UMBILICAL VEIN INJECTION OF 800 MICROGRAM MISOPROSTOL VERSUS OXYTOCIN IN THE MANAGEMENT OF RETAINED PLACENTA

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Submitted: 5/7/2018; Accepted: 5/11/2018; Published 21/12/2018

ABSTRACT

Background

The third stage of labor is timed from the delivery of the baby to the expulsion of the placenta and membranes. This normally takes five and fifteen minutes. It may be complicated with retained placenta. Consequently, intervention should be started promptly.

Objectives

We aimed to evaluate the effectiveness of umbilical vein injection of misoprostol (800 Microgram) versus oxytocin (20 units) for the treatment of retained placenta.

Materials and Methods

This is a double-blinded randomized clinical trial, conducted at the Maternity Teaching Hospital, Sulaimani, Kurdistan Region, Iraq, from October 1, 2016 to December 31, 2017. Fifty patients whom delivered vaginally and complicated by retained placenta were randomly allocated into two groups;group1 received 800 mcg of misoprostol (four Misotac® 200 mcg, Pfizer) and, group2 received 20 IU of oxytocin (NOVARTIS) each diluted in 20 ml of normal saline were infused through umbilical vein for the two groups respectively. The outcome was measured by using time interval of placental separation and amount of blood loss.

Results

The mean ± SD age was (30.5 ± 5.8) and (27.8 ± 5) for the oxytocin and misoprostol groups respectively. There were a statistically significant relationship between the type of drug injections and a statistically very highly significant difference between the type of drug injections and time interval for the placental separation (P-value of 0.04 and P-value of <0.001 respectively). There was also a statistical significant difference in the mean vaginal blood loss between the two groups (mean±SD=169.3±88.1 ml, mean± SD= 150±89.4 ml) in oxytocin and misoprostol groups respectively), (P-value = 0.03).

Conclusions

The intraumbilical vein injection of misoprostol was better than oxytocin for the reduction of time needed till placental separation and associated with less blood loss.

Keywords: *Intraumbilical vein injection; Retained placenta, Misoprostol, Oxytocin.*

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https://doi.org/10.17656/jsmc.10179

INTRODUCTION

Third stage of labor is the time from the delivery of the baby to the expulsion of the placenta and membranes [1]. Normal separation is believed to result from the contraction of uterus shearing the placenta from the underlying endometrium resulting in hematoma formation, venous occlusion and vascular rupture [1].

No consensus exists about the normal length of third stage of labor or the time at which the placenta should be termed (retained) and intervention should be started[3]. The intrapartum guidelines published by national institute for health and clinical excellence (NICEi guideline) suggest intervention when placenta has not been delivered within 30 minutes after birth with active management of the third stage or within 60 minute with physiological management of the third stage [3].

Herman et al. [4] first demonstrated by ultrasonographic study that retroplacental myometrial contraction is mandatory in order to produce shearing forces upon the interface between the placenta and myometrium and then it leads to its detachment. Moreover, he divided the third stage into four phases according to the ultrasound appearance as follows:

Latent phase: immediately follows delivery of the fetus in which all the myometrium contracts except for that behind the placenta, Contraction phase: the retroplacental myometrium will contract, Detachment phase where the placenta is sheared away from deciduas, Expulsion phase: the placenta is expelled from the uterus by uterine contraction.

The incidence of retained placenta (RP) is 1-2% of all deliveries worldwide, and the exact data is unknown. The prevalence of RP depends on the definition, but an interval of 30 minutes or greater occurred in 1-3.3% of deliveries in united states [5].

Risk factors of retained placenta include: multiparity, endometritis, induced or preterm labor, small placenta, previous surgical intervention to the uterus, use of oxytocin. Furthermore, placental retention may recur and the risk is two to four times greater in those with history of retention [6].

Modern active managements include the following [1, 7]:

1. Giving an intramuscular injection of 10 IU of oxytocin when the anterior shoulder of the baby is delivered, or immediately after delivery of the baby.

2. Early clamping and cutting of umbilical cord.

3. Controlled cord traction.

If placenta was not delivered after 30 minutes, consider emptying the bladder, breast feeding or nipple stimulation, and change of position –encourage an upright position. Then, if bleeding occurred immediately, inform anesthesia, insert two large bore cannulas, and commence 20 units of oxytocin infusion in one liter and continue in a rate of 60 drops per minute. Measure and accurately record blood loss, then prepare and after takening informed consent, transfer the patient to the theater for manual removal of placenta (MROP) [8]. Adequate analgesia is vital for effective MROP, and this will be achieved through regional or general anesthesia. Although general anesthesia helps to relax the uterus, it associates with a higher complication rates. Moreover, nitrates can be used for relaxation if the uterus was much contracted.

The WHO recommends umbilical vein injection of uterotonic drug as the first line of treatment for retained placenta. However, this treatment is not routinely used, probably because of the lack of a large randomized controlled trial, and dosage regimes. A cochrance collaboration review found that umbilical vein injection of oxytocin is not effective for the treatment of RP. A double-blinded, placebo-controlled trial including women in the UK, Uganda and Pakistan showed that umbilical vein injection of oxytocin had no clinically significant effect on the need for manual removal of placenta [9].

Misoprostol is a prostaglandin E analogue marked for the treatment of peptic ulcer and known for its use in medical abortion and labor induction, and is a promising option for PPH prevention and treatment particularly in developing countries. Furthermore, misoprostol has strong uterotonic effect which does not require refrigeration, and is not a contraindication for hypertensive or preeclamptic patient as in the case of ergot–based compounds. Moreover, misoprostol also seems more promising than other prostaglandins due to its lower cost and easier administration, and has uterotonic properties at all gestational ages [2, 3].

Oxytocin is mammalian neurohypophysial hormone and is produced in the supraoptic and paraventricular nuclei of the hypothalamus. Moreover, it is a neuropeptide that physiologically is a potent uterotonic stimulating the smooth muscle of the uterus and it also causes contraction of the epithelial cells surrounding

the mammary alveoli leading to milk ejection during lactation. Furthermore, the physiological effects of oxytocin are modified not only by circulating oxytocin, but also by the presence of oxytocinase and by number and capacity of oxytocin receptora. Additionally, oxytocinase is a glycoprotein aminopeptidase produced during pregnancy that degrades oxytocin. Enzyme activity in the placenta increases as pregnancy progresses and rises steeply at term and after delivery declines [10].

Complications of RP include: shock, postpartum hemorrhage, puerperal sepsis, and uterine sub-involution which may require hysterectomy.

Post partum hemorrhage due to RP can be treated through MROP or perhaps through umbilical vein injection of oxytocin with misoprostol for PPH prevention as it has been shown in five large trials that when misoprostol is given it is as effective as oxytocin for the management of PPH [11].

PATIENTS AND METHODS

A Double-blinded randomized clinical trial conducted at the Maternity Teaching Hospital in Sulaimani City, Iraq during the period from October 1st, 2016 to December 31st, 2017. Fifty patients were delivered vaginally and complicated by RP randomly allocated into two groups – 25 patients each, 800 mcg (microgram) of misoprostol (four Misotac® 200 mcg) and 20 units of oxytocin each diluted in 20 ml of normal saline were infused through umbilical vein for both groups respectively. The drugs were prepared by the researcher, but the doctor ─ who was responsible for the patient ─and the patients did not know the type of the drugs. In addition, permissions were taken from the doctors responsible for the care of their patients.

Inclusion criteria

1- Singleton pregnancy

2- Vaginal delivery

3- More than 28 weeks of gestation

4- Prolonged third stage of labor − more than 30 minutes − despite active management.

Exclusion criteria

1- Significant bleeding.

2- Multiple pregnancies.

3- Previous caesarean delivery.

4- Hemodynamic instability and severe anemia i.e. hemoglobin concentration <8 g/dl.

5- Chorioamnionitis.

6- Refusal of participation.

Informed consent was obtained from all patients after explanation of the study protocol. Injection of umbilical vein performed according to the Piping's method as follows: the cord was cut and a pediatric nasogastric tube of Fr. 6 was advanced into the umbilical vein, and when resistance was felt, the catheter was retracted one to two centimeter (cm) and then advanced further if possible. Sequentially, when the catheter could not be advanced further without using force, the drug was administered through the catheter. But, if the majority of the catheter was inserted before resistance was felt which indicates reaching the placenta, the catheter was retracted 3–4 cm to ensure that the tip was in the umbilical vein and not in a placental vessel. Furthermore, during the injection of the drugs, the cord was occluded by finger pressure around the catheter and clamped at the end. Finally, if spontaneous delivery of the placenta did not occur, delivery by gentle cord traction was attempted at 15 and 30 minutes after injection.

Manual removal of placenta (MROP) attempted under general anesthesia if placental delivery failed to occur within 30 minutes after the injection, or significant bleeding occurred. Additionally, the volume of blood loss from the time of umbilical vein injection to delivery of the placenta was measured by placing a pad of 45 gm under the patient's buttocks and it was weighed after delivery of the placenta using a dedicated electronic scale (up to 5 kg). The blood loss was calculated in ml (1 g =1 ml).

Women in both treatment groups were followed up for 24 hours after delivery, vital signs (blood pressure, pulse rate, temperature, and respiratory rate), and uterine fundal height, abnormal vaginal bleeding, and abdominal pain were recorded. Analgesics, and according to hospital guidelines Antibiotic prescribed.

We used "IBM SPSS Statistics version 20" for the analysis of the data. A P-value of ($\leq$0.05) was considered statistically significant, a P-value of (<0.01) as statistically highly significant, and a P-value 0f (<0.001) as statistically very highly significant relationship between the variables.

RESULTS

We collected 50 patients who delivered by vaginal route and complicated by retained placenta and randomly enrolled them into two groups−oxytocin and misoprostol intervention groups, Table 1.

The successful rate of separation was significantly higher in misoprostol group and its usage was also significantly decreased the time needed to achieve adequately contracted uterus (Table 2).

Our study showed a statistically significant difference in the mean vaginal blood loss volume after umbilical vein injection between the two groups (Table 3).

Table 1. Frequencies of patients' characteristic among both studied groups.

Variable	Oxytocin group	Misoprostol group
Age in year (Mean ± SD)	30.5 ± 5.8	27.8 ± 5
Nulliparity (frequency)	9 (36%)	12 (48%)
Multiparity (frequency)	16 (64%)	13 (52%)
Gestational age in week (Mean ± SD)	36.5 ± 3.6	38.5 ± 2.4
Cord length in cm (Mean ± SD)	45.6 ± 4.6	49.2 ± 4.4
Fetal weight in kg (Mean ± SD)	2.8 ± 0.86	3.2 ± 0.65

*** SD=Standard Deviation, cm = centimeter, kg = kilogram**

Table 2. The relationship between the type of drug injections with their outcomes and time interval for the placental separation.

Number of women (n=50)	Oxytocin group (n=25)	Misoprostol group (n=25)	P-value
Spontaneous placental separation (n=35)	17 (34%)	18 (36%)	0.04
MROP* (n=15)	8 (16%)	7 (14%)	
Time of placental separation after drug injection (minute)	17.5 ± 7.2	17.1 ± 5.5	<0.001

***MROP =Manual Removal of Placenta**

Table 3. Vaginal blood loss after misoprostol injection and after oxytocin.

Number of women (n=50)	Oxytocin group (n=25)	Misoprostol group (n=25)	P-value
Vaginal blood loss volume in ml (mean ± SD)	169.3 ± 88.1	150 ± 89.4	0.03

*** SD = Standard deviation**

DISCUSSION

Misoprostol is an analogue of prostaglandin E1 that interacts with specific receptors on myometrial cells which causes a cascade of events including a change in calcium concentration that initiates myometrial contraction, and softening of the cervix that leading to expulsion of the uterine contents; umbilical vein injection of misoprostol may result in local action at the base of the placenta [12].

The Cochrane review of umbilical vein injection for the treatment of RP found that injection of prostaglandin solution results in a highly significant reduction in the time interval of placental separation compared with injection of oxytocin [3]. In the current study, we found the same results in which misoprostol reduced the time needed till placental separation and better outcome (Table 2).

The etiology of RP could be attributed to retroplacental contractile abnormalities and efforts made to overcome this contractile failure by administering uterotonics to stimulate the retroplacental myometrium [12]. Our study confirmed the success of these drugs because the placenta was expelled in 70% of women involved. The successful rate of separation was significantly higher in misoprostol group, and its usage also significantly decreased the time needed to achieve adequately contracted uterus (Table 2).

Our study showed a significant difference in the mean vaginal blood loss volume (mean ± SD = 169.3 ± 88.1 ml in oxytocin group, and mean ± SD = 150 ± 89.4 ml for the misoprostol group) after umbilical vein injection between the two groups (P-value = 0.03). This finding differed from the study of Rajab et al. [3] who reported a mean volume of blood loss of 210 ml in the prostaglandin group and 231 ml in the saline group (P-value = 0.7). This difference may be due to the smaller sample size of their study (n = 17) and the different uterotonic drug that had been used ─ prostaglandin F2 alpha analogue.

The mean time from umbilical vein injection until separation of the placenta was shorter in the misoprostol group (17.1 ± 5.5 minutes) than in the oxytocin group (17.5 ± 7.2 minutes), and there was a significant relationship between the two groups (P-value of <0.001). Rajab et al. [3] reported no significant difference in the time to delivery of the placenta between the groups, but the study of Harara et al. [13] reported that the time to delivery of the placenta was significantly shorter in the misoprostol group (7.0 ± 2.2 minutes). This may be because they compared misoprostol with two other uterotonic drugs (ergometrine and normal saline) rather than with oxytocin as in the current study.

The method causes potent uterine contractions, resulting in the separation of the placenta. Morbidly adherent placentae are usually resistant to this line of management. This work showed that various intraumbilical injections of uterotonics (misoprostol 800 mcg─ microgram ─ dissolved in 20 ml ─ normal saline or oxytocin 20 IU in 20 ml normal saline) were comparably effective in treating retained placenta. Furthermore, the misoprostol group had a significantly shorter mean injection-to-separation time interval and better outcomes compared to the oxytocin group. In 2001, Hararaal. [13] studied 31 women with retained placenta and compared the efficacy of oxytocin 20 IU (n=19), ergometrine 0.2 mg (n=4) ─ both dissolved in 20 ml saline ─ to saline alone (n=8). They found that the success rate was 68.4% for oxytocin, 12.5% for saline alone, and 0% for ergometrine. Moreover, several studies achieved a success rate of placental separation ranged from 77-100% using different types of prostaglandins [13].

In conclusion; the intraumbilical vein injection of misoprostol was better than oxytocin for the reduction of time needed till placental separation and associated with less blood loss.

Acknowledgements

The authors are thankful to "Tropk for Computer and Scientific Research" for providing the data analysis, and edition and proof reading for this study.

Conflict of interest

Nothing to declare

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