hand, pyrexia and shivering was significantly higher in misoprostol group.

Conclusion: Results of this trial showed that sublingual misoprostol is more effective as compared to intravenous oxytocin infusion in terms of reduction of blood loss in first two hours at caesarean section. It offers several advantages over oxytocin including long shelf life, stability at room temperature and oral administration which makes it suitable uterotonic agent in low-resource areas.

Key words: Caesarean delivery, Intra-operative, Postoperative, Blood loss, Sublingual misoprostol, IV oxytocin infusion, Complications, operative time, Blood transfusion

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INTRODUCTION

One of the leading cause of maternal death is postpartum hemorrhage. Its incidence varies from 5-10% and 100 times more in under-resourced countries[1]. According to WHO 20 million morbidities worldwide are result of consequences of post-partum hemorrhage (PPH) and responsible for one third of maternal mortality.[1] Uterine atony accounts for 70% of primary PPH and many medical and surgical interventions are used to prevent and treat it.[2] Oxytocic agents used to prevent PPH are oxytocin, ergot alkaloids, ergonovine (ergometrine), methylergonovine, syntometrine (5IU oxytocin +0.5mg ergometrine) and prostaglandins.[3-5] Surgical interventions includes surgical compression sutures, selective arterial embolization, external aortic compression, intrauterine packs, non- pneumatic anti shock garments, recently recombinant activated factor VII.[6-10]

Though most obstetrician use IV oxytocin as a bolus or infusion to decrease blood loss during caesarean

section but it was seen that 10-42% females required additional uterotonic agents like ergot alkaloids or Prostaglandin (PG).[11]

Oxytocin is an injectable uterotonic, unstable at high temperature, require proper storage facilities, cold chain transport and have side effects like tachycardia, hypotension, nausea, vomiting, negative inotropic, antiplatelet, antidiuretic effects, and require trained birth attendants for its administration.[3] Misoprostol is PGE1 analogue, selectively binds with prostanoid receptors. Rectal, vaginal, sublingual, buccal and oral routes can be used to deliver it.[3] Misoprostol has been found very useful for induction of labour and cervical ripening.[12] It has longer half-life, noninvasive administration and maintains its stability at room temperature but have dose related shivering and pyrexia.[5, 13-15]

These properties of misoprostol have gained pronounced attention towards it as an active substitute for postpartum hemorrhage prevention and management in under developed countries. However uterotonic effects of oxytocin versus misoprostol in reduction of blood loss have been found inconsistent in published studies.[11, 16, 17] A study from Iran (2009) demonstrated that sublingual misoprostol at low dose (400ug) is more effective as compared to 20IU of oxytocin infusion. The blood loss was notably higher in the individuals treated with oxytocin than misoprostol (673.9ml Vs 608.9ml) respectively. Need for extra oxytocin treatment in the individuals treated with oxytocin was 36% while in misoprostol group was 14%.[16]

Another study from Nigeria (2011) showed that reduction in blood loss in group receiving misoprostol was significantly less than individuals receiving oxytocin (58.2 Vs 80.5 p-value=0.02). Harmful reactions like shivering and pyrexia was pronounced in individuals treated with misoprostol than the individuals treated with oxytocin (25/50 Vs 1/50 p-value<0.001).[11]

Meta-analyses of randomized trials (2013) shows that misoprostol administered by sublingual or oral route as compared with injectable oxytocin by intravenous infusion may be equally effective in prevention of PPH, but has more side effects like shivering ,pyrexia but it is dose related.[2]

World Health Organization (WHO) recommends the use of 10 units of oxytocin as compared to misoprostol to avoid hemorrhage after delivery.[18] Although many studies showed that misoprostol had advantageously been used to decrease the blood loss at caesarean section.[11, 16, 17] So we decided to determine whether this low-priced and extensively used misoprostol is better to prevent hemorrhage at caesarean section than the oxytocin infusion, which is the drug of the choice in reduction of blood loss at caesarean section.

METHODS

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 oxytocin as 80.5[16] respectively.

$$\mathbf{n}= \frac{2\sigma^2(z_1-\alpha+z_1-\beta)^2}{(\mu_1-\mu_2)^2}$$

n=41 cases in each group, μ_1=58.2ml, μ_2=80.5ml,
SD = 23.79

Non probability purposive sampling technique was used. All pregnant women with previous one caesarean section considered candidate for elective caesarean section after 37 completed weeks under spinal anesthesia. Women with placenta Previa, placental abruption, pre-eclampsia, eclampsia, over distended uterus due to polyhydramnios or multiple pregnancies. Women with history of previous major obstetric hemorrhage (>1000 mL). Women receiving anticoagulant treatment. Pregnant women with known history of medical disorders (blood discariasis, renal, cardiovascular, respiratory and metabolic disorders like diabetes mellitus, hypertension, thyroid disorders). Grand multipara (>5 pregnancies). Women with two or more caesarean sections. Women with history of rupture uterus.

The study was randomized controlled, single center, double blind trial of sublingual misoprostol versus intravenous oxytocin infusion for control of blood loss in women with singleton pregnancies at term who were scheduled for elective caeserean delivery at Lady Aitchison hospital under spinal anesthesia. Cases with placenta previa, placental abruption, pre-eclampsia, eclampsia, over distended uterus due to polyhydramnios or multiple pregnancies, women with history of previous major obstetric hemorrhage (>1000 mL), anticoagulant treatment, medical disorders (blood discariasis, renal, cardiovascular, respiratory and metabolic disorders like diabetes mellitus, hypertension, thyroid disorders), grand multipara (>5 pregnancies), two or more caesarean sections and with history of rupture uterus were excluded from study. After approval from ethical committee and taking informed consent 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 400µg sublingually immediately at time of skin incision or intravenous infusion of 20 units of oxytocin in 1000ml saline solution that was started at time of cord clamping at rate of 10ml/min for 30mins followed by 2ml/min for 6hrs. No stat dose of oxytocin was given in either group. Placenta was delivered by cord traction. When obstetrician noted poor uterine contraction, additional oxytocin was injected by anesthetist. After the procedure, obstetricians cleaned

all participant's vagina with sterile gauzes (4x4 gauze is 4 inches wide by 4 inches long (10.16 cm by 10.16 cm). The blood loss of all the participants was monitored for at least 2hrs post operatively. Blood loss was estimated separately by measuring the

- Blood volume in suction bottle
- Amniotic fluid volume was measured and subtracted
- Sponges, drapes and gauze pieces used for procedure were weighed preoperatively and post operatively.
- Blood clots retrieved were included in the blood loss estimation.
- Pads given to patients after surgery were weighed before and after use.

It was assumed that 1 gram increase in weight of pre weighed drapes, sponges and pads is equal to 1ml. The balance in grams was equated to total blood loss in milliliters. [20] Blood clots retrieved from vagina were collected in kidney dish and weighed. Post-operative blood loss was measured by doctor after first two hours of surgery. All these figures were noted on proforma, which was filled by researcher who calculated mean estimated blood loss. The main outcome measures were intraoperative blood loss and the need for additional uterotonic agents and postoperative hemoglobin (Hb) fall. Secondary outcome measures were shivering, pyrexia, nausea, vomiting, operating time, postpartum hemorrhage, blood transfusion.

Data was tabulated and analyzed by SPSS version 17. The quantitative data (age, gestational age at time of delivery, calculated estimated blood loss, preoperative hemoglobin, postoperative hemoglobin on third day was presented in the form of mean ± SD. Qualitative data type of anesthesia, indication for caesarean and type of caesarean section was given in frequency%. Independent sample t-test was used to estimate mean blood loss in all treatment groups. If normality assumption is not fulfilled then Mamn-Withey U test was applied. Preoperative and postoperative hemoglobin was assessed with paired sample test. P-value ≤0.05 was considered significant. Side effects of both treatment groups were compared by using chi-square test.

RESULTS

Table-1: There was no difference between the groups in age, duration of pregnancy

Variable	Misoprostol	Oxytocin	p-value
Age (years)	25.76±3.48	26.0±3.67	NS
Gestational age (weeks)	39.73±1.32	40.09±1.22	NS

There were significant differences in preoperative and postoperative Hb concentration as well as the amount of mean blood loss and need for additional uterotonic therapy between the two groups but need for blood transfusion was not statistically significant (Table 2).

Table 2.

Variable	Misoprostol	Oxytocin	p-value
Preoperative Hb(g\dl)	10.92±0.39	11.03±0.34	*0.177*
Postoperative Hb(g/dl)	10.38±0.42	10.0±0.45	*0.000165*
Mean estimated blood loss (ml)	612.68±20.97	691±39.50	*<0.0001*
Need for additional uterotonic therapy	3(7.32%)	25(60.98%)	<0.001
Need for blood transfusion	0(0%)	4(9.76)	0.065

Comparison of the side effects revealed that shivering and pyrexia in misoprostol were significantly higher from the other group. While hypotension and vomiting were more in oxytocin group (Table 3).

Table 3

		Sublingual Misoprostol		Oxytocin		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%	
Hypo tension	Yes	0	0%	20	49%	<0.001
	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%	

In the Misoprostol group mean Hb on third post-operative day was 10.38±0.42 g/dl while the minimum Hb on third postoperative day was 9.2 g/dl and maximum Hb on third postoperative day was 11.0 g/dl. While in Oxytocin group the mean Hb on third postoperative day was 10.0±0.45 g/dl. Minimum Hb on third postoperative day was 9.0 g/dl and maximum Hb on third postoperative day was 10.9 g/dl. Pre operatively mean Hb level was statistically same in both group but post operatively mean Hb level was significantly dropped in oxytocin group. i.e. p-value=0.000165. Mean blood loss was significantly higher in oxytocin group as that of Misoprostol. i.e. p-value<0.001.

DISCUSSION

Death due to pregnancy remains an important cause of premature mortality of women worldwide, estimating

500,000 women die per year and a quarter of them occurs because of hemorrhage. In developed and as well as under developed countries 1-5 % of the deliveries can lead into post-partum hemorrhage, which is one of the most common cause of maternal morbidity and mortality.[18]
Simply stating, post-partum hemorrhage is an equal opportunistic killer and no patient is immune from it, as it is evidently accepted that its occurrence is unpredictable. Earlier studies showed that oxytocin is more effective than oral misoprostol because misoprostol has slower onset of action.[19]

In this study Sublingual misoprostol was compared with IV oxytocin infusion to control blood loss at caesarean section. The patients who were given sublingual misoprostol showed considerably less mean estimated blood loss as compared to those patients who were given IV oxytocin infusion, i.e. 612.68ml vs. 691.71ml, p-value= 0.0001. Additional uterotonic therapy was required in oxytocin group for 25(60.98%) patients however in Sublingual misoprostol group only 3(7.32%) patients required additional uterotonic therapy. MB Bellad in this study reported that the mean blood loss in women who received 400ug sublingual misoprostol was 192 ± 124 ml, compared with the blood loss of 366 ± 136 ml in women receiving intramuscular oxytocin for the prevention of PPH.[20] Results of this study regarding blood loss were consistent with the results reported by MB Bellad. The Cochrane Review found no significant difference in mean scores of blood loss between sublingual misoprostol and injectable uterotonics, and no difference in prevention of PPH through these drugs.[4] However, the review combines different doses of misoprostol (50ug,35 400ug, and 600ug) and injectable uterotonics (ergometrine, syntometrine, and oxytocin) with variable doses and discrete effectiveness. In our study post-operative hemoglobin was decreased by -4.95% in sublingual misoprostol (Pre: 10.92 & Post: 10.38) and in oxytocin group post-operative hemoglobin was decreased by -9.33% (Pre: 11.03 & Post: 10.00). Chaudhuri et al. and Mobeen et al. did not find any considerable change in Hb.[21] In the study by Bellad et al. it was noted that there was significantly less drop in postpartum Hb in misoprostol group as compared to oxytocin group.[20] MB Bellad study detected that hemoglobin drop >10% in 45.6% women who received oxytocin as compared to misoprostol group in which hemoglobin drop was noted only in 9.7% women.[20]

Results of this study regarding additional uterotonic therapy showed that in women who were given sublingual misoprostol, among them 3(7.32%) women required additional uterotonic therapy. However, in oxytocin group 25(60.98%) women need additional uterotonic therapy. Need of uterotonic therapy is significantly high in oxytocin group. i.e. (p-value=0.001).

Priya in her study reported that two cases in misoprostol group and three cases in oxytocin group required additional oxytocin because of uterine atony.[22] Chaudhuri et al., in his study reported no statistical significance in the requirement of additional oxytocin in between the two groups in both the studies.[21] In Bellad et al. study, one case in misoprostol group required additional oxytocin whereas 8 cases in oxytocin group which was statistically significant (p=0.002).[20]

In the study of Elati et al., high risk cases were not included, so none of them required additional oxytocin as none of the group bleed more than 500 ml.[13] According to El-Refaey et al. study he had to use additional oxytocin for 9 cases of misoprostol group and for 11 cases of oxytocin group.[23] MB Bellad in his study stated that six of the women from oxytocin group required additional oxytocin, on the other hand not even a single case from misoprostol group required oxytocin to treat PPH (additional uterotonics, P= 0.001).[20]

Few studies have reported the additional need of uterotonic therapy for oxytocin as well as for sublingual misoprostol but in this study sublingual misoprostol group required no additional uterotonic therapy.[21] Bellad et al. described only a single event of retention of placenta in woman receiving oxytocin and in both groups blood was transfused to one women. That was a statistically insignificant.[20] In El-Refaey study he stated that blood transfusion was done in 9 women in misoprostol as compare to the 11 cases from oxytocic group.[23] A Elati in his study reported that neither blood transfusion nor additional uterotonics were required in women who were injected with oxytocin intramuscularly or sublingual misoprostol.[13] Beverly Winikoff in his study reported a significant blood transfusion rate as 8% for misoprostol group and 5% for oxytocin.[24]
In this study it was observed that women who were given sublingual misoprostol they did not require blood transfusion however women who were given oxytocin among them 4(9.76%) required blood transfusion. As per these findings blood transfusion was statistically lower in sublingual misoprostol and these results are same as described by Beverly Winikoff.[24]

Side effect profile of sublingual misoprostol showed that incidence of shivering was 54% followed by pyrexia (37%) and nausea (12%). So shivering was most common side effect of misoprostol. In oxytocin group the incidence of side effects was nausea (49%) and hypotension (49%) followed by vomiting pyrexia (7%) and shivering (5%). Nausea, vomiting and hypotension were considerably more in oxytocin group. i.e. (Nausea: 12% vs. 49%, p-value=0.0032, Vomiting: 0% vs. 29%, p-value=0.0029 & Hypotension: 0% vs. 49%, p-value=0.001). Conversely pyrexia and shivering were considerably more in misoprostol group. (Pyrexia: 37% vs. 7%, p-value=0.0013, Shivering: 54% vs. 5%, p-value=0.001).

We found increased rates of side effects with misoprostol versus oxytocin, as has been previously

reported.[25] Although misoprostol-related shivering is typically considered a nonserious side effect, prior studies have reported fever,[26,27] secondary psychological effects including anxiety, and perceptions of lack of body control.[28] The difference of nausea and vomiting in the two groups was significant.

MB Bellad study showed that side effects were less in oxytocin group than misoprostol group.[20] Mariana Widmer also reported a high frequency of shivering in women who were given misoprostol.[29] In this study 54% of the women had shivering who were given misoprostol. Al-Sawaf noted that shivering that occurred after oxytocin administration may be linked to its hemodynamic actions that causes shivering. In this favor, tachycardia was observed in women receiving oxytocin.[30] Oxytocin effects blood pressure and heart rate through these mediators, nitric oxide, atrial natriuretic peptide and alpha2-adrenoreceptors.[31]

In this study about 49% of the women suffered from hypotension who were given oxytocin. However, in misoprostol group none of the women experienced hypotension.

Beverly Winikoff also reported that Shivering (229 [47%] vs82 [17%]; RR 2·80, 95% CI 2·25–3·49) and fever (217 [44%] vs27 [6%]; 8·07, 5·52–11·8) were considerably more in misoprostol group as compare to the oxytocin group[24] Similar findings were also reported by Jennifer Blum Shivering (152 [37%] vs59 [15%]; RR 2·54, 95% CI 1·95–3·32) and fever (88 [22%] vs59 [15%]; 1·47, 1·09–1·99) were considerably more common with misoprostol as compare to oxytocin.[32]

CONCLUSION

Results of this trial showed that sublingual misoprostol is more effective as compared to intravenous oxytocin infusion in terms of reduction of blood loss in first two hours at caesarean section and is superior to oxytocin. Though the side effects like fever and shivering occur more with misoprostol than oxytocin but they occur only transiently and are self-limiting.

ETHICAL APPROVAL

The study was approved from Institutional Review Board of King Edward Medical University, Lahore, Pakistan, vide reference No. 95/RC/KEMU, dated August 30, 2014.

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AUTHOURS CONTRIBUTIONS

MJ, MI: Concept, Design, Manuscript writing Data collection, Data analysis