THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (July–August 2011) 61(4):408–412
DOI 10.1007/s13224-011-0060-5

ORIGINAL ARTICLE

A Study to Compare the Efficacy of Misoprostol, Oxytocin, Methyl-ergometrine and Ergometrine–Oxytocin in Reducing Blood Loss in Active Management of 3rd Stage of Labor

Gohil J. T. · Tripathi Beenu

Received: 8 June 2009 / Accepted: 5 May 2011 / Published online: 23 September 2011

Abstract

Objectives The purpose of the study was to compare the efficacy of misoprostol 400 μg per rectally, injection oxytocin 10 IU intramuscular, injection methylergometrine 0.2 mg intravenously and injection (0.5 mg ergometrine + 5 IU oxytocin) intramuscular on reducing blood loss in third stage of labor, duration of third stage of labor, effect on haemoglobin of the patient, need of additional oxytocics or blood transfusion and associated side effects and complications.

Study Design A prospective non-randomized uncontrolled study was carried out in the Department of Obstetrics and Gynecology, SSG Hospital and Medical College, Baroda enrolling 200 women and dividing them into four groups. Active management of 3rd stage of labor was done using one of the 4 uterotonics as per the group of the patient. The main outcome measures were the amount of blood loss, the incidence of postpartum hemorrhage and a drop in hemoglobin concentration from before delivery to 24 h after delivery.

Results Methylergometrine was found to be superior to rest of the drugs in the study with lowest duration of third stage of labor ($P = 0.000096$), lowest amount of blood loss ($P = 0.000017$) and lowest incidence of PPH ($P = 0.03$). There was no significant difference in the pre-delivery and the post-delivery hemoglobin concentration amongst the four groups with $P = 0.061$. The need of additional oxytocics and blood transfusion was highest with misoprostol as compared to all other drugs used in the study with $P = 0.037$ and 0.009, respectively. As regards side effects, misoprostol was associated with shivering and pyrexia in significantly high number of patients as compared to the other drugs used in the study while nausea, vomiting and headache were more associated with methylergometrine and ergometrine–oxytocin. However all the side effects were acceptable and preferable to the excessive blood loss.

Conclusion Methylergometrine has the best uterotonic drug profile amongst the drugs used, strongly favouring its routine use as oxytocic for active management of third stage of labor. Misoprostol was found to cause a higher blood loss compared to other drugs and hence should be used only in low resource setting where other drugs are not available. The role of misoprostol in third stage of labor needs larger studies to be proved.

Keywords Uterotonics · 3rd stage of labor · Post-partum hemorrhage · Brass-V drapes

Introduction

PPH is the most serious complication in obstetric practice. The greatest number of maternal deaths from hemorrhage

Gohil J. T., Associate Professor · Tripathi B., Senior Resident
Department of Obstetrics and Gynecology,
S.S.G Hospital & Medical College, Gujarat,
Baroda 390010, India

Gohil J. T. (✉)
D-S-1, Maniba Park, Sussen, Tarsali Road, Gujarat,
Baroda 390010, India
e-mail: aj_gohil@yahoo.com

is due to PPH, which is almost entirely a preventable condition. PPH occurs in approximately 4% of vaginal deliveries, and estimates are that it causes significant morbidity and 25% of all the maternal child birth related deaths [1]. The WHO defines PPH as blood loss of 500 ml or more in first 24 h post partum [2]. Postpartum blood loss is difficult to evaluate especially in developing country like India where most of the women are anaemic with poor reserve and this conditions are further aggravated by increased demand during pregnancy and blood loss during 3rd stage of labor [3]. The days of expectant management, the so called "hands off" [4] approach seems to be over, in view of serious consequences of PPH. An attempt was hence made to study the efficacy of various oxytocics i.e. oxytocin, methylergometrine, syntometrine and misoprostol in reducing blood loss in active management of third stage labor, at the Department of Obstetrics and Gynecology, SSG hospital and Medical College, Baroda.

Aims and Objectives

To study the effect of injection oxytocin 10 IU intramuscular, tablet misoprostol 400 μgms per rectally, injection Syntometrine (0.5 mg methylergometrine + 5 IU oxytocin) intramuscular, injection methylergometrine 0.2 mg intravenously on reducing blood loss in third stage of labor, duration of third stage of labor, effect on hemoglobin of the woman, need of additional oxytocics or blood transfusion and associated side effects and complications.

Material and Method

A prospective non-randomized uncontrolled clinical trial was carried out in the Department of Obstetrics and Gynecology, SSG Hospital and Medical College, Baroda from June 2007 to June 2008. Total 200 women were enrolled in the study. Women were allotted to one of the 4 groups once they fulfilled all the selection and exclusion criteria such that every 5th woman was in the same group. Active management of 3rd stage of labor was done in Group A with tablet misoprostol 400 μg per rectal, Group B with injection oxytocin 10 IU intramuscular, Group C with injection methyl ergometrine 0.2 mg intravenously and Group D with injection syntometrine (methyl ergometrine 0.5 mg + oxytocin 5 IU).

Women with singleton pregnancy, between 37 and 42 week of gestation, anticipated vaginal delivery, vertical lie, no high risk factors and ready to give written and informed consent were enrolled in the study. While women with hemoglobin <8 gm%, pregnancy induced hypertension, abruptioplacentae/Marginal placenta previa/lowlying, placenta, multiplepregnancy, grandmultipara, malpresentation, polyhydramnios, previous uterine scar, chorioamnionitis, prolonged labor, intra uterine fetal death, coagulation abnormalities. History of medical disorder—Asthma/epilepsy/heart or renal disease were excluded from the study. On admission to labor room, hemoglobin and blood grouping was done. All the women were followed through the 1st and 2nd stage of labor. After this calibrated BRASS $V^{(R)}$ DRAPE [5] was kept under the buttocks of the patient in such a way that whatever blood used to come out was collected in the receptacle. Cord was clamped and cut immediately, and baby handed over to pediatrician.

The residents avoided traction on the umbilical cord, until there was evidence of placental separation. As soon as signs of placental separation appeared the placenta was delivered by controlled cord traction. Time interval between the delivery of the baby and the placenta was noted. Duration of the 3rd stage was thus calculated. Pulse rate, temperature and blood pressure were recorded 1 h after delivery. Patient was kept in labor room under observation for a period of 2 h any complaint such as nausea, vomiting, fever, headache, chills, diarrhoea and shivering was noted. In case of marked bleeding and uterus remaining flabby, uterus was massaged and inj. $PGF_2\alpha$ 250 mg intramuscular was given. Blood transfusion given if required. Inspection of vulva for perineal tears and per-speculum examination for cervical tear was carried out and if present patients were not taken into series. A repeat hemoglobin estimation was done and 2nd post-partum day after 24 h. The statistical analysis was performed using student's t test for continuous variables and the χ^2 and fisher's exact test for categorical data. P value of <0.05 was considered statistically significant. Data were calculated as means, standard deviations (SD), numbers and frequency (%).

Results

The women in all the four groups were comparable as regards their age, weeks of gestation and mode of onset of labor. (Table 1).

There was no statistically significant difference amongst the groups as regards the duration of first and second stage of labor with P value of 0.11 and 0.43, respectively for stage one and stage two of the labor, showing that the groups were comparable as regards the 1st and 2nd stage of labor. The duration of third stage of labor was significantly reduced with methylergometrine with $P = 0.000096$ and lowest amongst the drugs used in the study. Methylergometrine given intravenously has immediate action and hence maximum reduction in duration of 3rd stage of labor.

Table 1 Demographic variables of the women

Parameters	Misoprostol ($N = 50$)	Oxytocin ($N = 50$)	Methyl-ergometrine ($N = 50$)	Oxytocin-ergometrine ($N = 50$)	P value	χ^2 value
Mean age (years)	25.7	24.1	24.8	25.1	0.18	1.6
Average weeks of gestation during delivery (± SD)	38.2 ± 1.022	38.2 ± 0.77	39.1 ± 0.99	39 ± 0.98	0.113	2.07
Mode of labor						
Induced labor	8(16%)	7(14%)	7(14%)	9(18%)	0.93	0.42
Spontaneous labor	42(84%)	43(86%)	43(86%)	41(82%)		

Student's test $P > 0.05$ not Significant for all of the above

SD standard deviation, *N* number of women

Misoprostol given per rectally has delayed onset of action and hence longer duration of 3rd stage of labor compared to methylergometrine. A study by Bamigboye et al. [6] compared rectal misoprostol with synometrine for the management of third stage of labor and found the same results. Ng et al. [7] carried out a multicentre randomized control trial of oral misoprostol and intramuscular Syntometrine in the management of third stage of labor. There was no significant difference between the two groups in the mean blood loss, incidence of PPH and fall in hemoglobin concentration. Need of additional oxytocic was higher in misoprostol (RR = 1.62) group but manual removal of placenta was reduced (RR = 0.29). Shivering and pyrexia was more common in the misoprostol group. Sanjay rao et al. [8] compared effectiveness of tablet misoprostol 400 μg orally to that of intramuscular oxytocin, 0.5 mg IV methylergometrine and 125 μg of intramuscular $PGF_2\alpha$ after the delivery of the baby. The results were compared in terms of fall in haemoglobin levels, mean duration of third stage of labor, amount of post partum hemorrhage and the need of additional oxytocics. The results were comparable in all the four groups.

The average amount of the blood loss with the four drugs in the present study was 355, 281, 243 and 260 ml, respectively with misoprostol, oxytocin, methylergometrine and ergometrine–oxytocin combination with $P = 0.000017$, showing that of the drugs used methylergometrine is the most effective drug in reducing the blood loss in third stage of labor. Of the drug used intravenous methylergometrine is the most effective drug in reducing the 3rd stage blood loss. The reduction in blood loss is particularly important in our country where most of child bearing population is anaemic. This reduction in blood loss reduce the incidence of post partum anaemia, infection and hence morbidity.

Considering PPH as a blood loss of ≥500 ml, 20% patients given misoprostol developed PPH as compared with 10, 4, 6%, respectively with group B, C and D with $P = 0.03$ (<0.05), which is statistically significant. Thus among the four methylergometrine was found to have the lowest blood loss, strongly favouring its routine use as oxytocic for active management of third stage of labor. There was no significant difference in the pre-delivery and the post-delivery hemoglobin concentration amongst the four groups with $P = 0.061$. E1Rafaey et al. [9] also reported no significant differences between misoprostol and oxytocin when comparing the drop in haemoglobin concentration. This can be explained by hemodilution that occurs during pregnancy so as to compensate for the loss during pregnancy. The post partum values of haemoglobin shows variable difference in different mothers hence we calculated the percentage difference, which was also not significant. The results of our study were comparable with that of the other studies. Mcdonald and Abbott (2007-cochrane review) [10] compared effects of oxytocin with ergometrine–oxytocin in reducing risk of PPH (i.e. blood loss of 500 ml) and found that ergometrine–oxytocin was associated with small reduction in the risk of PPH (odds ratio = 0.82) but more of nausea, vomiting and hypertension. Parson et al. [11] compared rectal misoprostol 800 μg versus oxytocin 10 IU intramuscular with delivery of anterior shoulder. The results were compared in terms of change in haemoglobin concentration before and after delivery, need of additional oxytocics, estimated blood loss, transfusion and medication side-effects. The results were comparable in both the groups.

Assessment of blood loss by visual estimation has shown to underestimate the true blood loss. A more objective method would be an assessment of the hematocrit concentration as suggested by ACOG. This is however not adopted in our study due to lack of resources. The need of additional oxytocics and blood transfusion was highest with misoprostol as compared to all other drugs used in the study with $P = 0.037$ and 0.009, respectively. The late absorption of rectal Misoprostol delays its effect in controlling hemorrhage during 1st hour of delivery leading to more need of oxytocic as compared to intravenous methylergometrine, which has immediate onset of action requiring rarely any additional oxytocic. Methylergometrine is associated with equal or lower blood loss as compared to oxytocin and ergometrine–oxytocin in most of the studies and hence should be a preferred drug for prevention

Table 2 Events in labor

	Misoprostol ($N = 50$)	Oxytocin ($N = 50$)	Methyl-ergometrine ($N = 50$)	Oxytocin-ergometrine ($N = 50$)	P value
Stage 1 (h) ± SD	9.27 ± 1.68	8.98 ± 1.90	8.79 ± 1.61	9.49 ± 1.55	0.11
Stage 2 (min) ± SD	28.41 ± 8.2	28.32 ± 7.76	27.56 ± 5.14	29.8 ± 5.97	0.43
Stage 3 (min) ± SD	7.84 ± 3.19	8.94 ± 4.18	7.18 ± 3.10	10.92 ± 5.92	0.000096
Amount of blood loss(ml) ± SD	355 ± 115.72	281 ± 131.27	243 ± 121.22	260 ± 140.49	0.000089
Blood loss of ≥500 ml	10(20%)	5(10%)	2(4%)	3(6%)	0.03
Pre delivery Hb1 (average)	10.23	10.04	10.08	10.52	
Post delivery Hb2 (average)	9.51	9.41	9.51	9.93	
Average difference Hb (1, 2) ± SD	0.72 ± 0.315	0.63 ± 0.30	0.57 ± 0.32	0.59 ± 0.32	0.06
Percentage difference Hb (1–2)/Hb × 100 ± SD	7.13% ± 3.39	6.49% ± 3.63	5.84% ± 4.04	5.67% ± 2.68	0.14
Need of additional Oxytocic	10(20%)	5(10%)	2(4%)	3(6%)	0.037
Need of blood transfusion	7(14%)	1(2%)	1(2%)	2(4%)	0.02

Table 3 Comparison of the side effects caused by the drugs

	Group A misoprostol ($n = 50$)	Group B oxytocin ($n = 50$)	Group C Methyl-ergometrine ($n = 50$)	Group D Oxytocin-ergometrine ($n = 50$)	P value (χ^2 value)
Headache	1	0	4	5	0.21(2.27)
Hypertension(BP ≥ 140/90 mmHg)	1	1	5	5	0.12(5.67)
Nausea	1	1	10	7	0.0002(14.1)
Vomiting	2	1	9	7	0.01(10.43)
Pyrexia >38°C	8	0	0	1	0.01(4.4)
Shivering	10	3	2	1	0.003(13.59)
Diarrhoea	3	0	0	1	0.61(0.26)

of PPH if not contraindicated. (Table 2). Hence role of misoprostol in third stage of labor needs larger studies to be proved.

There was increased frequency of headache in patients given methylergometrine and ergometrine–oxytocin. Ergotamine is the most potent vasoconstrictor. The dehydrogenated amino acid alkaloids are powerful alpha-adrenergic blocking agents, hence causing headache. Methylergometrine and ergometrine–oxytocin were associated with rise in blood pressure though the incidence is low and not statistically significant with $P = 0.12$. However, since hypertensive patients were not included in series, no untoward effect was seen due to this rise in blood pressure. There was higher incidence of nausea and vomiting in patients given ergometrine–oxytocin and methylergometrine as compared to other drugs. Ergotamine increases peristaltic activity and can potentate the action of neostigmine on the gut and hence causing nausea and vomiting. Misoprostol caused significantly higher rate of pyrexia and shivering ($P = 0.01$ and 0.003) as compared to other drugs used in the study. Shivering after misoprostol is due to centrally mediated PGE_1 effect associated with thermoregulatory physiology. Also the staffs were aware of the side effects leading to assessment bias. Diarrhoea was also caused more frequently with misoprostol. However the difference was not statistically significant. Lumbiganon et al. [12] report that though this may be of limited clinical concern, it can make the obstetrician suspicious of infection and cause unnecessary tests or initiation of antibiotic therapy. They also report a dose-related modest difference of 15% reduction in shivering when 400 mg is used instead of 600 mg. The advantages of the rectal route of misoprostol are less gastrointestinal side effects and advantageous especially in patients under anaesthesia and not able to tolerate orally. However, none of the side effects were life threatening or serious rather most of them subsided with 6–8 h post partum and very few patients actually required some treatment to alleviate them. These side effects are acceptable and preferable to excessive bleeding. Administration of the drug post-delivery should be done after proper counselling to mother regarding its side effects and their benign course (Table 3).

Conclusion

The main interest of the study was in trying to substitute intravenous methylergometrine and intramuscular oxytocin and ergometrine–oxytocin with per rectal misoprostol was to avoid use of intravenous canulas and needles which is most relevant in country like ours with a high incidence of HIV infection and where use of disposable needles and IV canulas are currently unattainable. Vaginal route of misoprostol has been used for termination of pregnancy but as this route is not feasible after delivery rectal route was chosen which also has practical advantage of ease of administration in the patients who are vomiting or unable to take orally or are under anaesthesia. Amongst the four drugs oxytocin had the least side effects and maximum benefits. Rectal misoprostol is superior to oral route for limiting the side effects while maintaining the uterotonic effects and can be considered as a uterotonic for third stage of labor only if methylergometrine or oxytocin cannot be used consistently and appropriately for various reasons like drug shortage, staff not knowing intravenous/intramuscular administration, storage and refrigeration problem etc.

The two major limitations of the study were, first the trial was not double blinded leading to biased results and secondly inability to eliminate the use of additional oxytocics and blood transfusion that results in a probability of masking the drop in hemoglobin concentration. Methylergometrine has the best uterotonic drug profile amongst the drugs used, strongly favouring its routine use as oxytocic for active management of third stage of labor. Misoprostol was found to cause a higher blood loss compared to other drugs and hence should be used only in low resource setting where other drugs are not available. The role of misoprostol in third stage of labor needs larger studies to be proved.

References

1. Maughan KL, Heim SW, Galazka SS. Preventing post-partum hemorrhage: managing the third stage of labour. AAFP. 2006;73(6):1025–8.
2. Fenton JJ, Baumeister LM, Fogarty J. Active management of third stage of labour among American Indian women. Fam Med. 2005;37(6):410–4.
3. Justus Hofmeyr G, Sandra Ferreira V, Nikodem C, et al. Misoprostol for treating post partum hemorrhage: a randomized controlled trial [ISRCTN72263357]. BMC Pregnancy childbirth. 2004;4:16.
4. Prendiville WJ, Elbourne D, Mc Donald S. Active versus expectant management in third stage of labour. Cochrane Database system Rev. 2000;(3):CD000007.
5. Patel A, Goudar SS, Geller SE, et al. Drape estimation vs. visual assessment for estimating postpartum hemorrhage. Int J Gynecol Obstet. 2006;95(3):312.
6. Bamigboyee AA, Merell DA, Hofmeyr GI, et al. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Acta Obstet Gynecol Scand. 1998;77:178.
7. Ng PS, Chan AS, Sin WK, et al. A multicentre randomized controlled trial of oral misoprostol and intramuscular syntometrine in the management of third stage of labour. Human Reprod. 2001;16(1):31–5.
8. Rao SB, Fonseca M, Ajmera S, et al. Is oral misoprostol a promising alternative to standard oxytocics in third stage of labour? Bombay Hosp J. 2002;44(1):30–5.
9. El-Refacy H, O'Brein P, Wale M, et al. Misoprostol in third stage of labour. Br J Obstet Gynecol. 1997;104:336–9.
10. Mac Donald SJ, Abbott JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for third stage of labour. Cochrane database of systematic reviews 2007.
11. Parsons SM, Walley RL, Crane JM, et al. Rectal misoprostol versus oxytocin in the management of third stage of labour. J Obstet Gynecol. 2007;29(9):711–8.
12. Lumbiganon P, Villar J, Gilda Piaggio A, et al. Side-effects of oral misoprostol during the first 24 hours after administration in the third stage of labour, BJOG, an international. J Obstet Gynecol. 2002;109:1222–6.