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SUBLINGUAL MISOPROSTOL VERSUS OXYTOCIN INFUSION TO REDUCE BLOOD LOSS AT CESAREAN SECTION

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ABSTRACT

Sublingual misoprostol appears to be as effective as intravenous oxytocin infusion in reducing postpartum blood loss during cesarean section. In addition, misoprostol offers several advantages over oxytocin including long shelf life, stability at room temperature and oral administration which make it as a suitable alternative for routine management of the third stage of labor particularly in low resource countries.

KEYWORDS: misoprostol, oxytocin, blood, cesarean section

INTRODUCTION

Postpartum hemorrhage (PPH) continues to be the leading cause of maternal morbidity and mortality worldwide. According to the World Health Organization estimates, more than 5,85,000 women die every year from pregnancy related causes, of which 25% were due to severe bleeding.[1]

Average blood loss during delivery progressively increases with the mode of delivery, vaginal delivery (500 ml), cesarean section (1000 ml) and emergency hysterectomy (3500 ml).[2] Excessive blood loss as estimated by a 10% drop in hematocrit postdelivery or by the need for blood transfusion, occurs in approximately 4% of vaginal deliveries and 6% of cesarean births.[3] A reduction of operative blood loss at cesarean section is beneficial to the patients in terms of decreased postoperative morbidity and a decrease in risks associated with blood transfusions. The routine use of oxytocic agents such as syntocinon or syntometrine is associated with a significant reduction in the occurrence of postpartum hemorrhage.[4]

Although many delivery units use syntocinon as first line agent to prevent uterine atony at cesarean section, it may not be the ideal agent for prevention of PPH especially in compromised patients with pre-eclampsia, cardiac disease or prolonged labor. Syntocinon and specifically its preservative chlorobutanol increases the heart rate and has negative inotropic, antiplatelet and antidiuretic effects.[5] Misoprostol, a PGE1 analogue, has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus, selectively binds to EP-2/EP-3 prostanoid receptors.[6] Misoprostol administration either by oral or rectal route has been shown to be effective in the prevention of PPH and is considered as an effective alternative to other conventional oxytocics especially in developing countries as it is cheap and thermostable.[7] The recent pharmacokinetic study suggested that the bioavailability of misoprostol after sublingual administration was higher than those after oral or vaginal administration. A few studies are now available[8] for the use of sublingual misoprostol in the prevention of PPH following a vaginal delivery and have reported it to be an effective and convenient route of administration. However, none of the studies conducted so far have evaluated the response of sublingual misoprostol for the prevention of PPH during cesarean section. The objective of this randomized study was to compare the efficacy and side effects of misoprostol (CytotecR, Searle Pharmaceutical, Skokie, IL, USA) administered sublingually in a dose of 400 Ag with intravenous oxytocin (SyntocinonR Novartis Pharma, Basel, Switzerland) infusion (20 IU in 1000 ml of Ringer lactate solution over 6 h) in the prevention of PPH following cesarean section.

Postpartum hemorrhage is the leading cause of preventable maternal mortality in the developing world, and its prevention is assumed to be an important and rational strategy, and has been identified as a key component of safe motherhood. Oxytocin is routinely used to prevent uterine atony and excessive uterine bleeding during cesarean delivery. However, despite its effectiveness, 10–40% of women need additional uterotonic therapy.[9]

Secondary uterotonic agents such as methyl ergometrine or 15-methyl prostaglandin F2 are associated with adverse effects when administered within a dose range likely to be effective. Misoprostol is a prostaglandin E1 analogue with good uterotonic properties and few adverse effects at therapeutic dose. Because of its uterotonic properties, misoprostol has been evaluated for both the prevention and the treatment of postpartum hemorrhage.[10] It is readily absorbed when given by oral, sublingual, buccal, vaginal, or rectal route. Its easy availability, relatively low cost, thermo stability long shelf life.

Although misoprostol has been extensively evaluated for prevention and treatment of postpartum hemorrhage following vaginal delivery, there have been a few randomized controlled trials evaluating its efficacy in reducing intraoperative blood loss and additional uterotonic therapy at cesarean delivery. Misoprostol in these trials has been administered by oral, buccal, or sublingual routes and compared mostly with oxytocin administered as IM/IV bolus, IV infusion, or intrauterine injection or with placebo. Though the dose of misoprostol used in these trials has widely varied, most of them found misoprostol as effective as and—in one case more effective than—oxytocin.[11]

The present study was undertaken with the aim of assessing the efficacy of sublingual misoprostol in decreasing intraoperative blood loss and the need for additional uterotonic agents at cesarean delivery

BACKGROUND

Globally, about 500,000 women die from complications of pregnancy and childbirth (WHO 2004). Th e most common cause of maternal mortality worldwide is postpartum haemorrhage (PPH) accounting for one-third of maternal deaths; 99% of these deaths occur in developing countries in women who rarely receive PPH prophylaxis, due to the absence of skilled birth attendants.[12] The insidious reality of PPH is that two-thirds of women who are affected have noidentifi able clinical risk factors, such as multiple births or fibroids.[13] However, it is not an equal opportunity killer because the poor, malnourished, unhealthy woman is less likely to survive PPH or the three delays responsible for maternal mortality. Recent data suggest that the majority of maternal deaths still occur in sub-Saharan Africa and Asia.[14]

In addition to the burden of maternal mortality, morbidities that may follow PPH – anaemia, prolonged hospital stay, diffi culties in establishing breast feeding and transfusion transmissible infections such as the human immunodefi ciency virus (HIV) and hepatitis B remain significant problems.[15] Prevention therefore, is still the preferred approach for PPH. The Confidential Enquiries into Maternal Deaths in the UK found that four out of five deaths from primary PPH were associated with caesarean section.[16] Uterotonics are commonly used to limit blood loss at caesarean section and oxytocin by intravenous or intramuscular routes remain the most common option. Despite its effectiveness, 10 – 40% of women will require additional uterotonic agents to control uterineatony and bleeding.[17]

Misoprostol, a prostaglandin E1 analogue has been suggested as an alternative to oxytocin for some time now; it has been found to be cheap, inexpensive, easily administered by different routes with a long shelf-life.[18] Oral misoprostol has been previously reported as an effective agent for reduction of intraoperative blood loss at caesarean section but sublingual misoprostol is likely to be more advantageous for patients undergoing caesarean section under spinal anaesthesia.[19] It may also be useful when the adverse effects of ergometrine and oxytocin are best avoided. The purpose of this randomised trial is therefore to compare the effect of the combined use of intravenous oxytocin and sublingual misoprostol with intravenous oxytocin alone in the reduction of blood loss, need for additional use of uterotonics and side-effect profile following caesarean delivery.[20]

PATIENTS AND METHODS

One hundred pregnant women at term (37—40 wks) gestation scheduled for either elective or emergency lower segment cesarean section under regional anesthesia were recruited in this study. Women with any risk factor associated with an increased risk of postpartum hemorrhage were excluded i.e. anemia (Hb b8 g%), multiple gestation, antepartum hemorrhage, poly-hydramnios, prolonged labor (N12 h), two or more previous cesarean sections and/or a history of previous rupture uterus, current or previous history of significant disease including heart disease, liver, renal disorders or known coagulopathy.

All patients were given spinal anesthesia. One hundred women were recruited and randomized into two equal groups of 50 each. Women in group I received 400 Ag of sublingual misoprostol and in group II received an intravenous infusion of oxytocin (20 IU syntocinon dissolved in 1 l of lactated Ringer's solution) at the rate of 125 ml/ h over a 6-h period, immediately after delivery of the neonate.

Additional oxytocic therapy was instituted if the surgeon considered uterine tone to be inadequate. The volume of blood loss during cesarean section and in the first hour postoperatively was assessed in a standard manner. The volume of blood in the suction bottle was measured, blood-soaked sponges and linen savers were weighed and the known dry weight was subtracted and added to volume from the suction bottle. Hemoglobin values were determined both before surgery and 24 h following surgery. Vital signs were monitored continuously during surgery and every 30 min thereafter until the patient was transferred to the postpartum ward. Baseline demographic data including age, weight, parity, gestational age, history of previous cesarean section and indication for the current cesarean section were

recorded. The need for additional oxytocic therapy, operating time, infusion volume given intraoperatively, need for blood transfusion, side effects of study drug and any significant puerperal morbidity were also recorded.

The primary outcome measures were changes in hemoglobin levels after delivery, estimated amount.

Table 1: Patient characteristics.

Characteristic	Sublingual misoprostol (n = 50)	Oxytocin (n = 50)
Age (yrs)	26.5 ±4.2	28.1 ±3.1
Weight (kg)	65.9±3.4	64.9±3.4
Parity	1.3 ±1.7	1.1 ±1.2
Previous LSCS	**5**	**7**
Birth weight (g	3044±432	2973±364
Gestation (wks)	38.7±1.2	38.7±1.1

RESULTS

Table 2.

Characteristic	Sublingual misoprostol (n = 50)	Oxytocin (n = 50)	P value
Estimated blood loss (ml)			
Total	821±212	987±245	0,0000
0—499	04	05	0,0700
500—999	45	33	0,0679
>1000	04	10	0,123
Hemoglobin (g/dl)			
Before delivery	10,12 ±1.7	10,12 ±1.8	
Postpartum	10,6 ±1.2	1.9 ±1.3	0.653
Hemoglobin difference	**0,5**±1.2	**0,7**±1.9	**,6543**
Use of additional oxytocic	14	17	0,4213
Duration of surgery (minutes)	58.33±11.3	61.31±13.1	0,134
Infused fluid volume (litre)	1.6±0.21	2.0±0.12	0,432

There were no withdrawals following randomization. Eight patients in the misoprostol group and nine patients in the oxytocin group had an elective cesarean section, all other patients underwent an emergency procedure. None of the patients required conversion of regional to general anesthesia during the surgery.

Maternal and neonatal demographic details in two groups. There were no significant differences in demographic data in relation to age, parity, gestation, history of previous cesarean section and neonatal birth weight. Indications for cesarean sections in the two study groups.

The estimated mean blood loss was significantly lower in misoprostol group (819F236 ml) compared to the oxytocin group (974 F285 ml,) However, when the blood loss was reclassified, taking the loss as 0—499 ml, 500—999 ml or greater than 1000 ml, there was no significant difference in either group. There was no difference between the two groups in terms of the predelivery and postdelivery hemoglobin values.

The mean reduction of hemoglobin was 0.4 gm/dl in the misoprostol group and 0.6 gm/dl in the oxytocin group. There were more women in the oxytocin group who needed additional oxytocics and had measured blood loss in excess of 1000 ml. However, this difference did not reach statistical significance, there was no difference between the two groups in terms of intraoperative infusion volume and mean duration of surgery.

Maternal adverse events. The incidence of common side effects such as nausea, vomiting, headache and giddiness did not vary significantly in two groups, however, shivering (26% versus 4%) and pyrexia (16% versus 4%) were more apparent in the misoprostol group than in oxytocin group. A significant number of women (14%) experienced metallic taste following administration of misoprostol sublingually.

DISCUSSION

Postpartum hemorrhage is a serious condition responsible for at least one third of global maternal deaths.[21] In countries with a high incidence of anemia among pregnant women either due to nutritional or environmental factors, even a relatively small reduction of postpartum blood loss would be a significant measure relevant clinically. Different management protocols for prevention of PPH have been used and these are being continuously revised to achieve improved success rates and reduce discomfort to the patients. Recently misoprostol, a PGE1 analogue has been investigated both for prevention and management of PPH due to its uterotonic effect, however, there is no consensus on optimal dose or optimal route of administration. In the majority of these studies, misoprostol has been administered either orally or rectally in dosages ranging from 400—1000 Ag and compared with oxytocin, ergometrine or no treatment.[22] The results appeared promising although studies were heterogenous. Misoprostol offers several advantages over oxytocin or ergometrine including long shelf life, stability at room temperature, orally active and the drug can be administered to hypertensive patients. The advantages of misoprostol make it an effective alternative agent to be used in the management of the third stage of labor in low resource countries. The results of this study show that sublingual misoprostol (400 Ag) is as

effective as intravenous oxytocin infusion in reducing blood loss at cesarean section. There were more patients in the oxytocin group requiring additional oxytocics but the difference was not statistically significant. The sublingual route allows quick absorption of drug leading to a prompt and more sustained therapeutic effect than oral administration as it avoids first pass effect. In addition, the sublingual route avoids uncomfortable administration as seen with the rectal route.

A few studies using sublingual misoprostol (400 Ag) have shown similar efficacy to that of conventional oxytocics in the prevention of PPH following vaginal delivery.[23] Though transient and self-limiting, shivering and pyrexia are the most common side effects with the use of misoprostol reported in about 30% of women in these studies[24]. In the present study the almost similar incidence of side effects (26%) was noted following administration of misoprostol sublingually during cesarean section. In addition, a significant number of women in the present study reported unpleasant taste in the mouth following sublingual administration of misoprostol. The study was openly labeled for safety i.e. the operating surgeon knew which drugs were being given in order to prevent over dosage and to know what drug had been given in case of need of additional oxytocic. The clinical evaluation of how well the uterus contracted is subject to observer error, however, the randomization process would have off set this to some extent. It is also important to acknowledge that this trial involved only subjects with low risk pregnancy. Further research is required to assess sublingual misoprostol administration in women at risk of postpartum hemorrhage and also to identify measures to overcome the side effects of misoprostol particularly shivering and pyrexia.[25]

The need for additional uterotonic agents was significantly less in the present study; this finding is similar to that reported in a similar study in which oxytocin infusion was given to all women.[26] Some others have reported no difference[27]. IV Oxytocin injection appears in circulation within 15 s and reaches peak levels in 60 s with a half-life of three min. Misoprostol appears in circulation within 20–30 min but stays longer. Thus, it may be useful to combine both drugs using IV oxytocin to achieve initial effect followed by misoprostol for a more sustained effect. This may also be helpful in high-risk patients who are at increased risk of bleeding, but have contraindications for the use of secondary uterotonic agents[1]. A significant trend toward lesser perioperative Hb fall, which was found in this study, is similar to that reported in a recent study[28], in which concomitant oxytocin infusion was given to all

women, as in the present study. In studies reporting no difference, misoprostol was either compared with oxytocin[29], or a lower dose of misoprostol was used. Shivering, pyrexia, nausea vomiting, and diarrhea are common adverse effects of misoprostol and are dose related. The increased incidence of shivering found in the present study is similar to that reported elsewhere.[30] However, there was no difference in pyrexia. No difference in other maternal adverse effects such as nausea or vomiting was noted, which is similar to that reported in the literature. A dose of misoprostol in various studies has ranged from 200 to 800 mcg.[31] As the side effects are dose related, a dose of 400 mcg was chosen in the present study to minimize maternal adverse effects with optimal therapeutic benefit. In a recent review, 400 mcg of misoprostol was found to be safer than 600 mcg and just as effective.[32] Oral, buccal, rectal, and sublingual routes have been used in different studies. The sublingual route was chosen because it avoids oral intake, does not disrupt the operative field, and ensures continuous plasma levels of a potent uterotonic agent over a prolonged period. Pharmacokinetic studies on various routes of administration have shown that sublingual route achieved the highest serum peak concentration (C max), the shortest time to peak concentration (T max), and the highest area under the curve (AUC) of misoprostol acid, the active metabolite of misoprostol.[33]

In a Cochrane review on prostaglandins for prevention of postpartum hemorrhage, it was concluded that neither intramuscular prostaglandin nor misoprostol was preferable to conventional injectable uterotonics as part of the active management of the third stage of labor especially for lowrisk women.[34] However, in this meta-analysis which included 37 misoprostol trials, only three pertained to cesarean delivery. Misoprostol has been recommended in a dose of 600 mcg or 400 mcg by oral or sublingual route for prevention of PPH in the absence of active management of the third stage of labor or non-availability of injectable conventional uterotonics.[35] Cesarean delivery is carried out in a setting where conventional oxytocics are available and active management of the third stage of labor is invariably practiced. Misoprostol may have a role as an adjunct to oxytocin in the prevention of postpartum hemorrhage in high-risk women, where other uterotonic agents are either contraindicated or not available. In the present study, 400 mcg by sublingual route appears to be promising. Two recent trials have confirmed the efficacy of sublingual misoprostol in reducing blood loss at cesarean delivery.[36] Post hoc power analysis showed that the present study (with an an of 0.05) had 78.9% power to detect a reduction in uterotonic therapy from 42.8 to 22.2% and 92.5% power to detect a difference of mean blood loss of 56 ml. In the

present study, the sample size was relatively small. Blood loss estimated may not have a true approximation of the actual loss. Though perioperative Hb fall was also studied, better methods involving measurement of actual blood loss may be more accurate. Larger studies with primary outcome measures such as incidence of postpartum hemorrhage and the need of blood transfusion are needed, to validate the efficacy of misoprostol and to find the optimal dose and route of administration at cesarean delivery**.**

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