Sublingual misoprostol for the prevention of postpartum hemorrhage

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ABSTRACT

الأهداف: مقارنة تأثير علاج الميزوبروستول (600µg) عندما يعطى تحت اللسان مع نفس حجم الجرعة عندما تعطى عن طريق الشرج للمرأة بعد الولادة مباشرة لخفض نسبة نزيف ما بعد الولادة.

الطريقة: أُجريت هذه الدراسة في مستشفى الثورة – صنعاء – اليمن، خلال الفترة ما بين 1 مايو 2007م وحتى 31 أبريل 2008م. تم تقسيم عدد 215 سيدة إلى مجموعتين بشكل شبه العشوائي. شملت المجموعة الأولى عدد 118 سيدة أعطين (600µg) من عقار الميزوبروستول تحت اللسان بعد الولادة مباشرة. أما المجموعة الثانية فقد شملت 97 سيدة تم إعطائهن الجرعة نفسها من الميزوبروستول عن طريق الشرج. تم قياس كمية النزيف وتحديد المضاعفات الجانبية للعلاج. كما تم تسجيل العوامل الإضافية لعضلات الرحم، نقل الدم ومدة المرحلة الثالثة.

النتائج: تبين أن 9 من أصل 118 في المجموعة الأولى واللاتي أُعطين العلاج تحت اللسان تعرضن للنزيف بعد الولادة، بالمقارنة مع 7 من أصل 97 في المجموعة الثانية واللاتي أعطين العلاج عن طريق الشرج. كان النزيف خفيفاً وأقل من 1000ml في المجموعة الأولى مقابل 1500ml في المجموعة الثانية، المخاطر النسبية المرافقة (1.05, 0.40 - 2.73) (95%). بلغ متوسط كمية النزيف (362.3±170ml) في المجموعة الأولى مقابل (342.3±154.7ml) في المجموعة الثانية. فقط 3 حالات (3%) من المجموعة الأولى تم إعطائهن موتر عضلات الرحم مقابل حالتين (2%) من المجموعة الثانية.

خاتمة: استخدام الميزوبروستول (600µg) تحت اللسان بعد الولادة له تأثير تقريبي مساوي لتأثيره عندما يعطى عن طريق الشرج وبنفس الجرعة في خفض معدل نزيف ما بعد الولادة. تعرض 40% من السيدات إلى نزيف شديد بعد الولادة في كلا المجموعتين أكثر من 1000ml واقل من 1500ml.

Objectives: To compare the effectiveness of misoprostol (600 µg) when administered sublingually with the same dose administered per rectum to patients, immediately after delivery in preventing postpartum hemorrhage (PPH).

Methods: This study was carried out in Al Thawra General Hospital, Sana'a, Yemen, from May 1, 2007 to April 31, 2008. A total of 215 women were recruited, and divided into 2 groups in a quasi-random fashion. Group I comprised 118 women, and was given 600 µg misoprostol sublingually immediately after delivery. The other group comprised 97 women (group II), and was given the same dose of misoprostol per rectum. The blood loss was measured, and the side effects of the misoprostol were assessed. The need for additional uterotonic agents, blood transfusion, and the length of the third stage labor were recorded.

Results: Nine patients in group I, and 7 patients in group II had PPH. Of these patients, blood loss was >1000 ml in 4 patients in group I, but <1500 ml in 3 patients in group II, (relative risk - 1.05, 0.40 - 2.73 confidence interval [95%]. The mean blood loss was 362.3 ± 170 ml in group I versus 342.3 ± 154.7 ml in group II. Only 3 cases (3%) of the patients in group I were given additional uterotonic agents versus 2 cases (2%) in group II.

Conclusion: Postpartum use of 600 µg misoprostol by sublingual route has a comparable effect in reducing PPH, as that of rectal route. It was observed that severe PPH (1000 ml but <1500 ml) had been observed in 40% of those who developed PPH in both groups.

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Excessive bleeding from the genital tract after birth, or postpartum hemorrhage (PPH) is a major cause of maternal death in many low-income countries.[1]

The global estimate is 140,000 death per year, one in every 4 minutes.[2] It generally accounts for 25-43% of maternal mortality worldwide.[3] In addition to death, serious morbidity may follow. Sequelae includes shock, coagulopathy, pituitary necrosis (Sheehan syndrome), and others.[2] In the developing countries, uncountable maternal deaths occur from bleeding during pregnancy, or labor in remote areas, where most births take place at home, and without auxiliary nurses. Midwives are not trained or certified to administer injectable drugs, in addition to the high incidence of anemia, and the unavailability of blood transfusion. The most common cause of PPH is uterine atony, which is responsible for up to 80% of primary PPH.[4] Retained products, genital tract trauma, and blood disorders are other causes of PPH. Postpartum hemorrhage is a preventable complication, and many deaths could be prevented with appropriate supplies and medications. Current standard practice for preventing PPH is the active management of the third stage of labor, which includes administering the uterotonic agents, controlled cord traction, and uterine massage after delivery of the placenta, as appropriate.[5] Crucial aspect of this management is uterotonic therapy. Oxytocin and ergometrine are the most common used agents. These drugs however, have to be administered parenterally, not stable at room temperature, and must be protected from light.[6] Misoprostol (Cytotec,® Pfizer, New York, USA), a prostaglandin E1 analog, registered for the prevention and treatment of gastric ulcers, is a well-known uterotonic agent.[7] However, oxytocin or ergometrine are the drugs of choice. Multiple randomized controlled trials (RCTs) and meta-analyses have shown that these 2 drugs are superior to misoprostol.[8,9] In low resource settings (cost, storage conditions, licensing of providers to administer parenteral medications, and so forth) when oxytocin or ergometrine is not an option, misoprostol may be a reasonable alternative. The drug is inexpensive, available in tablets, which can be administered rectally, orally, or sublingually, and does not need refrigeration, dark storage, or administration by skilled attendant.[10] However, several studies have shown a wide range of results, most of them demonstrated different levels of effectiveness according to the route of administration, dose, dosing schedules, and underlying risk factor. The use of misoprostol sublingually for those women who might refuse to receive misoprostol rectally, particularly when the drug is served by a male attendant is interesting. The purpose of this study was to compare the efficacy of misoprostol given sublingually, with the same dose administered rectally in preventing PPH.

Methods. This study was carried out in Al Thawra General Hospital, Sana'a, Yemen, from May 1, 2007 to April 31, 2008. Al Thawra Hospital is a referral center with 11472 deliveries occurring, during the study period. Of these, 17% had delivered by cesarean section. A convenient sample of 215 women were recruited for the study. Women included were singleton pregnant, 37 completed weeks or more, determined by the last menstrual period, and/or first trimester ultrasonography, in active labor, or under induction when vaginal delivery was anticipated, and had the ability to give informed consent. Any woman with traumatic or operative delivery, had medical illness particularly bronchial asthma, or risk factor for PPH was excluded from the study. We divided the participants in 2 groups. Group I (n=118) were given 600 μg (3 tablets) misoprostol sublingually, while group II (n=97) received the same dose per rectum. Information included in this study was: maternal age, parity, gestational age, episiotomy, maternal body weight (kg), and the length of the third stage of labor (minutes). Hemoglobin (Hb) level was taken after admission for each case. Immediately after delivery and umbilical cord clamping, each patient was given the drug either sublingually, or rectally as a quasi-random allocation. After drainage of the amniotic fluid, a clean large plastic bag was placed under the patient to collect the blood. The placenta and membranes were removed as usual. During the 2 hours following delivery, the patients were closely observed, noting for vital signs, and vaginal bleeding every 15-30 minutes. The symptoms related to the misoprostol side effects such as nausea, vomiting, shivering, headache, and feeling of hotness were subjectively assessed. The patient was then transferred to the postnatal ward when the bleeding was minimal. The collected blood was measured by a graduated measuring jar. The gauze used was also weighed. The Hb count was taken again, 24 hours later. However, if the patient was discharged early she was requested to check her Hb level, and inform us of the result by phone. Primary outcome measures were the incidence of acute PPH, and drop of Hb concentration was defined as blood loss of 500 ml or more, within 24 hours of delivery. Secondary outcome measures were the need for additional uterotonic agents, blood transfusion, and the length of the third stage of labor. For patients enrolled in this study, the participation was limited to those who were in a position to give a fully informed consent after they had given detailed information on the trial. The ethical clearance was obtained. Any patient with more bleeding detected by the clinician 15 minutes after delivery, considered to be caused by uterine atony, and requiring further management were given the routine treatment protocol for PPH. The basic components of the active management of the third stage of labor used in the hospital include oxytocin administration, immediately after delivery together with ergometrine if no contraindication, controlled cord

traction, and uterine massage after placental delivery, as appropriate. However, it is mostly selective for those women who have risk factors.

The collected data were analyzed using MedCalc 9.3 statistical program provided through the website: http://www.medcalc.be.[11] The results were presented as mean ± standard deviation, or percentages as appropriate. The differences were expressed as relative risks or mean differences (paired t-test or independent t-test) as appropriate, with 95% confidence intervals (CI). A *p*-value of <0.05 was considered significant.

Results. The mean age of group I was 22.8 ± 2.9 years, and 22.7 ± 3.0 years for group II, which was statistically similar (*p*=0.8046 [t-test]). There was no significant difference between the 2 groups with respect to parity, gestational age, maternal body weight, or initial values of Hb concentration (**Table 1**). Of the 215 women, 7.7% in group I, and 7.1% in group II had PPH, relative risk (RR) - 1.05, 0.40-2.73 (95% CI). Hemorrhage was mild >500 ml (4.3%) in group I, and less than 1000 ml (4.1%) in group II. Severe PPH (>1000 ml but <1500 ml) had developed in 4 out of 9 cases (44.4%) in group I, and in 3 out of 7 cases (42.9%) in group II. There was no blood loss more than 1500 ml in either group. The mean measured blood loss was 362.3 ± 170 ml in group I versus 342.3 ± 154.7 ml in group II. The mean drop of Hb concentration from admission-24 hours postpartum were 1.0 g/dl in group I, and 0.5g/dl in group II. The need for additional uterotonic agents (oxytocin and/or ergometrine) was observed in 3% of the patients in group I versus 2%

Table 1 - Baseline characteristics of the patients.

Characteristic	Sublingual misoprostol (n=118)	Rectal misoprostol (n=97)	*P*-value
Age, year Mean ± SD	22.8 ± 2.9 (22.27 - 23.329)*	22.7 ± 3.0 (22.095 - 23.305)*	0.8046
Parity, n (%)			
Primigravida	22 (18.6)	16 (16.5)	
Para 2 - 3	70 (59.3)	63 (64.9)	
Para 4 or more	26 (22)	18 (18.6)	
Gestational age, week Mean ± SD	38.2 ± 0.9 (38.04 - 38.36)*	38.1 ± 0.88 *(37.9 - 38.2)	0.4138
Maternal body weight, kg mean ± SD	57.4 ± 8 (55.94 - 58.859)*	56.5 ± 7.3 *(55.029 - 57.971)	0.3942
Initial Hb concentration, g/dL Mean ± SD	11.9 ± 1.5 (11.627 - 12.173)*	11.7 ± 1.5 (11.398 - 12.002)	0.3317

The values are presented as mean ± standard deviation (SD),
*95% confidence interval, Hb - hemoglobin

Table 2 - Primary outcome in patients.

Variable	Sublingual misoprostol n=118	Rectal misoprostol n=97	*P*-value
Blood loss, n (%)			
>1000ml	4 (3.4)	3 (3.0)†	0.9029
>500 ml but <1000	5 (4.3)	4 (4.1)‡	0.9670
<500 ml	109 (92.4)	90 (92.8)	
Measured blood loss, ml Mean ± SD	362.3 ± 170 *(331.306 - 393.294)	342.3 ± 154.7 *(311.121 - 373.479)	0.3725
24 hour, Hb concentration, g/dL Mean ± SD	10.9 ± 1.5 *(10.627 - 11.173)	11.2 ± 1.4 *(10.918 - 11.482)	0.1342
Duration of the third stage, minute Mean ± SD	9.7 ± 5.2 *(8.752 - 10.648)	8.95 ± 3.0 *(8.345 - 9.555)	0.2096
Episiotomy, no. (%)	21 (17.8)	16 (16.5)	
Use of additional uterotonic, no. (%)	3 (3.0)	2 (2)	
Blood transfusion, no. (%)	1 (0.85)	1 (1)	

The values are presented as mean ± Standard Deviation (SD) and (%). *95% confidence interval (CI),
†relative risk - 1.09, 0.2513 - 4.779 (95% CI), ‡relative risk - 1.027, 0.283 - 3.721 (95% CI),
Hb - hemoglobin

of those in group II. Only 2 cases in both groups had received blood transfusion. The mean duration of the third stage of labor in group I was 9.7 ± 5.2 minutes, in comparison to approximately 9 minutes in group II. There was no statistical significant difference between groups. T**able 2** shows the primary outcome. Mild to moderate perceived shivering was the most common side effect recorded in group I (mild - 8.5%, moderate - 3.4%). It was less frequently recorded in group II (mild - 4.1%, moderate - 1%). Nausea, vomiting, and hot flashes had occurred in various low rates. All of these side effects developed within 2 hours following drug administration. It was self-limiting (**Table 3**).

Discussion. The average blood loss in the third stage of labor is 250-350 ml, and 12% of patients loss more than 500 ml.[12] The exact incidence of PPH is difficult to determine, and ranges between 5-18% of live births.[10] However, when blood loss is quantitated objectively, the rate of PPH increases to 20%.[13] In reviewing the literature on the pharmacokinetics of misoprostol administered by various routes, the sublingual or buccal route has rapid uptake, prolonged duration of action, and greatest total bioavailability. The rectal route has slow uptake, but prolonged duration.[3,9]

Misoprostol tablet is very soluble, and can be dissolved in 20 minutes when placed under the tongue. The peak concentration is achieved approximately 30 minutes after sublingual and oral administration. The mean time to reach maximum plasma concentration after rectal administration is 40-60 minutes, although a recent study reported a much shorter time of 20 minutes.[14] Various trials and meta-analysis had shown that uterotonic agents used in the third stage of labor reduce the incidence of PPH by 30-40%.[6] Recently, misoprostol has been tested whether it is a suitable alternative to oxytocin in low-resource settings for the prevention of PPH. Certainly, the results are encouraging, and if administered rectally (400 µg), the drug is effective as oxytocin (10 IU) given intramuscularly in preventing PPH.[15] el-Rafaey et al[16] reported on the usefulness of misoprostol in reducing the amount of blood loss in the third stage of labor.

Misoprostol versus placebo was studied in multiple RCTs. Unfortunately, most of them were of small sample sizes and showed conflicting results of efficacy. A systematic review of these trials concluded that because of significant heterogeneity, a meta-analysis was not performed.[8] Only one RCT from Guinea-Bissau with adequate sample size, comparing misoprostol to placebo showed benefits.[12] Based on the study from Guinea-Bissau, 2 of the authors of a systematic review reported a quick review of observed clustering of maternal deaths reported in trials of misoprostol use in the third stage of labor.[17] Given the inconsistent results of efficacy of misoprostol in the active management of third stage labor, and the worrisome clustering of maternal deaths, the safety of misoprostol needs further assessment.

Our results showed that 3.4% of patients in group I had blood loss of more than 1000 ml, but less than1500 ml. This proportion was less (3%) in group II patients. That means the routine sublingual misoprostol may have a protective effect on severe PPH in excess of 1500 ml. This suggests the possibility that misoprostol may have an effect on more persistent bleeding, as it has longer time to peak levels (20-30 minutes).[17] The protective effect is more prevalent with rectal misoprostol administration. However, the difference between both routes was not statistically significant (p=0.3725 [t-test]).

Hoj et al[12] studied 661 women with uncomplicated vaginal delivery who randomly received either 600 µg sublingual misoprostol, or placebo control immediately after delivery. Significantly, fewer women in the misoprostol group suffered from severe PPH with a blood loss of 1000 ml (11% in group I versus 17% in group II, RR - 0.66, 95% CI; 0.45-0.98). The mean decrease in Hb concentration was 0.16 mmol/L (-0.01 mmol/L - 0.32 mmol/L) lower in the misoprostol group than the placebo group.[12] These results are consistent with our findings. With regard to the efficacy of misoprostol, our findings show that out of a total of 9 cases of PPH, 4 had severe PPH in group I versus 3 out of 7 in group II. This is in line with the results of most RCTs that assessed misoprostol against a placebo, and indicates that nearly half of women having PPH could suffer severe PPH.[10]

Shivering, nausea, and vomiting were the most adverse effects reported in our study. It was more frequent

Table 3 - The misoprostol adverse reactions reported in both groups.

Variable	Sublingual misoprostol (n = 118)		Rectal misoprostol (n = 97)	
Nausea, n (%)				
Mild	5	(4.2)	2	(2)
Moderate	-	-	-	-
Severe	-	-	-	-
Vomiting, n (%)			1	(1)
Mild	3	(2.5)	-	-
Moderate	-	-	-	-
Severe	-	-		
Shivering, n (%)				
Mild	10	(8.5)	4	(4.1)
Moderate	4	(3.4)	1	(1)
Severe	-	-		
Mild diarrhea, (%)	1	(0.85)	-	-
Headache, n (%)				
Mild	1	(0.85)	-	-
Moderate	-		-	-
Severe	-		-	-
Hot flashes, n (%)	4	(3.4)	1	(1)

in the sublingual group. The difference between the 2 groups may be related to the rapid absorption, and high bioavailability when given sublingually. Moreover, the rectal route can avoid gastrointestinal side effects. For this reason, many researchers have recommended that rectal misoprostol route can be used in patients who are vomiting, or unable to take oral medications, those who are under general anesthesia, or those with heavy vaginal bleeding.[19-21] However, these adverse effects were mostly mild, transient, and self-limiting. They should not be considered relevant outcome. We would recommend as others cited, that patients must be informed that shivering, mild nausea, vomiting, and hot flashes among other minor symptoms can be expected.

Serious morbidity did not occur in our study in either group. In our study, we observed that the patient's acceptability to place 3 tablets (600 µg) of misoprostol under the tongue for 20-30 minutes was low and inferior, compared to higher acceptability when the same dose was given per rectum. Despite this, there was no refusal rate noted. The majority of patients in this study have no preference as to the gender of the attendant.

In this study, we have many limitations. First, this study was conducted in one referral hospital, thus, the incidence of acute PPH presented in this study could not be generalized. Second, it was a preliminary study, and the number of women enrolled in this study was low. Despite this limitation, however, other studies published in the literature with higher women recruited, supported our results. Nevertheless, further studies on this issue are warranted.

In conclusion, we observed that sublingual misoprostol 600 µg when given immediately after delivery to prevent PPH has comparable effect on blood loss as that seen, when the same doses are given per rectum, as well as, with minimal side-effects. We believe that routine administration of misoprostol drug 600 µg (3 tablets) in either route immediately after vaginal delivery can be beneficial to reduce PPH in primary health setting of remote rural areas, where the facilities to give the routine injectable uterotonic agents are unavailable, and where misoprostol is the only feasible choice, keeping in view that severe PPH could complicate large proportion of women given the drug by either route.

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