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A RANDOMIZED COMPARATIVE STUDY TO COMPARE THE EFFICACY OF OXYTOCIN, MISOPROSTOL, 15- METHYL PGF2A AND METHYL ERGOMETRINE IN ACTIVE MANAGEMENT OF THIRD STAGE OF LABOR

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ABSTRACT
This is a randomised comparative study to compare the effect of injection oxytocin 10 IU intramuscular, 600µg misoprostol tablet per Rectal tablet, injection 15-methyl prostaglandinF2α 125 µg intramuscular and injection 0.2 mg methylergometrine intravenous in active management of third stage of labor (AMTSL). Non high-risk 1000 women at term gestation with singleton pregnancy were recruited and randomized into four groups (250/group), to receive any of these four drugs during AMTSL. Outcome parameters like amount of blood loss, duration of third stage of labour, fall in hematocrit and side effects were compared using ANOVA/KruskalWallis, Post Hoc test, student's t test and χ^2 test. Subjects who received methylergometrine and oxytocin had least amount of blood loss (144.78±54.155ml and 160±57.341ml respectively) and Methylergometrine group (5.81±1.320min) had significantly longer duration of third stage of labor as compared to other groups. Oxytocin was found to be significantly better in reducing blood loss in third stage of labor.

KEYWORDS: AMTSL, oxytocin, methylergometrine, misoprostol, 15MethylprostaglandinF2α Word count-2498.

INTRODUCTION
The period from delivery of the baby to complete delivery of placenta and its attached membrane is the third stage of labour.[1] Routine use of active management of third stage of labour (AMTSL) for all singleton vaginal deliveries is recommended by the International Federation of Gynaecologists & Obstetricians (FIGO) and the International Confederation of Midwives (ICM), and by WHO(2003).[2,3]

AMTSL includes administration of uterotonics immediately following delivery of baby, early clamping of umbilical cord and controlled cord traction for delivery of placenta.[4] AMTSL prevents postpartum hemorrhage (PPH) by over 60% (RR 0.38,95%CIl 0.32-0.46).[5] PPH is the leading cause of maternal death worldwide, with an estimated yearly mortality rate of 140,000, or one maternal death every 4 minutes.[6] PPH occurs in 5% of all deliveries.[7,8]

Uterotonics used in AMTSL include oxytocin, misoprostol, methyl ergometrine and 15 methyl prostaglandin F2α. This study is conducted with aims of comparing these four drugs and finding a single effective and safe drug for AMTSL. These all four uterotonics were not compared to each other in any of the previous studies found in literature.

MATERIAL AND METHODS
This is a randomized comparative parallel group multiple arm study conducted at Department of Obstetrics & Gynecology, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi after approval from the Institutional Ethics Committee from 1st January to 31st December2013. Registration (Retrospective) number-CTRI/2015/06/005918. All non-high-risk pregnant women at 37 to 40weeks of gestation who delivered vaginally were included in the study. Pregnant women with any high risk factor and those had labor induction were excluded from the study.

Sample size was calculated based on the data regarding amount of blood loss in third stage of labor from a previous study where four drugs were compared.[9]By keeping α error at 0.05 and power 80 by using ANOVA Test with n=4 group the sample size came out to be 250 in each group. This study included 1000 pregnant women during delivery. Subjects were divided into four equal groups by computer generated random number table. Group A received Inj Oxytocin10 IU intramuscular, Group B received Tab Misoprostol 600µg per rectal, Group C received Inj 15-methyl prostaglandin F2α 125µg intramuscular and Group D received Inj Methylergometrine 0.2 mg intravenous. Written informed consent was taken from subjects who satisfied the inclusion criteria after explaining the study methodology. A detailed obstetric, family, personal and medical history was taken. General, systemic and thorough obstetric examination was done. First and second stage of labor was monitored using partograph. Women receiving oxytocin infusion for augmentation in the first stage of labor were included and the infusion was stopped at the end of second stage of labor. When all the amniotic fluid drained out, Kelly's douche pad was placed under the patients buttocks. Immediate cord clamping was done. According to computer generated random allocation of group either one of the uterotonics were administered immediately following delivery of the baby. The third stage was managed by awaiting for signs of placental separation and the placenta was delivered by controlled cord traction. Bloodloss during third stage of labor was measured by collecting blood in a tub through Kelley's douche pad and measured in a measuring bottle and also by weighing the fresh preweighed pads and then soaked pads after the third stage of labor. The pads were weighed and their difference then converted into ml by following formula, amount of blood loss in ml=amount of blood loss in grams×1000/1060, as the density of blood is 1060. Duration of third stage of labor was noted and any prolongation of third stage (>15 min), the need for use of other oxytocics and any case had retained placenta was also noted. The hematocrit of the patient was checked on admission to labor room and 24 hours after delivery. Maternal pulse and blood pressure was measured immediately after delivery and repeated after 1hour. All the subjects were instructed regarding any side effects of drugs like fever, shivering, nausea, vomiting, diarrhoea etc to inform within 24 hours of delivery and the same were checked till one hour after delivery before they were shifted out to postnatal ward from labor ward. The primary outcome measure was amount of blood loss during third and fourth stage of labor. The secondary outcomes were duration of third stage of labor, change in hematocrit from predelivey to 24 hour postpartum, administration of other oxytocics or blood transfusions, any side effects of the drugs/complications within 24 hours of delivery.

All the data were presented as range (minimum/maximum), means and standard deviations (SD) for quantitative variables and for categorical variables numbers and frequencies (%) under different group. The statistical analysis was performed using ANOVA/Nonparametric Kruskal Walls(in case data do not follow normal distribution) test followed by Post Hoc test(Tukey HSD) for more than two groups and student's t test/ non parametric Mann Whitney test for continuous variables in two groups and the χ^2test/Fisher's exact test for categorical data between/among different group. P value of <0.05 was considered statistically significant. Analysis was done by SPSS statistical software version 16.0.

RESULTS

The demographic characteristics of the patients were depicted in Table-I. There are no significant difference between the groups regarding age, parity, educational and socioeconomic status and mode of delivery. All perineal tears were of first or second degree. Maternal parameters are presented in Table-II.The lowest mean blood loss was seen in the participants who received methylergometrine. The difference in blood loss was statistically significant between all the groups (p <0.001). Figure-1 depicts the amount of blood loss in all four groups. A blood loss of <100ml was recorded in methylergometrine group and oxytocin group. The difference in mean blood loss was not significant between Group A and D (p=0.118) and Group B and C (p=0.883) but was statistically highly significant between groups A and B, A and C, B and D and C and D (p<0.001).

The duration of third stage of labor ranged from 3 to 9 minutes. The subjects who received oxytocin and methylergometrine had significantly shortest and longest duration of third stage of labor respectively (p <0.001). The difference in the mean duration of third stage of labor was statistically highly significant among all groups (p<0.001) except between Group B and C (p=0.909). Figure-2 depicts the duration of third stage of labor in all the groups. Duration of third stage of labor in the range of 8-10 minutes is found in 2.8% of women in Group D (p <0.05). None of the subjects had prolonged third stage of labor (>30min) or retained placenta.

There was a significant fall in postpartum hematocrit of all four groups, maximum reduction being in 15methylprostaglandin$F_{2\alpha}$ group. Additional uterotonics (i.v oxytocin infusion or i.v methylergometrine or i.m. 15methylprostaglandin$F_{2\alpha}$or misoprostol) were required in 14 subjects. Blood transfusion was not required in any group. A significant increase in blood pressure was seen in subjects of all four groups, greatest increase being in methylergometrine group.

Table-III shows the side effects/ complications of the drugs used. While comparing in between groups regarding complications (PPH), Group A and B (p=0.315), group A and C (p= 0.019), group A and D (p= 0.317), group B and C (p= 0.127), group B and D

(p=0.082) were comparable but group C and D had significant difference (p=0.004). The intergroup and intragroup comparison of systolic and diastolic blood pressure of four groups before and after delivery was statistically significant (p<0.001). Group C had highest incidence of nausea and vomiting while women in group A and D did not had (p<0.001). Transient (<4 hour) pyrexia of 100-101^{o}F found in 26 women of group B. All the side effects were self limiting.

Table: I, Demographic characteristics of all the cases.

Characteristics	GroupA(N=250)	Group B(N=250)	Group C(N=250)	Group D(N=250)	*p*-value
Age in yrs (n%) ≤20 21-25 26-30 >30 (Mean ±SD)	26(10.4%) 120(48%) 93(37.2%) 11(4.4%) 24.95±3.35	20(8%) 116(46.4) 103(41.2) 11(4.4%) 25.19±3.20	29(11.6) 120(48) 87(34.8) 14(5.6%) 24.88±3.59	20(8%) 114(45.6) 102(40.8) 14(5.6%) 25.33±3.60	0.805
Population. (N%) Urban Rural	207(82.8) 43(17.2%)	208(83.2) 42(16.8%)	205(82) 45(18%)	198(79.2) 52(20.8%)	0.651
Educational status (N%) Literate Illiterate	182(72.8%) 68(17.2%)	186(74.4%) 64(25.6%)	182(72.8%) 68(17.2%)	189(75.6%) 61(24.4%)	0.868
Parity- Primi(N%) Multi (N%)	97(38.8%) 153(61.2%)	112(44.8%) 138(55.2%)	123(49.2%) 127(50.8%)	101(40.4%) 149(59.6%)	0.082
Mode of delivery (N%) NVD NVD with Epi NVD with tear	60(24%) 162(64.8%) 28(11.2%)	58(23.2%) 161(64.4%) 31(12.4%)	42(16.8%) 183(73.2%) 25(10%)	60(24%) 169(67.6%) 21(8.4%)	0.234

NVD-Normal Vaginal delivery. Epi- Episiotomy.

Table-II, Maternal parameters of all the cases.

parameters	Group-A (N=250)	Group-B (N=250)	Group-C (N=250)	Group-D (N=250)	P value
Amount of blood loss (ml)in 3rd stage.	160.33±57.341	208.54±83.480	213.68±106.270	144.78±54.155	<0.001
Duration of 3rd stage of labor(min)	4.74±1.01	5.19±0.93	5.13±0.97	5.81±1.32	<0.001
% of hematocrit fall after delivery (% reduction)	1.7292±1.0338 (5.54%)	2.8872±1.6389 (8.70%)	2.9080±1.8697 (8.79%)	1.4892±0.8956 (4.54%)	<0.001
increase of systolic BP(mmHg)	1.828±4.905	2.032±4.480	1.400±6.274	4.704±4.686	<0.001
increase in diastolic BP(mmHg)	4.008±4.703	2.872±5.148	2.592±6.666	6.048±4.806	<0.001
Need for additional uterotonic. No (%)	1(0.4%)	3(1.2%)	10(4%)	0(0%)	<0.001

All values are presented as Mean±SD, unless mentioned.

Table: III side effects of the drugs and complications in each group.

Side effects/ complications	Group A (N=250)	Group B (N=250)	Group C (N=250)	Group D (N=250)
Nausea. N (%)	2(0.8%)	2(0.8%)	5(2%)	5(2%)
Vomiting N(%)	1(0.4%)	2(0.08%)	44(17.6%)	7(2.8%)
Diarrhea N (%)	0(0%)	1(0.4%)	15(6%)	0(0%)
Fever	0(0%)	26(10.4%)	1(0.4%)	0(0%)
Shivering. N (%)	0(0%)	1(0.4%)	0(0%)	0(0%)
Postpartum hemorrhage. No (%)	1(0.4%)	3(1.2%)	8(3.2%)	0(0%)

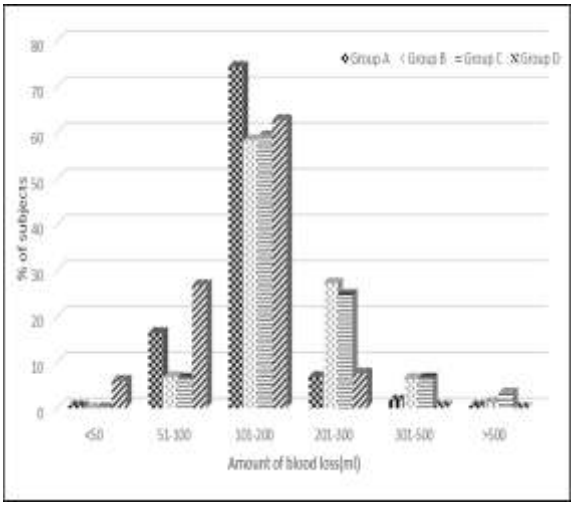

Figure: 1 Distribution of amount of blood loss among different groups.

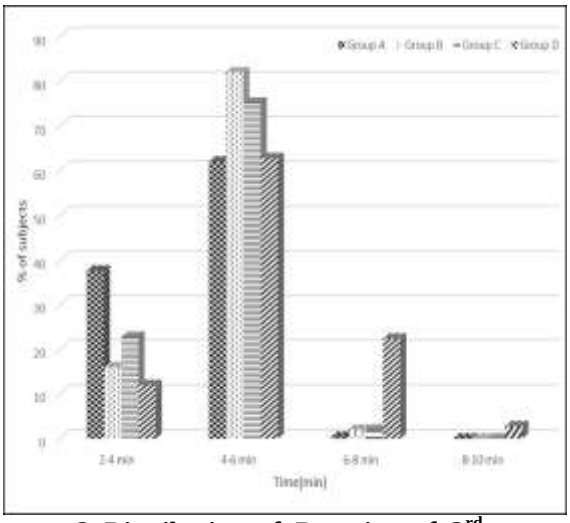

Figure: 2 Distribution of Duration of 3rd stage of labor among different groups.

DISCUSSION

In the present study majority of subjects belongs to 21-25 years age group. This is similar to study by Vaid A.[10] Majority of subjects were from urban population. In a systematic review Carroli G found that studies performed in urban areas showed lower prevalence of PPH than those in rural areas.[11] Majority of the subjects in all groups were multiparous. Most of the women in all the groups had vaginal delivery with episiotomy which is similar to Study by Gohil J.T.[9] The amount of additional blood loss attributed to episiotomy can be up to 300ml and episiotomy is one of the risk factors for PPH.[12]

In the present study, mean blood loss was lowest in methylergometrine group. Oxytocin and methylergometrine were equally efficacious in reducing blood loss in third stage of labor. Similar results seen in study by Ezeama C O.[13] 15methylprostaglandin$F_{2\alpha}$ group had maximum blood loss more than 500ml. On multiple comparisons: Group A was significantly better in reducing blood loss than group B and C ($p<0.001$), Group A and D were comparable and were significantly better than group B and group B and C were comparable in reducing blood loss in third and fourth stage of labour. Study by Kundodyiwa TW found comparable amount of blood loss between oxytocin and oral misoprostol group.[14] The discrepancy in the results between their study and present study could be because of oral misoprostol used in their study which has an earlier onset of action and earlier peak plasma levels of the drug as compared to rectal misoprostol used in present study. Study by Kustagi and Verghese found comparable results in terms of reduction of blood loss between methylergometrine and carboprost tromethamine.[15] Studies by Mansouri H.A and Singh G showed misoprostol as a better or equally effective alternative to conventional uterotonics,[16,17] Study by Vaid A showed that sublingual misoprostol 400µg appears to be as effective as intramuscular 0.2mg methylergometrine and intramuscular 125 µg Carboprost in reducing blood loss.[10] In the present study intravenous methylergometrine was used that has rapid onset of action than intramuscular route thereby increasing efficacy. Study by Singh G found sublingual misoprostol was significantly more effective than intravenous either oxytocin or methylergometrine.[17] A RCT by Mansouri HA showed oral misoprostol has significantly more blood loss than rectal misoprostol.[16]

In the present study incidence of PPH was significantly increased in group C than group A ($p=0.019$) and group D ($p=0.004$), and comparable with group B ($p=0.217$). Rate of PPH between group B and D were comparable ($p=0.082$). Study by Chabbra S found similar incidence of PPH in misoprostol and methylergometrine group.[18] Study by Amant F observed PPH in 8.3% of the cases in the misoprostol 600µg group and 4.3% in methylergometrine IV 0.2mg group ($p=0.57$).[19] In the present study occurrence of PPH in group A and B were comparable ($p=0.315$). Similar results were seen in other studies.[14,20] In the present study there was no difference in rate of PPH between group A and D ($p=0.317$). Similar results were seen in one study, using 10 IU oxytocin Intravenous or 0.25mg ergometrine Intravenous [18/393(5.9%) vs. 12/297(4.0%),$p=0.54$][21] In contrary to the present study, one study showed that occurrence of PPH in misoprostol group was 20% vs. 4% in methylergometrine group($p<0.05$).[9] In the WHO multicenter randomized trial, Gulmezoglu AM study using 600µg 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 of 1000 ml($p<0.0001$).[22]

The duration of third stage in the present study was shortest in oxytocin group, longest in methylergometrine group ($p<0.001$), and comparable between group B and C ($p=0.909$). Other Studies also showed similar results.[13,15] Studies by Gohil J T and Kustagi showed shorter duration of third stage of labor in

methylergometrine group.[9,15] In the present study there were no cases of retained placenta which could be because of early clamping of umbilical cord and immediate controlled cord traction for delivery of placenta.

Hematocrit concentration estimation is an objective method for assessment of blood loss. This was however not adopted in many studies. In the present study postpartum hematocrit fall was maximum in group C and least in group D ($p<0.001$). Study by Ezeama found significant difference in the mean hematocrit on second day postpartum using Oxytocin vs. methylergometrine.[13]

In the present study the need for additional uterotonics was higher in 15methylprostaglandin$F_{2\alpha}$ group and lowest in methylergometrine group. ($p=0.001$) In the study by Gohil JT, the need of additional uterotonics was highest with misoprostol and lowest with methylergometrine ($p=0.037$).[9] Need for additional uterotonic was significantly higher in oxytocin group as compared to methylergometrine group in Ezeama C O (2014) study.[13] In study by Vaid A no significant difference was seen in requirement of additional oxytocic in all groups.[10] In the present study the requirement of oxytocics was more with misoprostol than methylergometrine may be due to the late absorption of rectal misoprostol. In the WHO multicenter trial, 15% of misoprostol group and 12% in the oxytocin group required additional oxytocics. No significant difference in use of additional uterotonics were seen between oxytocin and misoprostol group in Kundodyiwa TW study.[14] In study by Parsons the need for additional uterotonics in misoprostol group was lower than the oxytocin group [9/223(4%) vs. 19/224(8.5%); RR0.48(95% CI 0.22-1.03].[23]In the present study the maximum rise in systolic as well as diastolic blood pressure was seen in methylergometrine group. Similar results were seen in other studies.[15,17] In study by Ezeama C O diastolic hypertension was significantly more common in the ergometrine group (OR 0.00; 95%CI0.00-0.75, $p=0.007$).[13]

The most common side effects found in the present study were vomiting, diarrhoea (15methylprostaglandin$F_{2\alpha}$) and transient pyrexia (misoprostol). Women in group A and D did not have diarrhea, vomiting and shivering. ($p<0.001$) Similar results were seen in other studies.[9,10,14,17,23] In a study by Orji E nausea, vomiting, headache and increased blood pressure were significantly more common in the ergometrine group. [20] In the study by Gohil JT there was higher incidence of nausea and vomiting in patients given ergometrine-oxytocin and methylergometrine.[9]In a study by Mansouri H A fever, shivering and GI symptoms were significantly higher with oral misoprostol than rectal misoprostol($p<0.05$).[16] In the present study rectal misoprostol was used and hence had lesser side effects. In the present study none of the subjects from all four groups required blood transfusion. In the study by Vaid A (2009) one woman received blood transfusion in the misoprostol group.[10]

CONCLUSION

Intramuscular Oxytocin was found to be the safest uterotonic drug with shortest duration of third stage of labor, least side effects and technically easier to use even in situations where intravenous access is unavailable. Methylergometrine is equally efficacious as Oxytocin, strongly favouring their routine use as preferable uterotonics. Misoprostol and 15methylprostaglandinF2α were not as efficacious as oxytocin and methylergometrine but both were comparable among each other in most parameters. Misoprostol was significantly better than 15methylprostaglandinF2α in preventing postpartum hemorrhage.

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