Misoprostol versus Prostaglandin F2α in the Third Stage of Labour

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Abstract

Objective: To compare the oral misoprostol with intramuscular prostaglandin F2α in the management of the third stage of labour.

Method: One hundred and ninety-eight patients were randomized to receive 600 μg misoprostol orally (n=96) or 250 μg prostaglandin F2α intramuscularly (n=102). Primary outcome was blood loss determined by estimation and change in hemoglobin values from admission to postpartum day 1. Secondary outcomes included additional oxytocic need, blood transfusion, manual removal of placenta, length of the third stage of labour. Potential side effects related to prostaglandins were also recorded.

Results: The baseline variables were similar. Blood loss of >500 mL occurred in 9.3% of the misoprostol group and 3.9% of the prostaglandin F2α group. Additional oxytocic therapy was required by 12.5% and 5.8%, respectively. Transfusion need was found similar in both groups. There was no difference in both groups with respect to prepartum and postpartum hemoglobin levels. Shivering and pyrexia were seen predominantly in misoprostol group. On the other hand, nausea, vomiting, diarrhea, and postpartum hypertension were seen predominantly in prostaglandin F2α group.

Conclusion: Combination of oral misoprostol with rapid onset parenteral oxytocic may not only be more effective therapy, but also reduce dose-dependent unpleasant side effects.

Key words: postpartum hemorrhage, prostaglandins, misoprostol, prostaglandin F2α

Özet

Doğumun III. Evresinde Misoprostol ve Prostaglandin F2α'nın Karşılaştırılması

Doğumun III. evresinde misoprostol ve prostaglandin F2α'nın etkinliği karşılaştırıldı. Normal gebeliği olan 198 hasta, 250 μg intramüsküler prostaglandin F2α ya da 600 μg oral misoprostol alacak şekilde randomize edildi. Postpartum kanama insidansı, ek oksitosik ilaç ve kan transfüzyon ihtiyacı, hastaneye kabul ve postpartum 1. gün hemoglobin düzeyleri, prostaglandinlere bağlı muhtemel yan etkiler ve hastaların obstetrik öyküleri kaydedildi. Çalışmaya alınan 198 hastanın 96'sına oral misoprostol, 102'sine intramüsküler prostaglandin F2α tedavisi uygulandı. Postpartum kanama insidansı misoprostol grubunda %9.3, prostaglandin F2α grubunda %3.9 bulundu. Ek oksitosik ihtiyacı, sırasıyla %12.5 ve %5.8 idi. Postpartum transfüzyon ihtiyacı ve grupların prenatal ve postpartum hemoglobin düzeyleri benzer bulundu. Titreme ve ateş şikayeti daha çok misoprostol uygulanan hastalarda görülürken, ishal, bulantı, kusma ve postpartum hipertansiyon daha çok prostaglandin F2α kullanan hastalarda görüldü. Bu çalışmada, postpartum kanamanın önlenmesinde, özellikle erken postpartum dönemde misoprostol, prostaglandin F2α'ya oranla başarısız bulundu. Misoprostolün hızlı etkili parenteral bir oksitosik ile kombinasyonu hem daha etkili bir tedavi sağlayacak, hem de yan etkileri en aza indirecektir.

Anahtar sözcükler: postpartum hemoraji, prostaglandinler, misoprostol, prostaglandin F2α

Introduction

The third stage of labour is potentially the most hazardous part of childbirth for the mothers, mainly because of the risk of postpartum hemorrhage which is a leading cause of maternal death not only in developing countries, but also in developed countries (1). Active management of this stage which involves prophylactic administration of an uterotonic agent, early cord clamping and cutting, and controlled cord traction has been shown to reduce the incidence of postpartum blood loss. With routine prophylactic administration of uterotonic drugs, the risk of postpartum hemorrhage could be reduced by approximately 30 to 40% (2-4).

However, traditionally oxytocin and ergometrine or a combination of both has been the first approach for postpartum hemorrhage; more recently prostaglandin analogues, with few side effects associated with the natural prostaglandins, have attracted widespread attention because of their strong uterotonic effect and shown to reduce the postpartum blood loss effectively (5-7). To best of our knowledge, all prostaglandins currently available have been used successfully in the treatment of uterine atony and various routes of administration such as intrauterine, intramyometrial, transabdominal and intracervical, transvaginal, intravenous, intramuscular, vaginal and rectal have been described, even for the same drug but there is no consensus on optimal prostaglandin preparation, dose and route of administration. We therefore con-

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Table 1. Demographic characteristics

Characteristics	Misoprostol (n=96)	PGF2α (n=102)	P
Mean age (years)	29.4±5.8	31.4 ±6.1	NS
Gravida	5.8 ± 1.49	5.4 ±1.59	NS
Parity	3.6±1.2	3.8± 0.8	NS
Mean gestational age (wk)	39.6 ±0.8	38.5 ± 0.6	NS
Birth weight (g)	3245±565	3450 ±415	NS

Values are given as ±SD
NS: Not significant

ducted a randomized controlled trial to compare the efficiency and safety of intramuscular prostaglandin F2α (PGF2α) and oral misoprostol in the management of the third stage of labour.

Material and Methods

Women who anticipated a vaginal delivery at Şanlıurfa State Hospital were invited to participate in the study. One hundred and ninety-eight women, with singleton pregnancies at term, and who did not require augmentation with oxytocin, were recruited to the study after informed consent was obtained. Exclusion criteria included placenta previa, multiple pregnancy, intrauterine death, gestational age less than 32 weeks, women with history of postpartum hemorrhage, women in their sixth pregnancy or more, prior caesarean section and pre-eclampsia.

When vaginal delivery became imminent, the patients were randomized by the computer-generated study boxes which were containing either misoprostol (Cytotec®, Ali Raif, Turkey) or PGF2α (Hemabate®, Farmacia, Germany). For misoprostol group three capsules (200 µg) of misoprostol were administered orally and for PGF2α group 250 µg PGF2α was administered intramuscularly after cord clamping. After delivery, the uterus was massaged and the placenta was extracted by controlled cord traction. If placenta was not delivered after 30 to 60 minutes, it was removed manually. Additional oxytocic drug was not given but the midwives were instructed to do so if they felt that there was a clinical indication.

The main outcome of the present study was to ascertain the rate of postpartum hemorrhage in groups of women given oral misoprostol and intramuscular PGF2α. Postpartum hemorrhage was defined as an estimated blood loss of >500 mL measured by midwife. Secondary outcomes included need for blood transfusion, and further oxytocic drugs. We also recorded the length of the third stage, the rate of manual removal of placenta. Maternal hemoglobin and hematocrit values were measured prenatally and 24 hours after delivery. Potential adverse effects of misoprostol, and PGF2α, were also recorded: nausea and vomiting, diarrhea, shivering, and hypertension (defined as a diastolic blood pressure >90 mmHg or a systolic blood pressure >140 mmHg).

Statistical analysis was performed using the Statistical Package for Social Science for Windows (SPSS, Inc.). Differences between two groups were assessed using chi square test for categorical variables data and Mann-Whitney U test for continuous variables. A *P* value of <0.05 was considered as statistically significant.

Results

The present study included 198 women, 102 receiving intramuscular 250 µg PGF2α and 96 receiving 600 µg oral misoprostol. Demographic characteristics and labour variables are summarized in Table 1. The age, gravida, parity, abortion, gestational age, and birth weight were similar in both groups, indicating that baseline characteristics of patients selected remained similar in both arms of the trial. Primary and secondary outcomes are shown in Table 2. Although patients receiving misoprostol showed a tendency for increased blood loss and needed more additional oxytocic drugs, no differences were found between two groups regarding the hemoglobin level one day after delivery and need for blood transfusion. Postpartum hemorrhage was found to be 9.3% in misoprostol group and 3.9% in PGF2α group. The need for additional oxytocic therapy was found to be 12.5% and 5.8%, in misoprostol and PGF2α groups, respectively. The median length of the third stage of labour was 5 minutes in misoprostol group, and 4.5 minutes in PGF2α group. There was no difference in the incidence of prolonged third stage of labour, and the need for manual removal of placenta.

Table 2. Effect of oral misoprostol 600 µg compared with intramuscular PGF2α 250 µg in the third stage of labour

Outcome measures	Misoprostol (n=96)	PGF2α (n=102)	P
Postpartum hemorrhage >500 mL	9 (9.3)	4 (3.9)	<0.001
Additional oxytocic need	12 (12.5)	6 (5.8)	<0.001
Transfusion	3 (3.1)	2 (1.9)	NS
Manual removal of placenta	2 (2.08)	2 (1.9)	NS
Third stage of labour >30 min	2 (2.08)	1 (0.95)	NS
Hb (g/dL) prepartum	10.2 ± 1.3	10.5 ± 1.2	NS
Hb (g/dL) postpartum	9.2 ± 0.8	9.4 ± 1.2	NS

Values are given as n (%) or ±SD as appropriate

Table 3. Side effects of oral misoprostol compared with intramuscular PGF2α

Side effects	Misoprostol (n=96)	PGF2α (n=102)	P
Diarrhea	2 (2.08)	21 (20.5)	<0.001
Shivering	13 (13.5)	4 (3.9)	<0.001
Pyrexia	8 (8.3)	2 (1.9)	<0.001
Nausea-vomiting	5 (5.2)	18 (17.6)	<0.001
Hypertension (>140/90)	4 (2.16)	16 (15.6)	<0.001

Values are given as n (%)

Side effects are listed in Table 3. Patients receiving misoprostol were associated with a significantly higher rate of shivering and pyrexia as compared with the PGF2α; on the other hand, significantly more women in PGF2α group developed nausea, vomiting and diarrhea after injection when compared with misoprostol. All these patients with nausea and vomiting responded well to the metaclopramide injections. The diarrhea was watery, no-bloody, but very frequent and foul-smelling, and usually developed within an hour of injection. No medication was started for diarrhea and conservative measures were remedy for all.

Discussion

The routine use of oxytocin has been effective in reducing the incidence of postpartum hemorrhage. Though various oxytocics like ergometrine, oxytocin and prostaglandins are available, no single drug has emerged the most superior or 'drug of choice'. The use of prostaglandins in postpartum hemorrhage was first described in 1976 (8). Since prostaglandins play a fundamental role in physiological homeostasis cascade including vasoconstriction provoked by myometrial contraction and intravascular thrombosis in placental bed induced by platelet adhesion, and fibrin formation (9), prostaglandin analogues use for postpartum hemorrhage would be expected to result in possibly more sustained therapeutical effect in target organ tissues than other conventional oxytocics. There have been numerous reports of superior haemostatic effect of prostaglandins, especially in case with severe postpartum hemorrhage due to uterine atony (10-12). Their dramatic effect in the arrest of hemorrhage when the other oxytocics have failed, justifies the conclusion that use of prostaglandins reduces the number of cases that may need uterine packing, internal artery ligation and even hysterectomy (7).

To best of our knowledge, there is no consensus on optimal prostaglandin analogue, its dose or route of administration in the management of postpartum hemorrhage. There has been no randomized controlled trial comparing intramuscular PGF2α and oral misoprostol. In our trial, it was found that PGF2α was better than misoprostol in controlling blood loss during the third stage of labour. Patients given oral misoprostol showed increased blood loss and needed more additional oxytocic drugs. However, somewhat surprisingly, there was no difference between two groups with respect to hemoglobin levels 24 hours after delivery and need for transfusion. This may be explained by that hemorrhage early in the third stage of labour probably could not be prevented by oral misoprostol, and then we speculate that the superior prophylactic effect of PGF2α over oral misoprostol may be related to the late onset of action of oral misoprostol or time to reach peak plasma concentration after its oral administration. It would be unlikely that a problem related with late onset of action of oral misoprostol occurs, since it was reported that absorption of misoprostol is very rapid, being detected in the circulation within 2 minutes of its oral ingestion (13). However, misoprostol has been shown to reach its peak plasma concentration at 30 min. after oral ingestion (14), which might explain the lower effectiveness. On the other hand, there were no differences between both groups in postpartum hemoglobin and hematocrit values, and this may be explained by a sustained contraction of the uterus and subsequent reduction of blood loss in the hours of delivery in misoprostol group or method of determination of blood loss which was based on subjective visual observation of the midwife rather than an objective measurement. Therefore, we believe that, combining of the visual blood loss determination with changes in hemoglobin and hematocrit values may be a more reliable estimation of blood loss. It is possible to conceive that the concomitant administration of misoprostol with PGF2α or parenteral oxytocic would result in a more effective postpartum blood loss reduction: parenteral oxytocic for the prevention of immediate uterine bleeding after delivery and oral misoprostol for the reduction of blood loss in the hours following delivery.

In the present study, analysis of side effects showed that shivering and pyrexia were most frequently seen in the misoprostol group. Both shivering and pyrexia occurring with use of misoprostol are likely to be a prostaglandin side effect on central thermoregulatory centers. Shivering was an undesirable side effect, though it was self-limiting and responded to chlorpheniramine. In a similar way, pyrexia may be of limited clinical concern, however it can make the obstetrician suspicious of infection and cause unnecessary tests or initiation of antibiotic therapy. Nausea, vomiting, and diarrhea were unpleasant side effects occurring frequently in the PGF2α group.

Diarrhea was a major adverse reaction associated with PGF2α. In our experience, it was a serious side effect that could not be described as moderate. In agreement with our result, Chua S, et al. also reported a statistically significant increase in the incidence of profuse frequent diarrhea with use of PGF2α. In their randomized controlled study, they concluded that use of 125 µg PGF2α had the disadvantage of higher cost and diarrhea (7). One of the striking findings of the present study was the greater incidence of hypertension

seen in patients who received PGF2α. Lack of hypertension with misoprostol use may be an advantage especially for women with pre-eclampsia.

It is our opinion that the use of intramuscular PGF2α for prevention of postpartum hemorrhage is more effective than oral misoprostol administration. However, prostaglandin related side effects associated with PGF2α, such as nausea, vomiting, hypertension, and especially diarrhea, make this prophylactic regimen difficult and impractical. It seems that use of oral misoprostol is less effective in very early postpartum period than in the hours following delivery; hence, we think that a combination of misoprostol with rapid onset parenteral oxytocic would be more appropriate in the future therapy.

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