EFFECT OF SUBLINGUAL MISOPROSTOL VERSUS INTRAVENOUS OXYTOCIN ON REDUCING BLOOD LOSS AT CESAREAN SECTION

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Submitted: 24/5/2019; Accepted: 29/10/2019; Published: 21/12/2019

ABSTRACT

Background

Oxytocics are routinely used in an attempt to prevent excessive blood loss during cesarean section. Misoprostol, a potent uterotonic agent, has been reported to be useful in the prevention and treatment of postpartum hemorrhage by several investigators but its use during cesarean section has not been described.

Objectives

To compare the effectiveness of sublingual misoprostol administered immediately after delivery of the neonate at cesarean section under spinal anesthesia, with intravenous oxytocin infusion in prevention of uterine atony and thereby reducing blood loss at cesarean section and prevention of postpartum hemorrhage.

Patients and Methods

This study is a prospective, comparative randomized study. One hundred women with singleton term pregnancy undergoing elective lower segment cesarean section under spinal anesthesia were included in this study, divided into two groups each group contains 50 cases, they were randomly allocated to receive either misoprostol 400 g sublingually or intravenous infusion of 20 units of oxytocin soon after delivery of the neonate. The main outcome measures were change in PCV percentage, the need for additional oxytocic and drug-related side effects are compared in both groups in this study.

Results

The PCV percentage which estimated was non significantly lower in the oxytocin group compared to the misoprostol group (32.3± 2.9 ml versus 33.1±3.2 ml; p-value = 0.23). There was a non-significant difference in mean of time of operation between two groups (33.7±5.2 in oxytocin group versus 33.8 ±3.9 in the misoprostol group, p-value=0.91). There was a need for additional oxytocic therapy in 4 cases (8%) in the oxytocin group which is lower than the misoprostol group which was 6 cases (12%). The incidence of side effects such as nausea lower in oxytocin group 2 cases (4%) vs 8 cases (16%) in misoprostol group, shivering and hyperthermia was lower in oxytocin group 1 case (2%) compared to misoprostol group 8 cases (16%) while hypotension was more in oxytocin group 6 cases (12%) vs 3 cases (6%) in misoprostol group.

Conclusions

Sublingual misoprostol was as effective as i.v. oxytocin infusion in reducing blood loss at cesarean section, and prevent postpartum hemorrhage, it offers several advantages over oxytocin, including long half-life, stability at room temperature, and oral administration, which make it a suitable uterotonic agent in low-resource areas The drug side effects were mild, transient, not life-threatening and self-limiting.

Keywords: *Cesarean section, Oxytocin, Sublingual misoprostol, Oxytocin infusion, Blood loss.*

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https://doi.org/10.17656/jsmc.10227

INTRODUCTION

Caesarean section, also known as C-section or Caesar, is a surgical procedure in which incision are made through a mother's abdomen (laparotomy) and uterus (hysterotomy) to deliver one or more babies [1].

Confidential Enquiries into Maternal Deaths have enabled the risks associated with the different methods of delivery to be analyzed; case fatality rate for all Caesarean sections is five times that for vaginal delivery, although for elective Caesarean section the difference does not reach statistical significance [2].

Hemorrhage account for 6 percent of deaths associated with CS and unknown proportion of operative morbidity. This complication may be due to the operative procedure as a consequence of damage to the uterine vessels or maybe incidental as a consequence of uterine atony or placenta praevia [3, 4].

Postpartum hemorrhage is probably one of the most common obstetric emergencies, and the third most common cause of death after thrombosis and preeclampsia [5]. PPH is classified as primary or secondary. Primary PPH occurs within the first 24 hours after the delivery, and the secondary PPH occurs after 24 hours till 12 weeks postpartum. Others defined PPH as a 10% drop in hematocrit from admission or requiring blood transfusion [6, 7].

Primary postpartum hemorrhage (PPH) is usually defined as blood loss more than 500 ml in the first 24 hours following a vaginal birth or a loss of greater than 1000 ml following caesarean birth. Even with an accurate measurement method, the quantity of blood loss is often less important than its effect on the woman, which depend on her blood volume and any underlying health factors [8, 9]. The incidence of PPH in the developed world is 4-6% complicates vaginal deliveries [10]. While the incidence of massive postpartum hemorrhage in the UK has been reported as 6.7 per 1000 deliveries [11].

The most common cause of PPH is uterine atony (failure of contraction and retraction of myometrial muscle fiber, it accounts for 90% of cases [12], followed by genital tract trauma which accounts for 10% of cases [13]. two-third of women who have PPH have no risk factor, there, for all women are considered at risk[13].

Coagulopathy is a rare cause of postpartum hemorrhage, it may be congenital e.g Von Will brand disease, or it may be acquired which includes anticoagulant therapy, and consumptive coagulopathy resulting from obstetric complications [14].

Current standard practice for prevention PPH is a procedure called "active management of the third stage of labor". Active management is a set of clinical interventions design to speed the delivery of placenta (this normally takes 5-10min not more than 30min) and prevent uterine atony [15].

There are many maneuvers that may be employed to manage such cases, which range from bimanual compression, infusions of oxytocin and administration of 15-methyl prostaglandin F2a to conservative surgical procedures such as uterine compression sutures (B-Lynch), systemic pelvic artery devascularization, Radiographic embolization [16], to the more radical, but life-saving, hysterectomy (subtotal hysterectomy is an acceptable alternative to total hysterectomy particularly in the unstable patient [17].

Uterotonic drugs used to reduce intra operative bleeding. Oxytocin is an octapeptide hotmone (mammalian hormone) secreted from the supraoptic and paraventricular nuclei of the hypothalamus [18].

Oxytocin has a peripheral (hormonal) action, also has actions in the brain. It is peripheral hormonal action include:

1- Causes uterine contraction, which is important for cervical dilatation before birth and causes contractions during the second and third stage of labour [19] Oxytocin acts directly on myofibrils to augment the number of contracting myofibrils producing uterine contraction [19]. As pregnancy progress the number of oxytocin receptors in the uterus increase (by 100 folds at 32 weeks and by 300 folds at the onset of the labour) [20].

2- There are number of studies, which show the relationship between oxytocin and human sexual response, and the number of actions of oxytocin in the brain [21]. Oxytocin is secreted into the blood at orgasm in both sexes. In males: Oxytocin may facilitate sperm transport during ejaculation [22].

Oxytocin given as a dilute solution produced no circulatory changes; hence it is preferable to be administered in such fashion rather than by bolus injection [23].

Misoprostol is a synthetic analogue of prostaglandin E1(methyl ester of P.G.E) [24]. Misoprostol is the most interesting drug to be used recently because it is effective, inexpensive (when compared with P.G.E2) and marketed for its ulcer-healing properties [25]. Misoprostol exerts its effects on the gastrointestinal mucosa by increasing bicarbonate secretion and by increasing mucosal blood flow [26]. Also, misoprostol

inhibits the secretion of acids [27].

Naturally occurring PG E1 is ineffective after oral administration because it is unstable in an acid environment. It is also quickly degraded when administered parentally giving in to practice clinical utility [28]. It is originally developed for the treatment of peptic ulcer licensed for oral use [29]. In July 2003, Gynuity Health project and family care international launched an initiative to evaluate misoprostol as alternative therapy for postpartum hemorrhage prevention and bringing misoprostol to market, assist in registering the drug for these indications [30].

The aim of this study is to compare the effectiveness and safety of sublingual misoprostol with intravenous oxytocin infusion administrated after delivery of fetus in reducing blood loss at cesarean section. Also to compare side effects of oxytocin and misoprostol which use in controlling postpartum blood loss in cesarean section.

PATIENTS AND METHODS

This study is a prospective, single-center, observational study trial of sublingual misoprostol (misoprostol group) versus i.v. oxytocin infusion. Oxytocin group for control of blood loss in women with singleton pregnancies at term who were scheduled for elective cesarean delivery at Sulaimani Maternity Teaching Hospital under spinal anesthesia between the first of October 2012 till the first of April 2013.

One hundred patients with singleton gestation who admitted to hospital for elective caesarian section agreed to participate in this study.

Inclusion criteria

1- Term singleton pregnancy.

2- Cephalic and breech presentation.

3- Intact membrane.

4-Absence of labor sign.

5- Viable fetus.

We excluded patients with:

1-Multiple gestation.

2-Placenta Previa.

3-Antepartum hemorrhage or unexplained vaginal bleeding.

4- intrauterine fetal death.

5-Patients under general anesthesia.

6-Febrile women for any reason.

7-Other exclusion criteria were pre-existing medical illnesses.

One hundred pregnant women admitted to the hospital for elective cesarean section were included in this study, verbal consent was taken from participant in the study, history and examination notes, vital sign were recorded (pulse rate, blood pressure ,and temperature), routine laboratory studies (PCV, blood group and RH) were done before operation. Demographic characteristic of each patient was assessed including the age, parity, occupation, residence, gestational age that was determined by LMP and /or early ultrasound and the cause of cesarean section was listed for each patient. Pregnant women divided into two groups, each group contains 50 patients.

Group 1: Received 20 units of oxytocin infusion intravenously (Oxytocin group). Group 2: Received 400 micrograms of misoprostol tab sublingually (Misoprostol group).

The participants were randomly allocated to receive either misoprostol 400 micrograms sublingually or i.v. infusion of 20 units of oxytocin immediately after the delivery of the baby. Both trial medications were administered by the anesthetists. The blood loss during the first 24 h after surgery, while the patient was in the recovery room measured by the difference in PCV levels before and 24 h after delivery and the need for additional uterotonics and drug-related adverse effects were recorded in both groups and compared.

All data were analyzed using SPSS version 19.0. Using the x2-test and the student t-test. A probability p-value < 0.05 was considered statistically significant.

RESULTS

Demographic table

As shown in Table 1 maternal age (years) in oxytocin group : 18 cases (36%) between (20-29 years), 30 cases (60%) between (30-39 years) , 2 cases (4%) 40 years compared with the misoprostol group when we have: 20 cases (40%) between (20-29 years), 26 cases (52%) between (30-39 years), 4 cases (8%) 40 years respectively.

The mean age in oxytocin group was 31.1±3.9 compared with 31.1±5 .5 misoprostol group. About parity, we have:

5 cases (10%) nullipara in oxytocin group, and 4 cases (8%) nullipara in misoprostol group. From p1 to p4 we have 45 cases (90%) in the oxytocin group compared with 34 cases (86%) in the misoprostol group. No case p5 in the oxytocin group, while we have 3 cases (6%) p5 in the misoprostol group.

About Gestational age we have 30 cases (60%) between 37-40 weeks in oxytocin group compared with 39 cases (78%) in misoprostol group, while we have 20 cases (40%) 40 weeks in oxytocin group compared with 11 cases (22%) in the misoprostol group.

Results: During the study period 100 cases enrolled as sample size.

Main outcome measures

Table 2 shows some of the main outcome measures :

•The change in PCV: in the first 24 hours after surgery was non significantly less in the oxytocin group (32.3 ± 2.9) vs misoprostol group (33.1 ± 3.2), (p-value 0.23).

• The mean operative time was very close to each other in the oxytocin and misoprostol group (33.7± 5.2)min vs (33.8 ± 3.9)min, respectively (p-value = 0.913).

• About additional drugs, 4 cases (8%) in oxytocin group required additional IV infusion of oxytocin ranging between 20-40 units after an initial dose of oxytocin which was 20 units, while 6 cases (12%) in misoprostol group required additional IV infusion of oxytocin after an initial dose of 400 g of misoprostol.

• Two cases in the oxytocin group (4%) required blood transfer while one case (2%) in misoprostol group required blood transfusion to correct excessive blood loss due to PPH.

Table 3 shows the drug-related side effects observed in the two groups.

Table 1. Demographic table, Number of cases (N) and percentage (%) for each Oxytocin and Misoprostol group over Maternal Age, residence, Occupation, Parity, and Gestational age variables.

Cases		Oxytocin group Case (n=SO) N (%)	Misoprostol group Case (n=SO) N (%)
Maternal Age by year	< 20	0 (0.0)	0 (0.0)
	20-29	18 (36.0)	20 (40 . 0)
	30 - 39	30 (60.0)	26 (52.0)
	40	2 (4.0)	4 (8.0)
Age Mean ±SD		31.1±3.9	31.1±5.5
Parity	Nulliparaa para	5 (10.0)	4 (8.0)
	Para 1- 4	45 (90.0)	43 (86 .. 0)
	Para 5	0 (0.0)	3 (6.0)
Gestational age by week	37-40	30 (60.0)	39 (78.0)
	40	20 (40.0)	11 (22. . 0)

Table 2. Main outcome measures of the study.

Outcome measures	Oxytocin group (n=50)	Misoprostol group (n=50)	P-Value
Preoperative PCV (%) (mean±SD)	36.3 ± 3.0	36.5 ± 3.1	0.697 (NS)
Postoperative PCV (%)(mean±SD)	32.3 ± 2.9	33.1 ± 3.2	0.23 (NS)
Change in PCV	4.0	3.4	-
Time of C/S per Min .	33.7± 5.2	33.8 ± 3.9	0.913 (NS)
added oxytocin (20 - 40 unit)	(48)%	6 (12%)	-
Received blood	(24)%	1 (2%)	-

Table 3. Adverse effects (side effects) encountered in the two groups.

Adverse effects	Oxytocin (n=50) N(%)	Misoprostol (n=50) N (%)
None	27 (54.0)	22 (44.0)
Nausea	2 (4.0)	8 (16.0)
Vomiting	2 (4.0)	1 (2.0)
Headache	2 (4.0)	2 (4.0)
Shivering/hyperthermia temp 38°c	1(2.0)	8 (16.0)
Hypotension	6 (12.0)	3 (6.0)

DISCUSSION

This study compares the efficacy of sublingual misoprostol with i.v.oxytocin infusion as a uterotonic agent during CS immediately after the extraction of the baby. Lesser PCV changes were found in the oxytocin group compared with the misoprostol group in this study, which was (32.3±2.9) vs (33.1±3.2) respectively (p-value=0.23). This observed difference was not found to be statistically significant, in a similar study by Kola M. Owonnikoko, et. al (2011). In Nigeria there was more blood loss in misoprostol group which is non-statistically significant, the mean blood loss in oxytocin group (30±5) vs (31±5) in misoprostol group (p value=0.796) [31].

The difference in the timing of the operation does not seem to have a major effect on the primary outcome measures, in this study meantime was (33.7±5.2) in oxytocin group vs (33.8±3.9) in misoprostol group (p-value = 0.913) which is non-statistically significant, this agreed with Kola M. Owonnikoko, et. al (2011) in Nigeria the mean operative time was also non-statistically significant (45.9±5.2) in oxytocin group vs (47.2±2.5) in misoprostol group [31].

The need for additional oxytocin in this study was more in oxytocin group 4 cases (8%) vs 3 cases (6%) in misoprostol group while, in Kola M. Owonnikoko, et. al (2011) in Nigeria 24 21 cases (42%) of participant in oxytocin group need additional IV infusion oxytocin range from 20-40 IU while 24 case (48%) participant in misoprostol group required additional IV infusion of oxytocin after an initial 400 microgram of misoprostol to achieve uterine tonicity [31].

The incidence of shivering/pyrexia was lower in the oxytocin group 1 case (2%) than misoprostol group which was 8 cases {16%), this agreed with study by Kola M. Owonnikoko, et. al (2011) [32] in Nigeria, in which also significantly lower incidence of shivering/pyrexia in oxytocin group (2%) than misoprostol group (54%) [31].

Headache in both studies was similar, while hypotension was more in this study 6 cases (12%) in oxytocin group vs 3 cases (6%) in the misoprostol group. Hypotension may be exaggerated by spinal anesthesia. There is no

drug-related adverse effect reported in the neonates. This study also agreed with another study done by Ganesh Acharya et. al (2001) [33] in Scandinavia, when change in PCV was close to each other in both studies and was statistically non-significant (p-value= 0.85), in Ganesh Acharya et. al (2001) compared with this study in which (p value is 0.796), which is also non-significant statistically The need for additional oxytocin to overcome uterine atony in Ganesh Acharya et. al (2001) study was 3 cases in oxytocin group (6%) vs 2 cases in misoprostol group (4%) which is not statistically significant and agreed with this study in which 4 cases (8%) in oxytocin group and 6 cases (12%) of misoprostol group need additional oxytocin, which is less in oxytocin group than misoprostol group [33].

The need for blood transfusion was 1 in the oxytocin group (2%) and 1 in the misoprostol group (2%), which is not statistically significant and agreed with this study. The incidence of side effect was not serious and where noted in either group [33].

In another study by Lapaire et al (2006) [32] In Switzerland, blood loss was less in the misoprostol group which is not statistically significant and this agreed with our recent study. Another study by Vimala et. al (2006) in India there was significant lesser blood loss in the misoprostol group compared with the oxytocin group. The difference in timing of operation does not seem to have a major effect in the primary outcome measures [34].

The limitation of this study was in our method of estimating blood loss at surgery may be too cumbersome for many researchers. Described the use of calibrated drapes, which provided a method of blood collection that was accurate, easy to use and inexpensive. Further studies to evaluate the use of sublingual misoprostol in normal vaginal delivery and compared with oxytocin in management of third stage of labor to test its effectiveness in reducing PPH.

In conclusion, sublingual misoprostol was observed to be as effective as i .v. oxytocin infusion in reducing postpartum blood loss during cesarean section and may be an effective alternative to the traditional oxytocics in the tropics. Besides, misoprostol offers several advantages over oxytocin, such as longer half-life, stability at room temperature and oral administration, which make it a suitable alternative to the routine oxytocin in the management of the third stage of labor, particularly in low-resource tropical-climate countries.

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