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A randomised control study: To evaluate the effect of oxytocin plus misoprostol versus oxytocin or misoprostol alone in reducing blood loss at cesarean section

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Abstract
Purpose: To compare the effect of oxytocin plus misoprostol versus oxytocin or misoprostol alone in reducing blood loss at ceasarean section.
Methods: This randomized control study included 126 primigravida patients undergoing lower segment cesarean section under spinal anesthesia and fulfilling selection criteria. Patients were randomly allocated to one of the three groups to receive 20 IU infusion of oxytocin (Group-O), 400 µg sublingual Misoprostol tablet (Group-M) or 200µg Misoprostol tablet plus 10 IU infusion of oxytocin (Group-M+O) after delivery. The main outcome measures-Blood loss, Heamoglobin values measured both before and 24 hr following surgery, adverse effects were recorded.
Results: There Mean blood loss during surgery was significantly less in combined lower doses of oxytocin plus misoprostol in compared to using higher doses of oxytocin and misoprostol alone (p<0.001). Mean haemoglobin changes significantly less in M+O group in compared to other group(P<0.001).
Conclusion: The combined use of lower dose of oxytocin plus misoprostol significantly decrease the amount of blood loss during and after cesarean section and minimal side effects compared to higher dose of oxytocin and misoprostol alone.

Keywords: Misoprostol oxytocin postpartum haemorrhage blood loss caesarean spinal anesthesia

Introduction

Postpartum period is a time of relief and joy for all involved but there are potential danger links for mother during this period. Among three stages of labor, mortality and morbidity mostly occur in the third stage of labor (As a result of PPH) [1]. Postpartum heamorrhage is an important cause of maternal mortality, accounting for nearly one quarter of all maternal deaths worldwide. Atonicity is the most common cause [2]. Postpartum heamorrhage is defined as any amount of bleeding from or into the genital tract following birth of the baby upto the end of the puerperium, which adversely affects the general condition of the patient evidenced by rise in pulse rate and falling blood pressure is called postpartum hemorrhage [3]. PPH has also been defined as either a 10% change in the haematocrit between admission and postpartum period or a need for blood transfusion [4].

Postpartum heamorrhage is defined as blood loss of >500 ml after vaginal delivery or a loss >1000 ml after caesarean delivery and >1500 ml after caesarean hysterectomy [5].

Etiology of postpartum heamorrhage-[6].

a. Atonic PPH (80 to 85%)
b. Traumatic PPH (20%)
c. Retained product of conception
d. Combination of traumatic and atonic causes.
e. Blood coagulation disorders

Heamorrhage remain the leading cause of maternal mortality, accounting for approximately 25% of deaths [7]. It has now been accepted that in order to decrease the incidence of PPH and its morbidity various measures are needed to be accepted. Use of uterotonics play an important role in management of atonic PPH. There are three main group of oxytocic drugs: Oxytocin, Ergot Alkaloids, and Prostaglandins. Incidence of fatal PPH has decreased because of active management of third stage of labour, which includes controlled cord traction, uterine fundal massage and administration of pharmacological uterotonic. These includes oxytocin, ergometrine, and prostaglandins [8]. Uterotonics, helps in preventing or stopping excessive blood loss from an atonic uterus during caesarean section [9].

Misoprostol is used in obstetrics and gynaecology, for induction of labour, cervical ripening before surgical procedures, and the treatment of postpartum haemorrhage. Misoprostol's advantages over other synthetic prostaglandin analoges are its low cost, long half-life, heat stability, and worldwide availability [10].

Oxytocin is a short amino-acid polypeptide hormone used to stimulate uterine contractions [11]. Although oxytocin is the gold standard drug for prevention and treatment of pph, it requires cold storage, sterile equipments and trained personale [12]. A synergistic effect of two agents allow a reduction in dose for both agent and therefore limit the side effects while improving the efficacy. The combined use of lower dose of oxytocin and misoprostol decrease the blood loss after cesarean section with minimal side effects compared to oxytocin infusion and misoprostol alone.

Aim & Objectives

To compare the effect of oxytocin plus misoprostol versus oxytocin or misoprostol alone in reducing blood loss during cesarean section.

Material and Methods

This Prospective hospital based randomized control study was conducted in Department of Obstetrics & Gynaecology, SMS Medical College, Jaipur (Rajasthan) from January 2016 to February 2017. Obtaining informed and written patient consent.

One hundred twenty six primigravida singleton term pregnancy undergoing lower segment cesarean section under spinal anesthesia and fulfilling selection criteria was included in the study. Exclusion criteria included women with any risk factor of postpartum heamorrhage i. e. Anemia, Antepartum Heamorrhage, Poly-Hydramanios, Pregnancy induced hypertension, Multiple pregnancy, Bronchial asthma, Diabetes Mellitus, Previous caeserian section, Fibroid uterus, Heart disease, Liver disease, Renal disorders, Coagulation abnormalities. Patients were randomly allocated to one of the three groups of 42 each by chit method. The Oxytocin group (Group-O) received 20 IU infusion ofoxytocin in 500cc ringer lactate solution at the rate of 500 cc per hr and The Misoprostol group (Group-M) received 400 µg sublingual Misoprostol tablet after delivery. The combined misoprostol-oxytocin group (group M+O) received 200 µg Misoprostol tab plus 10 IU infusion of oxytocin in 500cc ringer lactate at the rate of 500 cc per hr after delivery. The main outcome measures were the determination of blood loss at ceasarean section, change in heamoglobin levels and drug related side effects. The determination of blood loss by measuring volume of blood in the suction bottle and blood soaked sponges. Heamoglobin values were measured both before and 24 hr following surgery. The sample size is calculated at 80% study power and α- error of 0.05 assuming standard deviation of 109.1 ml blood loss as found in seed article [The Journal of Obstetrics and Gynaecology of India (November-December 2015) 65(6):376-381]. For minimum detectable difference of 75 ml in blood loss 42 patients in each group are required as sample size. All the data collected was analyzed. Statistical analysis was performed using chi-square test for qualitative data and student t test was used for quantitative data.

Result

This study was conducted in the department of Obstetrics and Gynaecology, SMS Medical College Jaipur (Rajasthan) from January 2016 onwards. One hundred twenty six primigravida patients undergoing lower segment cesarean section under spinal anesthesia and fulfilling selection criteria was included in the study.

Table 1: Comparison of Mean Blood loss (ml) among the Study Groups

Group	N	Mean	Std. Deviation
Group M	42	290.8	35.16
Group O	42	291.1	34.58
Group M +O	42	250.1	28.48
Multiple comparison	M vs O	M vs M+O	O vs M+O
P value	0.973	<0.001	<0.001

ANOVA test: F=21.56 at 125 degree of freedom; *P*<0.001(S)

Table 2: Comparison of Mean Haemoglobin change (gm/dl) among the Study Groups

Group	N	Mean	Std. Deviation
Group M	42	0.99	0.27
Group O	42	0.92	0.28
Group M +O	42	0.51	0.27
Multiple comparison	M vs O	M vs M+O	O vs M+O
P value	0.267	<0.001	<0.001

ANOVA test: F=37.25 at 125 degree of freedom; P<0.001 (S)

Table 3: Side effects observed among the Study Groups

Complication	Group M	Group O	Group M+O	P value*
Nausea	5(11.9%)	5(11.9%)	3(7.1%)	0.710 (NS)
Vomiting	3(7.1%)	0(0%)	2(2.8%)	0.233(NS)
Dyspnea	0(0%)	1(2.4%)	0(0%)	0.365(NS)
Shivering	6(14.3%)	1(2.4%)	2(4.8%)	0.081(NS)
Fever	7(16.7%)	0(0%)	0(0%)	<0.001(S)
Chest pain	0(0%)	5(11.9%)	1(2.4%)	0.025(S)

Table 1 shows the mean blood loss in ml was significantly lower in group M+O (250.1±28.48 ml) than in group M (290.8 ± 35.16 ml) and in group O (291.1 ± 34.58 ml). (p<0.001) Table 2 shows the haemoglobin decrease slightly after birth in all three groups, but the mean decline of haemoglobin in group M+O (0.51±0.27gm/dl) was smaller than that in group M change (0.99 ± 0.27 gm/dl) and in group O(0.92 ± 0.28gm/dl) (p<0.001). The mean decline of haemoglobin between the three groups were statistically significant (*P*<0.001). Table 3 shows, no significant difference in terms of intraoperative and postoperative side effects including nausea, vomiting, dysnoea shivering and chest pain were found in three groups but incidence of pyrexia higher (16.7%) in group M it was found to be statistically significant i. e. p<0.001.

Discussion

This study demonstrated that the amount of blood loss during and after caesarean section was significantly lower in combined use of lower doses of oxytocin and misoprostol in compared to using higher doses of oxytocin and misoprostol alone, and combined use of lower doses of oxytocin and misoprostol was not associated with any serious side effects. The mean decline of haemoglobin in group M+O significantly was smaller than that in group M and in group O.

Mean blood loss was 290.8±35.16 ml in group M and 291.1±34.58 ml in group O and 250.1±28.48 ml in group M+O. There is no significant difference in blood loss in misoprostol or oxytocin alone given in patients. There was less blood loss in combined use of lower doses of oxytocin and misoprostol in compared to using higher doses of oxytocin and misoprostol alone.

Our finding also were consistent with Pakniat H *et al* (2015) study, which reported that the mean blood loss during surgery was significantly lower in group MO compared to other groups (P=0.04) [14]. Madhuri Alwani *et al* (2014) study which reported that there was no significant difference between the two groups about in incidence of PPH. They concluded that Misoprostol may be considered as an alternative for oxytocin in low resource clinical settings. (P=0.04) [15]. J Hua, *et al* (2013) conducted a study that a meta-analysis comparing the efficacy of misoprostol with that of oxytocin in reducing blood loss during caesarean section They concluded that The results suggest that misoprostol is as effective as oxytocin for reducing blood loss during caesarean section [17].

Mean haemoglobin change 0.99±0.27 in group M and 0.92±0.28 in group O and 0.51±0.27 in group M+O. It is statistically significant *P*<0.001. Post op haemoglobin decreases in all these three groups but individually in group M and group O decrease in haemoglobin is statistically is not significant when compared to each other but statistically significant when group M+O separately compared to group M and group O *P*<0.001.Mean haemoglobin changes significantly less in M+O group in compared to group M and group O. Our finding also were consistent with Pakniat H *et al* (2015) study which reported that hemoglobin decreased slightly after birth in all of three groups, but the mean decline of hemoglobin in MO group was smaller than that in the O group and in the M group. The difference of the mean decline of hemoglobin between the three groups were statistically significant (*P*=0.001) [14]. Fazel MR1, *et al* (2013), Savita Rani Singhal *et al* (2010) and Robert L Walley *et al* (2000) also conducted a study that decrease in hemoglobin level in the two groups was not statistically significant [16, 18, 19].

In our study no significant difference in terms of intraoperative and postoperative side effects including nausea, vomiting, dysnoea shivering and chest pain were found in three groups but incidence of pyrexia higher (16.7%) in group M it was found to be statistically significant i. e. *p*<0.001. Our finding also were consistent with Essam Rashad Othman *et al* (2016) study which reported that the major side effect was shivering and Minor side effects were fever, diarrhoea and rigors less in rectal group 12.94% as compared to sublingual group 32.35% [13]. J Hua, *et al* (2013) conducted a study that the incidence of postoperative shivering/pyrexia was significantly higher in the misoprostol group, compared with the oxytocin group [17]. Owonikoko KM *et al* (2011) conducted a study that The incidence of adverse effects like shivering/pyrexia was significantly higher in the misoprostol group than in the oxytocin group *P*<0.001 [9]. Postpartum haemorrhage is an unpredictable and rapid cause of maternal death worldwide. Uterine atony is the most common cause of postpartum haemorrhage. It is perhaps the most amenable to prevent also.

Conclusion

Based on the data found in our study we observed that a synergistic effect of two agents allow a reduction in dose for both agent and therefore limit the side effects while improving the efficacy. The combined use of lower dose of oxytocin plus misoprostol decrease the blood loss after cesarean section with minimal side effects compared to oxytocin infusion and misoprostol alone in higher doses.

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