Role of Intaumbilical Misoprostol in Prevention of Postpartum Hemorrhage

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Abstract

Background: Prostaglandins have mainly been used for postpartum hemorrhage (pph) when other measures fail,misoprostol, a new and inexpensive prostaglandin E1 analougue,has been suggested as an alternative for routine management of he third stage of labour.

Aim o the study: To determine the efficacy of intraumbilical oxytocin administration compared with intraumbilical misoprostol administration for prevention of postpartum hemorrhage.

Materials and methods: Prospective study done at Babylon Hospital for Maternity and Pediatrics from February 2009 to September 2009.

study involved 75 women in their 3rd. stage of labor subdivided into 3 groups 25 for each received either 30 i.u oxytocin in 30 ml saline or 800 mcg of misoprostol dissolved in 30 ml of saline 3rd group was control received only 30 ml of saline injected into the placental bed via umbilical vein using pipingas technique .

The primary outcome measured was duration of 3rd stage of labor , amount of blood loss and need for manual removal of placenta. P-value of <0.01 considered statistically significant.

Results: All groups are comparable in their demographic criteria. Intraumbilical injection of misoprostol associated with shorter duration of 3rd stage of labor (2.5 ± 0.2 min) compared with oxytocin group (3.5 ± 1.1 min) and control group (5.56 ± 2.2 min) p value <0.0001. Blood loss was comparable in both misoprostol and oxytocin group (31.6± 15 ml and 33.2±18.7 ml respectively, p-value >0.05) which was significantly lower than control group (147.1 ± 99 ml) p value <0.0001. No reported cases of retained placenta in both oxytocin and misoprostol groups compared with 2 cases (8%) in control group. Further uterotonic drugs required in 20% of control group. No significant side effects reported in all study groups.

Conclusion:

1- Intaumbilical injection of 800 mcg misoprostol dissolved in 30 ml of saline using pipingas technique was more effective than intraumbilical oxytocin in shortening the duration of 3rd stage of labor and both reduce the incidence of postpartum hemorrhage.

2- the intraumbilical injection of uterotonics is non- invasive ,effective and clinically safe method for management of 3rd stage of labor and prevention of postpartum hemorrhage.

الخلاصة

دراسة مستقبلية أجريت في مستشفى بابل للنسائية والأطفال خلال الفترة من شباط 2009 لغاية أيلول 2009

تضمنت الدراسة 75 امرأة في المرحلة الثالثة من الولادة واللواتي لديهن عوامل خطورة للنزف ما بعد الولادة والتي تتضمن المتعددة الولادات ,الحمل بتوأم او أكثر, كبر حجم الجنين,الولادة الطويلة أو العسرة,فقر الدم,تاريخ سابق للنزف ما بعد الولادة.
وان 75 امرأة تم تقسيمهن الى 3 مجاميع (25 في كل مجموعة) وتم حقنهن عن طريق الوريد السروي بعد ولادة الجنين باستخدام طريقة ببنكاز بأحد الأدوية التالية
1- 30 وحدة من الاوكسيتوسين مذابة في 30 مل من المحلول الملحي الطبيعي.
2- 800 مايكروغرام من عقار الميزوبوستول مذابة في 30 مل من المحلول الملحي الطبيعي.
3- 30 مل من المحلول الملحي الطبيعي فقط(مجموعة السيطرة).
نتائج الدراسة: أظهرت الدراسة أن استعمال الاوكسيتوسين والميزوبروستول عن طريق الوريد السروي يؤدي إلى تقليل فترة المرحلة الثالثة من الولادة وتقليل كمية الدم المفقودة بصورة ملحوظة مقارنة بمجموعة السيطرة.
كما أظهرت الدراسة ان الميزوبوستول أكثر فعالية من الميزوبروستول من حيث تقليله لفترة المرحلة الثالثة من الولادة بينما كانت كمية الدم المفقودة متقاربة بين المجموعتين.
استنتج من هذه الدراسة ما يلي:
1-ان استخدام الميزوبروستول المذاب في المحلول الطبيعي والذي يعطى عن طريق الوريد السروي باستخدام طريقة ببنكاز قد ادى الى تقليل فترة المرحلة الثالثة من الولادة بدرجة ذات مغزى احصائي.
وكذلك ادى الى تقليل نسبة حدوث النزف ما بعد الولادة.
2-ان حقن محفزات الرحم عن طريق الوريد السروي هي طريقة مؤثرة ,غير مخترقة وسريريا امينة في معالجة المرحلة الثالثة للولادة.

Introduction

Postpartum hemorrhage (pph) remains a major killer of women wide world. Postpartum hemorrhage, traditionally define as the loss of more than 500 milliliters of blood following delivery, occurs in up to 18 percent of birth [1, 2].
PPH is considered severe when blood loss exceeds 1000 milliliters or result in homodynamic instability [3]. Even with appropriate management, three percent of vaginal deliveries will result in severe pph [4].
National statistics suggest that approximately 8% of maternal death is caused by pph. In industrialized countries, pph usually ranks in the top 3 causes of maternal mortality, along with embolism &hypertension [5].
The third stage of labour is potentially the most hazardous part of labour for the mother. The main risk is that of pph with its subsequent morbidity [6].
The duration of the third stage is important because the prevalence of postpartum hemorrhage increased as the duration lengthens [7]. There is no universally accepted criterion for the normal length of the third stage ,90% of placenta will be delivered within 15 minutes,97% were delivered within 30 minutes of birth[8].
The rise of oxytocic drugs for the prevention of pph has been regarded as one of the most enduring advances in the medical science [6]. The best preventive strategy of pph is active management of third stage of labour.
Oxytocin is the preferred uterotonic agent for preventing pph because its at least as effective and has fewer side effects than the ergot alkaloids & prostaglandins [2, 9, 10]. It reduces rate of pph by 40 %[11]. However, oxytocic agents are not stable at high ambient temperature therefore require special storage requirements (e.g. refrigeration), it should be stored between 2-8 centigrade and protected from light [6]. The notion oxytocin may be delivered directly to the retro-placental myomaterium by injecting it into the placental bed via the umbilical vein has stimulated a lot of interest.
Trials to date have mainly used a dose of 10-20 I.U oxytocins, although doses of up to 100 I.U have been reported [12]. Further improvement in success rates have been claimed for high- dose oxytocin administered by first canulating the umbilical vein, which

has been shown to improve delivery of drug to the placental bed[13].

Prostaglandin in general have been used in obstetric for at least two decades & are widely used.

Misoprostol (cytotec) a synthetic E1 analogue is commonly used for medical abortion, cervical ripening & induction of labour [14]. In the management of the third stage of labour, they have mainly be used for intractable pph as a last resort when other medical interventions did not suffice [10]. They not have been useful initially in active management of the third stage of labour [15, 16, 17, and 18].

It can be given orally, vaginally, sublingually or rectally, sometimes in combination. Dosage range from 200-1000 micrograms [19, 20, 21]. Higher level &larger doses are associated with more side effects including shivering, pyrexia, diarrhea, nausea & vomiting [19, 22].

However, use of misoprostol has several advantages; it is inexpensive, can be administered orally & does not require refrigeration [23, 24, and 25].

It is easier to use than other prostaglandins, heat & light stable &would appear to be an excellent candidate for study [12].

The compound was basically stable for 6 days in water & in saline ,whether they stored at 4 centigrade or at room temperature, however only half of the dosage of misoprostol was recovered in the solution. Therefore, misoprostol dosage should be adjusted before clinical application [26].

Contraindications to use misoprostol are severe asthma, active cardiac, pulmonary, renal or hepatic disease & hypersensitivity to drug [27].

Subject and methods

A prospective clinical study included 75 women in the third stage of labour done at Babylon Hospital for Maternity& Children in the labour room during the period from February 2009 to September 2009.

Inclusion criteria: women at high risk of PPH including grandmultiparous, multiple pregnancy, macrosomia, prolonged labour, anemia, & previous history of PPH.

Women with active cardiovascular disease, renal, hepatic, or pulmonary disease are excluded from the study.

The studied 75 women will be sub-divided into 3 groups (25 for each), injected into their umbilical vein after clamping it, by either of the following drugs:

1. 30 I.U oxytocin dissolved in 30 ml normal saline or
2. Misoprostol 800 mcg dissolved in 30 ml normal saline alone.
3. 30 ml normal saline alone (control).

The primary outcomes were amount of blood loss, duration of third stage of labour, use of additional uterotonic, need for manual removal of placenta, blood transfusion & side effects of drugs (fever, shivering & diarrhea).

The blood loss in the third stage was measured by collecting the blood lost in graduated clean plastic cap. Pipingas et al. compared various methods of Intaumbilical injections, using injections of radio-opaque dye into the delivered placenta to enable radiological comparisons. They found that the method of injection used in most trials (injection of oxytocin diluted in 20 – 30 mills saline & injected directly into the umbilical vein) only in capillary filling in 60% 0f cases (Pipingas et al., 1993).

As a result of their studies they proposed that the oxytocin should be diluted in 30 mills of saline & injected down an infant nasogastric feeding tube which has been passed along the umbilical vein. They suggest that after re-cutting the cord (in order to achieve a clean end for insertion of the tube) a

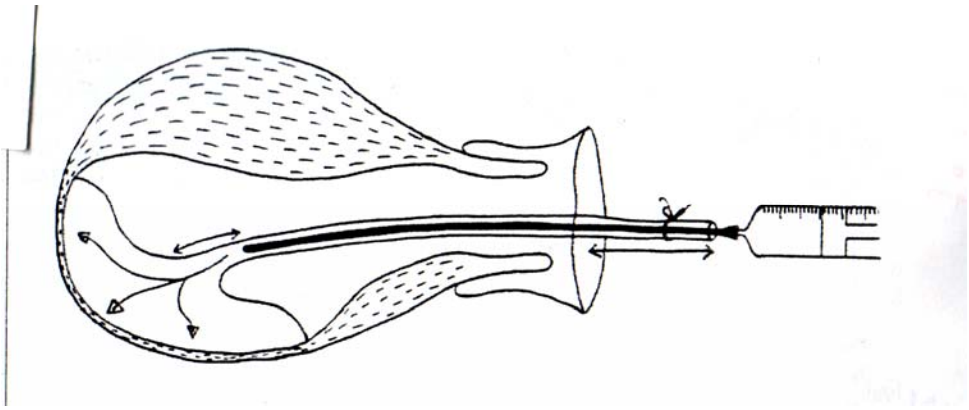
size 8 naso – gastric tube is passed along the vein until resistance is felt.

The tube is then withdrawn by 5 cm to allow for any divisions of the vein prior to its insertion into the placenta. This method resulted in complete filling of the placental bed capillaries in all patients studied (Pipingas et al. 1993).

Technique of Intraumbilical vein injection:

One prepared syringe (size 60 ml) was obtained from the refrigerator of the delivery suit.

A size 8 nasogastric catheter was inserted along the umbilical vein, if resistance was felt; the catheter was retracted by 1-2 cm & then advanced further if possible then injection of prepared solution.



Pipingas technique

A nasogastric tube is threaded down the umbilical vein to the placental bed & then withdrawn by 5 cm & tied; 30 ml of solution is then injected down the catheter. This technique achieved optimal filling of the placental bed Capillaries

Results

Description of study groups:

A total of 75 women in their 3rd stage of labour were divided into 3 groups, 25 women for each. 1st group was control and received intraumbilical normal saline (30 ml). 2nd group received intraumbilical oxytocin (30 unit in 30 ml normal saline).

3rd group received intraumbilical misoprostol (800mcg dissolved in 30 ml normal saline).

Data from those patients were collected and included in the groups to which the patients were divided.

The groups were comparable with regard maternal age, number of previous miscarriages. The mean gestational age according to last menstrual period was 38.9 ± 1.4 wks. in control group compared with 38.8 ± 1.1 wks.and 38.7 ± 0.5 wks. in oxytocin and misoprostol groups respectively .

Table 1. characteristics of study groups

Variables or parameters	Group 1 control	Group 2 oxytocin	Group 3 misoprostol	P - value
Age (years)	27.8 ±5	27.36 ± 11.6	31.56 ± 5.6	>0.05
Parity (n.)	1.5 ± 1.8	3.08 ± 2	5.16 ± 3.1	<0.005
Miscarriages (n.)	0.2 ± 0.3	0.2 ± 1	0.32 ± 0.4	>0.05
G.A (wks)	38.9 ± 1.4	38.8 ± 1.1	38.72 ± 0.5	>0.05

Labour was accelerated in 16 patient of control group compared with 10 and 12 patients in oxytocin and misoprostol respectively.

While spontaneous labour occur in 9 patient of control group compared with 13 and 10 patient of oxytocin and misoprostol groups respectively.

Induction of labour occur only in 2 patient of oxytocin group and 3 patient of misoprostol group (Table 2).

Table 2. the type of labour in study groups

Type of labour	Control group	Oxytocin group	Misoprostol group	p-value
*Accelerated	16 64%	10 40%	12 48%	>0.05
*Spontaneous	9 36	13 52%	10 40%	>0.05
*Induction of labour	0 0%	2 8%	3 12%	>0.05

Table 3. show risk factors in both oxytocin and misoprostol group .

Risk factors	oxytocin Group	Misoprostol Group	P - value
Grandmultiparity	13 52%	16 64%	>0.05
Anemia	6 24%	5 20%	>0.05
Previous hx of PPH	3 12%	1 4%	>0.05
Multiple pregnancy	3 12%	2 8%	>0.05
Polyhydramnios	0 0%	1 4%	>0.05

The outcome of therapeutic trial:

It has been found in this trial that intraumbilical injection of oxytocin and misoprostol associated with significant shortening of 3rd stage of labour 3.5 ± 1.1 and 2.5 ± 0.2 respectively compared with 5.56 ± 2.2 for control group .p value < 0.001 (table 4).

Also there is significant reduction in the amount of blood loss during 3rd stage, it was 33.2 ± 18.7 and 31.6 ± 15 ml for oxytocin and misoprostol groups respectively compared with 147.1 ± 99 ml for control group, p value < 0.0001.

5 patients in control group required additional use of oxytocic drugs (oxytocin and Ergometrin) due to inertia and only 1 patient in control group had blood loss > 500 ml (primary postpartum hemorrhage) due to inertia , required blood transfusion and oxytocic drugs .

In this trial, 2 cases of retained placenta in control group where manual removal of placenta was performed.

Regarding side effect:

There is no reported side effect in all groups apart from shivering that occur in only 1 patient of misoprostol group and last for few minutes and subsided spontaneously.

No reported cases of Allergic reaction in all study groups.

Table 4. the outcome of therapeutic trial

Parameters	Control group	Oxytocin group	Misoprostol group	p-value
Length of 3rd stage (min)	5.56 ± 2.2	3.5 ± 1.1	2.5 ± 0.2	< 0.001
Amount of blood loss (ml)	147.1± 99	33.2±18.7	31.6 ± 15	<0.0001
Need for blood transfusion	1 4%	0	0	NS*
Need for subsequent oxytocis drugs	5 20%	0	0	NS*
Manual removal of placenta	2 8%	0	0	NS*
Blood loss > 1000 cc	1 4%	0	0	NS*
Side effect				
Nausea and vomiting	0	0	0	NS*
Diarrhea	0	0	0	NS*
Shivering	0	0	1 4%	NS*
Fever	0	0	0	NS*
Allergic reaction	0	0	0	NS*

P- value < 0.01 is statistically significant
NS*(not significant)

Comparison between oxytocin and misoprostol:

It has been found in this study that intaumbilical misoprostol was associated with significant effective reduction in the duration of 3rd stage of labour (2.5 ±0.2 min and 3.5±1.1 min respectively) p-value <0.0001 which statistically of high significance.

While there was no statistical significant difference between oxytocin and misoprostol regarding the amount of blood loss (33.2±18.7 ml and 31.6±15 ml respectively) p value >0.05 which was not significant. table 5.

Table 5. difference between oxytocin and misoprostol groups

parameters	Oxytocin group	Misoprostol group	p- value
Length of 3rd stage (min)	3.5± 1.1	2.5± 0.2	<0.0001
Blood loss (ml)	33.2 ± 18.7	31.6 ± 15	>0.05

Discussion

PPH is one of the obstetrical complications that obstetricians fear most [28]. Although risk factors & preventive strategies are clearly documented , not all cases are expected or avoidable.

Uterine atony is responsible for most cases & can be managed with uterine massage in conjunction with oxytocin , prostaglandins & ergot alkaloids [29].

Prevention , early recognition & prompt appropriate intervention are the keys to minimizing its impact.

Practices should be established to facilitate the identification of women who may be at a particularly high risk for PPH & to allow prompt intervention should excessive bleeding occur[27]. Risk factors include prolonged labour , history of PPH, multiple pregnancy , fetal macrosomia, &high parity [3,30,31]. However , PPH occurs in women with no risk factors so providers must be prepared to treat it at every delivery [3,4].

Misoprostol (cytotec) is a prostaglandin that increases uterine tone & decreases bleeding postpartum [32].

Misoprostol is effective in treatment of PPH but side effects may limit its use [19,20].

As side effects are dose – related research should be directed towards establishing the lowest effective dose for routine use , & the optimal route of administration [10].

Misoprostol by virtue of their strong uterotonic features , they have an apparent superiority in the management of PPH & appear to be ideal agents for prophylactic use in the third stage in labour [6]. One case of PPH was prevented for every 18 women treated [33] .

A randomized , double – blind , placebo- controlled trial was used to asses the effectiveness of an intraumbilical injection of oxytocin on the duration of the third stage .

There was no difference in the duration of the third stage between the two groups (7.8± 6.1 min. in the saline – only group (30 ml) versus 5.9 ± 2.6 min. in the oxytocin group (20 U oxytocin 30 ml of saline) .

The percentage of undelivered placentas beyond 15 minutes was significantly lower in the oxytocin group (zero in the oxytocin group versus 12.5% in the saline – only group [34].

Umbilical vein injection of saline solution plus oxytocin appears to be effective in the management of retained placenta.

The difficulties in implementing this intervention are related to the training of personnel in the technique of giving injections into the umbilical vein [35].

In our study the duration of 3rd stage of labour was shorter in

misoprostol group (2.5±0.2 min.) compared with oxytocin group (3.5±1.1 min.) and saline only group(5.56±2.2 min.) p value<0.001 which is statistically of highly significant.

Twelve trials were included , umbilical vein injection of saline solution alone did not show any significant difference in the incidence of manual removal of the placenta (relative risk RR 0.97 ; 95 % confidence interval (CI) : 0.83 to 1.14).

Saline solution with oxytocin compared with saline solution alone showed a significant reduction in manual removal of the placenta (RR : 0.79 ; 95% CI : 0.69 to 0.91).

No discernible difference was detected in length of third stage of labour , blood loss , & blood transfusion .

In our study blood transfusion required in only one patient in saline only group.

There were no significant between saline solution plus prostaglandin & saline solution plus oxytocin (RR : 0.10 ; 95% CI : 0.01 to 1.59).

There was a statistically significant lower incidence in manual removal of placenta in the prostaglandin group compared to saline alone . (RR: 0.05 ; 95% CI: 0.00 to 37) [36] .

A double blind , clinical trial was performed intraumbilical oxytocin with normal saline group alone .

The blood loss was 263.7± 220.9 ml in oxytocin group versus 286.7 ±230.4 in saline group (p=0.68) .

Duration of third stage of labour 265.3 ± 383.9 seconds in oxytocin group versus 197.1 ± 314.9 in saline group (p=0.44).

There was one retained placenta in oxytocin group & two in saline group (RR :0.5) .

There was no side effects in any group [37].

In our study blood loss was significantly lower in both oxytocin and misoprostol group (33.2±18.7 ml and 31.6±15 ml respectively) compared with saline only group (147.1±99 ml.) ,p value <0.0001 .

Also there was significant lower incidence of manual removal of placenta in both oxytocin and misoprostol group (zero) compared with saline only group (8%).

Further randomized study comparing the effectiveness of intraumbilical injection of oxytocin versus saline alone performed on 79 women .

There were fewer undelivered placentas beyond 15 minutes in the oxytocin group versus 12.5 percent in the saline – only group . However , there was no difference between the two groups in the duration of the third stage [34].

There are scarce data comparing injectable prostaglandins with the conventional injectable uterotonic on severe PPH .

A study performed at Princess Margaret Hospital concluded that misoprostol (800 mcg) dissolved in 30 ml normal saline & administered by intraumbilical injection using the Pipingas technique significantly reduces the need for manual removal for retained adherent placenta [38] .

WHO multicenter randomized trial of misoprostol in the management of the third stage of labour.

Misoprostol use was associated with a significantly higher incidence of shivering (3.48 & raised body temperature (7.17) in the first hour after delivery [39].

In our study there was only one reported case of shivering in misoprostol group which last few minutes and resolved spontaneously,this may be related to the route of administration of misoprostol as most of the reported

side effects in previous studies associated with either oral or vaginal and rectal routes.
No reported side effects in both oxytocin and saline only groups.

Recommendations

1.Early recognition , systematic evaluation & treatment , & prompt fluid resuscitation minimize the morbidity & mortality associated with PPH , regardless of cause .
2. Active management of the third stage should be utilized to decrease postpartum blood loss , length of third stage , and the incidence of PPH.
3.Misoprostol has advantages for prevention in low- resource settings because it is effective , inexpensive v, heat stable & simple to administer .
4.Larger trials are needed to assess the effect of Misoprostol on hysterectomy rates & maternal mortality rates , as well as its side – effect profile .
Establish whether it should be used as a first – line or second – line treatment option , evaluate the lowest effective dose & the optimal route of administration .

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