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ROLE OF SUBLINGUAL MISOPROSTOL FOR PREVENTION OF POST PARTUM HAEMORRHAGE DURING CAESAREAN SECTION

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Abstract:

Post-Partum hemorrhage remains the leading cause of maternal deaths worldwide & in low income countries. Increasing rate of caesarean section leads to increase in incidence of PPH as it is one of the predisposing risk factor for development of PPH. Misoprostol is inexpensive, easily available and has been broadly studied in the prevention and treatment of PPH after vaginal delivery; however, its use in conjunction with Cesarean section is not investigated much. The objective of our study was to compare the efficacy and safety of sublingual misoprostol in prevention of post-partum hemorrhage during caesarean delivery with conventional uterotonic agent Oxytocin 30 I U infusion slowly given intravenously.

*The **primary outcome measures** were to measure the mean intraoperative and postoperative blood loss, the mean decrease in Hemoglobin, andhematocrit and the use of any additional uterotonic agents. **Secondary outcome measures need** of blood transfusion, any surgical intervention needed for PPH including hysterectomy, B-Lynch, uterine packing, or any other procedure and length of stay in hospital.*

***DESIGN;** A randomized clinical trial conducted at Zia Uddin Hospital Karachi, Pakistan.*

***METHOD:**. Two hundred fourteen (214) pregnant women delivering by cesarean section, divided in two groups.*

Group A :women received sublingual misoprostol 600 microgram at the delivery of baby by C/Section on the time of cord clamping and Oxytocin 30 units in 1000ml of Ringer Lactate slow IV infusion .

Group B :women received 30 units of Oxytocin infusion only. Visual assessment of blood loss was calculated by measuring blood in suction apparatus and weighting of sterile swabs and gauze. Blood loss was calculated based on hemoglobin& hematocrit levels before and after caesarian section.

RESULT:

GROUP A

Intra-Operative (2.91 ± 1.575 VS 3.08 ± 1.760) and post-operative blood loss (1.62 ± 0.832 VS 2.01 ± 0.966) was reported reduced in Group A.The post-operativehemoglobin was better as compared to group B. There were less use of other uterotonic agents and blood transfusion in group A woman. No additional surgical procedure for prevention and treatment was needed in any women of group A.

GROUP B.

intraoperative blood loss was higher. Calculated hematocrit post operatively were reduced (10.68 ± 0.941 VS 9.71 ± 0.833). There was need of additional uterotonic agents (21%)and surgical procedures (7%) to prevent severe hemorrhage in this group. Blood transfusion was needed in 13 % patients.

CONCLUSION:

Misoprostol reduced blood loss during and after caesarean section significantly thus reducing the incidence of postpartumhemorrhage,blood transfusions and severe maternal morbidity.

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INTRODUCTION:

Post Partum hemorrhage remains the leading cause of maternal deaths worldwide & in low income countries and is arguably preventable[1]. Its prevention is assumed to be an important and rational strategy, and has been identified as a key component of safe motherhood. The risk of PPH is much higher for women undergoing cesarean delivery (CD)[2]. The American Congress of Obstetricians and Gynecologists (ACOG) defines PPH as the loss of more than 500 mL of blood after vaginal delivery and the loss of 1,000 mL or more after CD[3].Excessive blood loss is estimated by a 10% drop in the hematocrit value post delivery or by need for blood transfusion. This occurs in approx. 4% of vaginal & 6% of caesarean[4].

Based on world health organization data, probability of maternal mortality caused by postpartum hemorrhage is 1 in 1000 deliveries in developing countries, including Ethiopia. According to two different studies which were done in Jima and Kersa revealed that postpartum hemorrhage was the first leading cause of maternal mortality which accounts for 54% and 46.5% maternal mortality respectively[5]. According to the Pakistan Demographic and Health Survey of 2006-2007, 27.2% of maternal deaths were caused by PPH[6].

Increasing rate of caesarean section worldwide leads to increase in incidence of PPH. caesarean section is one of the predisposing risk factor for development of PPH. Cesarean delivery, often performed because of "dystocia", may predispose a patient to uterine atony. This has been traditionally attributed to either myometrial fatigue or impaired contractility at the site of the uterine incision. Oxytocin is regarded as the gold standard uterotonic agent[7] but only has a half-life of 4–10 min[8] therefore, at cesarean section oxytocin must be administered as a continuous intravenous infusion to attain sustained uterotonic activity throughout the surgical procedure and immediate postpartum period. However, despite its effectiveness, 10–40 % of women need additional uterotonic therapy [7-8]. Secondary uterotonic agents such as methyl ergometrine or 15-methyl prostaglandin F 2 Alpha are associated with adverse effects when administered within a dose range likely to be effective[7-9]. Oxytocin causes tachycardia, hypotension, and negative inotropic effect and has an antidiuretic action.

Misoprostol is a prostaglandin E1 analog proven in several randomized controlled trials to be effective in preventing PPH because of its strong uterotonic effects [10]. In addition, Misoprostol is inexpensive, stable at room temperature, and easy to administer Because of its uterotonic properties, Misoprostol has been evaluated for both the prevention and the treatment of postpartum hemorrhage [11]. It is readily absorbed when given by oral, sublingual, buccal, vaginal, or rectal route. Its easy availability, relatively low cost, thermo stabilitylong shelf life, and ease of administration, all of which appear to make it particularly suitable for use in low resource settings in developing countries. In addition, Misoprostol is inexpensive, stable at room temperature, and easy to administer. Misoprostol has been broadly studied in the prevention and treatment of PPH after vaginal delivery; however, its use in conjunction with Caesarean section has not been investigated as much [11].The sublingual route is recognized as having the greatest benefit due to its rapid uptake, long-acting effect, and greatest bioavailability compared with other routes of Misoprostol administration [12].However, Misoprostol has limited side effect, for example fever, shivering, and nausea, which are transient & dose dependent[13]. The main objective of this study was to see the role of Misoprostol in prevention of PPH in caesarean deliveries. The prevalence of primary PPH is 3.63%[14]. We wanted to prevent PPH especially after Ceasarean Section with techniques which are cost effective and easy to administer so that we reduce maternal morbidity and mortality.

OBJECTIVES:

To compare the efficacy and safety of sublingual Misoprostol in prevention of PPH during caesarean delivery with conventional uterotonic agent routinely used 30 IU oxytocin infusion slowly given IV.By this study we would be able to prevent the primary PPH which is a cause of major morbidity as well as mortality in our country by applying this described regime. It will be cost effective for the patient too as currently uncontrolled PPPH lead to

prolonged hospitalization, use of other surgical procedures or even hysterectomy which is a burden for the patient.

OPERATIONAL DEFINITIONS

PPH: BLOOD Loss of > 1000ml during CS.

INTRAOPERATIVE BLOOD LOSS: calculated by measuring blood in suction apparatus and weighting of sterile swabs and gauze.

PERIOPERATIVE HB FALL: will be calculated from preoperative and post-operative second day Hemoglobin testing.

PYREXIA: defined as temperature more than 38.0 C.

MATERIAL AND METHODS:

SETTING:

This Randomized Controlled trial was conducted at department of Obs & Gynea Ziauddin hospital Keemari and Clifton campus from Jan2018-Jan2019.The required Sample size was calculated using OPENEPI sample size calculator of about 214 patients and divided equally in two groups. Each group had 107 participants.

SAMPLE SELECTION:

INCLUSION CRITERIA:

- All women undergoing elective or emergency caesarean section under spinal anesthesia.
- Informed consent

EXCLUSION CRITERIA:

- Women with bleeding disorders,
- Caesarean section under general anesthesia
- H/o eclampsia/fits

OUTCOME MEASURES:

Primary outcome measures:

The primary outcome measures were the mean intraoperative and postoperative blood loss, the mean decrease in Hemoglobin, and hematocrit also the use of any additional uterotonic agents.

Secondary outcome measures: blood loss > 500 and >1000 ml, blood transfusion needs, mean post-operative Hemoglobin, blood transfusion needs, surgical intervention needed for PPH including hysterectomy- LYNCH, uterine packing, or any other procedure, mean postoperative Hemoglobin, length of stay in hospital,

SIDE EFFECTS, shivering, nausea, vomiting pyrexia >38, diarrhea, abdominalpain, headache.

DATA COLLECTION PROCEDURE:

After Informed consent both written and verbal, Demographic data including age, parity, education, occupation, previous obstetrical history filled in questionnaire. The calculated sample size divided in two groups, Group A women received sublingual Misoprostol 600 microgram after the delivery of baby by c/section at time of cord clamping and oxytocin 30 units in 1000 mL of Ringer lactate slow IV infusion and group B women received 30 units of oxytocin drip only after the delivery of baby by c/section at time of cord clamping. The efficacy of Misoprostol 600ug and oxytocin 30units in group one and only inj. oxytocin 30units in 1000ml of ringer lactate in group two observed in patients by loss of blood calculated by measuring blood in suction apparatus and weighting of sterile swabs and gauze.Further blood loss assessed by pre-operatively and post –operatively heamoglobins levels.

DATA ANALYSIS PROCEDURE:

After collection of data, analysis done by using statistical Package for Social Science (SPSS) software Version 20. Chi-square test applied for categorical variable and two sample t-test for continuous variables applied.

RESULTS:

Two Hundred Fourteen Women met the inclusion criteria and recruited for the study. This study comprises both the elective and emergency C/section. The Demographic data of the both groups shown in table 1.

Table 1. Demographic Characteristics of both groups:

Demographic Characteristics	Group: A Inj, Oxytocin 30units infusion + Sublingual Misoprostol 600ug n=107	Group: B Inj. Oxytocin 30units infusion n=107
Age In Groups	2.1869±1.10001	2.1963±1.12802
Gestational Age	38.1215±1.45829	38.0748±1.50283
Parity	2.5514±2.38404	2.6729±2.39014

There were no significant differences in mean age, Parity, gestational age in both groups regarding the demographic data.

Table 2. Blood Loss During and After C/Section (Primary Outcomes)

Blood Loss During and after C/Section	Group: A Inj, Oxytocin 30units infusion + Sublingual Misoprostol 600ug n=107	Group: B Inj. Oxytocin 30units infusion n=107
Intra-Operative Blood Loss	2.91±1.575	3.08±1.760
Post-Operative Blood Loss	1.62±.832	2.01±.966

The intra-operative blood loss was reported reduced in Sublingual Misoprostol + Inj.oxytocin infusion Group (2.91±1.575) as compared with Inj.oxytocin infusion group (3.08±1.760). Sublingual Misoprostol + Inj.oxytocin infusion Group reported reduction in Post-Operative blood loss (1.62±.832) as compared with Inj.oxytocin infusion group (2.01±1.966) as shown in table 2.

Table 3. Secondary Outcome measures:

Characteristics	Group: A Inj, Oxytocin 30units infusion + Sublingual Misoprostol 600ug n=107	Group:B Inj. Oxytocin 30units infusion n=107
Pre-Op Hb	11.1290±.90314	11.1000±.80891
Post-Op Hb	10.68±.941	9.71±.833

There was no any significant difference in Pre-Operative Hb in both groups but Mean Hb levels were reduced in Inj.oxytocin infusion Group (9.71±.833) as compared with Inj.oxytocin infusion+ sublingual Misoprostol group (10.68±.941) as shown in table 3 which shows that the blood loss was less in group A women & they were less anemic post operatively also.

Table 4. Adverse effects of the drugs:

Characteristics	Group: A Inj, Oxytocin 30units infusion + Sublingual Misoprostol 600ug n=107	Group: B Inj. Oxytocin 30units infusion n=107
Pyrexia	2	1
Shivering	8	4
Nausea	3	5
Vomiting	0	7

Side Effects Nausea and vomiting reported in more cases of only Inj.oxytocin infusion group as compared with Inj.oxytocin infusion + sublingual Misoprostol group. Moreover Shivering is reported more in Inj.oxytocin infusion + sublingual Misoprostol group as compared with Inj.oxytocin infusion group.

DISCUSSION:

This randomized controlled trial shows that combination of Oxytocin & misoprotol were less likely to have PPH as compared to those receiving oxytocin only.

A placebo-controlled community based trial conducted in india showed 50% reduction in PPH with misoprostol[15]. Sood et al (2012) studied the effect of misoprostol and placebo sublingual to control intra-operative blood loss, perioperativeHb change in misoprostol group was significantly lower[16] as similar occurred in our study.Kundodyiwa et al found 15.2% incidence of PPH with misoprostol[17] but in our study there was no incidence of PPH with misoprostol.

In another study of two placebo –controlled trials an adjunct use of misoprostol confirmed that there is significant reduction of blood with the use of misoprostol[18]. In our study both intra-operative and postoperative blood loss significantly reduced in misoprostol group. Lokugamage Au et al conducted randomized single blinded two centre study in south Africa,28.1% difference between misoprostol and syntocinon group,concluded that misoprostol is

better than syntocinon infusion in treating the PPH caused by uterine atony[18].

Othman ER et al conducted a randomized clinical trial,mean blood loss was significantly reduced in misoprostol group,however changes in hematocrit level (pre & post) was comparable between both group[18], the similar was in our study.

In regards of side effects, shivering was higher in misoprostol group as compared to oxytocin group in our study. In one of the study, incidence of shivering & pyrexia was more in misoprostol group[19]. Kundodyiwa et al (2001) study, shivering and fever was more in misoprostol group. In the study of Kosar Centre, application of additional oxytocin required in oxytocin group which may be due to shorter half life of oxytocin compared to misoprostol[20]. Similarly, in our study additional oxytocin required in oxytocin group. Baskett et al and Haque et al reported no case of blood transfusion need in their studies[21], as no transfusion required in any case in our study.

CONCLUSION:

Misoprostol is an effective therapy for primary PPH.However, improvements in PPH treatment, regardless of the uterotonic, should start with a timely and correct diagnosis that can lead to an appropriate case management. Women with prior exposure to prophylactic oxytocin, as well as those without exposure to oxytocin and in settings where oxytocin is not available, could all benefit from the therapeutic properties of this drug. Women undergoing cesarean section and at risk of PPH could also benefit from the efficacy of misoprostol in conjunction with oxytocin.

Conflicts OF Interest:

The authors report no conflicts of interest in this work.

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