Misoprostol for induction of labor in women with severe preeclampsia at or near term

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ABSTRACT

الأهداف: معرفة مدى تأثير علاج الميزوبروستول في تحريض الولادة للنساء المصابات بمقدمة الارتعاج الشديد وعندما تكون حالة عنق الرحم غير مهيأة للولادة بعد مرور 36 أسبوع من الحمل .

الطريقة: أُجريت هذه الدراسة الاستطلاعية المقارنة في مستشفى الثورة العام، صنعاء، اليمن، واستمرت خلال الفترة من يونيو 2009م إلى يونيو 2010م. شملت الدراسة 113 امرأة ممن تتماشى صفاتهن مع شروط الدراسة، وتم تقسيمهن إلى مجموعتين: مجموعة الدراسة (العدد:56)، ومجموعة الشاهد (العدد:57). لقد أُعطيت مجموعة الدراسة 50 ميكروغرام من الميزوبروستول عن طريق المهبل كل 4 ساعات وإلى حد أقصى يصل إلى 6 جرعات، بينما لم تُعط مجموعة الشاهد شيئاً. لقد تم تجميع بيانات كافة المشاركات في الدراسة وعمل مقارنة فيما بينها وكانت هذه البيانات كالتالي: عمر المريضة وقت الحمل، ومدة الحمل، وعدد الولادات السابقة، وحالة عنق الرحم الأولية، ومعدل العمليات القيصرية، وحالة الأجنة أثناء وبعد الولادة.

النتائج: أشارت نتائج الدراسة إلى حدوث الولادة المهبلية عند 69.6% من النساء في مجموعة الدراسة، بينما كانت في مجموعة الشاهد 15.8% (p<0.0001). وقد أُجريت العمليات القيصرية على 30.3% من المشاركات في مجموعة الدراسة، فيما أُجريت على 84.2% من المشاركات في مجموعة الشاهد (p<0.0001). وكان متوسط الوقت منذ أول جرعة ميزوبروستول إلى وقت الولادة 12.12±2.1 ساعة، وبلغ متوسط الجرعات 2.77±1.3. لم يكن هناك اختلافاً واضحاً بين المجموعتين فيما ترتب على علاج الميزوبروستول من مضاعفات مثل اضطراب نبضات القلب، ومؤشر أبغار، والدخول إلى وحدة العناية المركزة.

خاتمة: أثبتت الدراسة فعالية إعطاء علاج الميزوبروستول عن طريق المهبل وبمقدار 50 ميكروغرام كل 4 ساعات، حيث أنه أدى إلى تهيئة عنق الرحم وحدوث الولادة الطبيعية لدى هذه المجموعة من النساء.

Objectives: To examine the misoprostol efficacy and safety in induction of labor of women with severe preeclampsia at or near term when the cervix is unfavorable.

Methods: A prospective comparative study was conducted in Al-Thawara General Hospital Sana'a, Yemen, from June 2009 to June 2010. One hundred and thirteen women met the inclusion criteria. They were divided into 2 groups. The study group (n=56) and the control group (n=57). The study group were given 50 µg of Misoprostol intravaginally every 4 hours to a maximum of 6 doses. Maternal age, gestational age, parity, initial cervical status, the rate of cesarean section, and neonatal outcomes were analyzed and compared to the control group.

Results. The vaginal delivery was achieved in 69.6% in the study group versus 15.8% in the control group (p<0.0001). The overall cesarean section was performed in 30.3% of the study group versus 84.2% (p<0.0001). The mean time from insertion to delivery was 12.12±2.1 hours and the mean dosing was 2.77±1.3. There were no significant differences between the 2 groups in the frequency of abnormal fetal heart rate, Apgar score and admission to the neonatal intensive care unit.

Conclusion: Misoprostol when given intravaginally in 50µg 4-hourly dosing regimen is an effective agent for ripening the cervix in this group of women.

Saudi Med J 2011; Vol. 32 (7): 679-684

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Received 30th January 2011. Accepted 28th May 2011.

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Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Preeclampsia complicates 5-8% of pregnancies,[1] and severe preeclampsia is responsible for an important proportion of fetal and maternal morbidity and mortality.[2] Preeclampsia is usually defined as severe in the presence of systolic blood pressure >160 mmHg or diastolic blood pressure >110 mm Hg, with severe proteinuria (at least 5 gms per 24 hours period). In addition, it is considered severe in the presence of eclampsia, pulmonary edema, symptoms suggestive of significant end-organ involvement (such as persistent headache, visual disturbances, epigastric or right upper quadrant pain) oliguria <500 ml/24 hours, hemolytic anemia, thrombocytopenia, severe intrauterine growth restriction, or oligohydramnios.[3]

Delivery remains the only definite treatment. There is a general agreement to terminate the pregnancy when maternal or fetal conditions are deteriorated, or once 34 week's gestation is reached.[2] However, the mode of delivery after 34 week's in women with severe preeclampsia with unfavorable cervix remains a controversial issue in obstetrics.[4] It is generally more convenient to choose cesarean section rather than induction of labor because a low Bishop score is associated with a high failure rate of vaginal delivery.[5] There are various rates of the successful induction of labor reported in the literature for women with severe preeclampsia. However, many trials found that the cesarean section rates increase when induction is decided and thereby generate additional morbidity and cost.[6] Others report the safety and value of induction of labor even when preterm.[7] Use of agents to ripen the cervix prior to conventional methods of induction is the standard practice.[8] Misoprostol is a synthetic analogue of prostaglandin E1 often used to enhance success.[7,8] We hypothesized the use of intravaginal Misoprostol for induction of labor in women with severe preeclampsia after 34 weeks gestation when the termination is decided in an unfavorable cervix, could reduce the cesarean section rate. The purpose of this study was to determine the rate of vaginal and cesarean deliveries after induction of labor with intravaginal Misoprostol in women with severe preeclampsia with unfavorable cervix after 36 weeks gestation, in comparison to that having the same conditions and without induction.

Methods. This is a prospective cohort study conducted in Al-Thawra General Hospital, Sana'a, Yemen between June 2009 and June 2010. During the study period, there were 113 women admitted to the delivery room with severe preeclampsia. They are all included in this study. The inclusion criteria were: 1) Pregnant woman with severe preeclampsia, 2) thirty-six weeks gestational age or more, 3) singleton pregnancy, 4) cephalic presentation, 5) intact membranes, 6) bishop score <6, and 7) reassuring fetal heart pattern. The exclusion criteria were: abnormal fetal heart pattern, malpresentation, estimated fetal weight ≥4000 g or evidence of cephalopelvic disproportion, ruptured membranes, any contraindication for Misoprostol including pre-existing cardiovascular disease, asthma, renal or hepatic disorders, severe anemia and coagulopathy, previous uterine scar, suspected chorioamnionitis, parity ≥5, and other obstetric indication for cesarean section.

These women were divided into 2 groups, the study group (n=56) was assigned to receive intravaginal Misoprostol drug and the control group (n=57) were left without intervention until spontaneous improvement of the cervix occurred or the time-limit of 24 hours had elapsed and then delivered by elective cesarean section. The study and control groups were selected randomly by 1:1 ratio to receive either Misoprostol or none. All women with severe preeclampsia were subjected to detailed history, physical and obstetric examination and laboratory screening. Hemoglobin level, platelet count, uric acid, liver function tests, renal function tests, 24 hour urine protein collection and urinalysis were obtained. Foley's catheter was inserted and ultrasonography for fetal assessment as presentation, amniotic fluid index, estimation of fetal size, location of the placenta and gestational age estimation. The consent from all participants were obtained after full explanation of the study purposes. The following data were obtained from each patient: age, parity, gestational age, (determined by either last menstrual period (LMP) or first trimester ultrasonography), past obstetric history including previous preeclampsia, previous cesarean section, past medical history, antihypertensive agents taken, Bishop score at admission, Apgar score at 1 and 5 minutes, neonatal outcome and need for admission to neonatal intensive care unit (NICU), and postpartum hemorrhage. Vaginal examination was performed initially and then every 4 hours to determine the Bishop score by the same person if possible and the changes were recorded.

For the study group, we used Misoprostol tablet of 200 µg and only 50 µg (1/4th tablet) was inserted into the posterior vaginal fornix sequentially every 4 hours up to a maximum of 6 doses or until adequate uterine contractions (≥3 per 10 minutes of 40 seconds duration or more each), cervical ripening (Bishop score >8) had developed or 24 hours had elapsed without response. The medication was discontinued at any time when one of the following developed: Worsening of the condition despite the medication, Non-reassuring fetal heart pattern (defined as persistent fetal tachycardia >160 bpm, bradycardia <110 bpm), prolonged decelerations, moderate to severe variable deceleration,

Abnormal uterine activity. This is defined as: (a) tachysystole, ≥6 uterine contractions in 10 minutes for 2 consecutive 10 minutes windows, (b) hypertonus, as a single uterine contraction of at least 2 minutes, (c) hyperstimulation syndrome, as the presence of tachysystole or hypertonus associated with abnormal FHR preterns. When these complications did occur, they were treated by left lateral position, nasal oxygen and by sublingual 10mg nifedipine with no further redosing of Misoprostol.

For all women with severe preeclampsia, the blood pressure is controlled with hydralazine drip or nifedipine 10 mg orally and magnesium sulfate is also given prophylactically against convulsion. All women who were given Misoprostol were monitored for blood pressure every 30 minutes, fetal heart rate every 30 minutes, frequency and duration of uterine contractions every 30 minutes and subjectively assessed for severity of the condition as headache, blurring of vision, epigastric pain and also for the Misoprostol side effects namely; nausea, vomiting, shivering, feeling of hotness, diarrhea, pre-labor rupture of membranes did not preclude further Misoprostol dosing if Bishop score still <8. Women who achieved Bishop score of ≥8 without labor progress, the augmentation of labor was used. Artificial rupture of membranes was performed when seemed clinically safe and cervical dilatation was more than 3 cm. Three hours later, oxytocin drip was given when adequate uterine contractions were not ensued. The protocol for oxytocin administration was followed: dilution of 5 units of oxytocin in 500 ml of normal saline. The infusion starting at 5 mu/minute (10 drops) and escalated by 10 drops per minute every 30 minutes until 3 uterine contractions in 10 minutes were achieved and maintained.

Failure of induction was defined as failure to achieve vaginal delivery within 24 hours starting at the first time of Misoprostol insertion. The woman therefore, was labeled as unfavorable patient and cesarean section was carried out. This study was carried out according to the Helsinki Declaration principles and the ethical approval was obtained from the hospital ethical committee.

Statistical analysis. Data were processed using SPSS version 11.0 (SPSS Inc. Chicago, IL, USA). Mean and standard deviation as well as proportion were used as appropriate for describing data. Chi square test (x^2) was used for qualitative variables and student-t test for quantitative variables. 95% confidence intervals (CIs) for independent variables were calculated as appropriate. P value <0.05 was considered statistically significant.

Results. The maternal age, parity, gestational age and initial Bishop score for the study and control group are presented in **Table 1**. Among the total of 113 cases included in the study, 69.6% of women (39/56) in the study group had successful induction and delivered vaginally. Approximately 15.8% of women (9/57) in the control group were delivered vaginally. The difference between the 2 groups was statistically significant (p<0.0001). The mean of initial Bishop score in the 2 groups was not statistically different (p>0.05). For the study group, the mean Bishop score after 12 hours (3 doses; 150 µg Misoprostol) was 8.22 ± 1.8; range 6-12. There were 8 cases (14.3%) that showed no response after the final (6th) dose of Misoprostol and therefore, recorded as failed induction. The mean Misoprostol dosing was 2.77 ± 1.3 and the mean hours for ripening the cervix in the responsive women was 10.8 ± 4.8. The main time from insertion to delivery for those who showed successful induction was 12.12 ± 2.1 hours. A significant number in the induced group 29 cases (51.8%) delivered vaginally within 12 hours. The cesarean section was performed for 30.3% of the study group versus 84.2% of the control group. The difference was statistically significant (p<0.0001). The indications for cesarean sections after induction were failure of induction 8 cases (14.3%) and fetal distress 9 cases (16%) including 3 cases (5.4%) that developed tachysystole. These women demonstrated excessive uterine contractions after the second Misoprostol dose. These findings precluded redosing of Misoprostol and the women were referred for cesarean operation.

For the control group, 6 cases (10.7%) developed fetal distress and the remaining 42 cases (73.7%) had elective cesarean section. There was no significant difference between the groups in relation to the fetal distress (p>0.05). The recorded fetal distress was in the form of tachycardia (>180 bpm) and variable deceleration. Twenty-three cases (41%) of the study group received oxytocin augmentation due to inefficient uterine contraction. Maternal side effects of Misoprostol medication including nausea, vomiting, shivering, fever and so forth were uncommon. **Table 2** presents the obstetric findings and outcomes.

Discussion. Our results showed that the vaginal delivery was achieved in 69.6% of women in the study

Table 1 - Characteristics of the study and control groups.

Variable	Study group (n=56)	Control group (n=57)	*P*-value
Age, year	26.5 ± 5.3	25.36 ± 4.5	NS
Gestational age, (week)	37.9 ± 1.2	37 ± 1.17	NS
Gravidity			
Para 1	20 (35.7)	27 (47.4)	NS
Para ≥2	36 (64.3)	30 (52.6)	NS
Initial Bishop score	4.6 ± 0.4	4.5 ± 0.5	NS

The data presented as mean ± standard deviation, and n (%).
NS - non-significant

Table 2 - Obstetric findings and outcome.

Variable	Study group (n=56)	Control group (n=57)	*P* value	95% confidence interval
Bishop score after 12 hours	8.22 ± 1.8	5.31 ± 0.6	<0.0001*	2.41-3.41
Mean misoprostol dosing	2.77 ± 1.3			
Mean induction time, h	10.8 ± 4.5			
Insertion to delivery time	12.12 ± 2.1			
Oxytocin augmentation	23 (41.0)			
Need for ARM	9 (16.0)			
Spontaneous vaginal delivery	39 (69.6)	9 (15.8)	<0.0001*	36.71-70.89
Vaginal delivery ≤12 hour	29 (51.8)			
Vaginal delivery ≤24 hour	10 (17.8)			
Cesarean section	17 (30.3)	48 (84.2)	<0.0001*	36.82-70.98
Indications for cesarean section				
Failed induction versus elective	8 (14.3)	42 (73.7)	<0.0001*	42.98-75.82
Fetal distress	9 (16.0)	6 (10.5)	NS	
Postpartum hemorrhage	4 (7.1)	5 (8.8)	NS	
Preterm labor	13 (23.2)	11 (19.2)	NS	
Apgar score <7				
1 min	19 (34.0)	13 (22.8)	NS	
5 min	7 (12.5)	4 (7.0)	NS	
Admission to NICU	5 (9.0)	3 (5.2)	NS	
Still birth	1 (1.8)	-		
Misoprostol side effect		-		
Nausea	5 (9.0)	-		
Vomiting	4 (7.1)	-		
Shivering	6 (10.7)	-		
Fever	3 (5.3)	-		

The data presented as mean ± standard deviation, n (%).
*highly significant, ARM - artificial rupture of membrane, NICU - neonatal intensive care unit.
NS - not statistically significant

group who were induced by intravaginal misoprostol. These findings are consistent with other studies.[1,9,7] However, strong variations exist in the literature as which mode of delivery is considered appropriate for this group of women, and deciding on this issue is often difficult and influenced by other variables such as low Bishop score and high failure rate of vaginal delivery.[5] The failure of induction is attributed to many hypotheses proposed. One potential explanation is that preeclampsia causes placental insufficiency and/or abruption of the placenta with a resultant non-reassuring fetal heart pattern.[1] The fetus, thus poorly tolerates labor induction. Furthermore, in the setting of induction, several variables can have a significant impact on the induction success such as magnesium sulfate which is commonly given for seizure prophylaxis in this population and poses tocolytic effects on the uterus. In addition, it has been shown that it may decrease fetal heart variability and both effects could contribute to failure of induction.[1] However, these potential adverse effects of magnesium sulfate have been debated by other studies,[10] and the definitive effects need further assessment.

On the other hand, some authors advocate that the labor is easier to induce in women with preeclampsia based on an increase in their baseline uterine contractility compared to women without preeclampsia,[1] but there is no well-documented evidence to support this belief. Our investigation could not support such observation as 41% of the study group received oxytocin augmentation that suggests the uterine contractility was not adequately triggered by misoprostol alone. The high successful induction rate observed in this study could be explained: Firstly, our population had advanced gestational age (≥36 weeks). Nassar et al[11] found that the advanced gestational age affects positively the induction success ranges from as low as 31.6% at ≤28 weeks gestation to as high as 62.5% at >32 weeks. Secondly, the high proportion of our population (64.3%) had previous vaginal delivery at least once which is considered as a potential predictor of successful labor induction.[12]

Although, there are large discrepancies among different trials with regards to the cesarean section rates in severe preeclampsia before 34 weeks, the disparity also presents at or near term. The cesarean delivery rates have been reported to range between 18-37.3% in some studies.[13-15] Generally, the cesarean section rates are affected by obstetrical factors (nulliparity, previous scar, obesity), institutional differences (hospital type, size, patient insurance), and also across the levels of hospital care.[16]

Mostello et al[16] found a higher cesarean section rate (38%) for women with severe preeclampsia at term when managed in primary care versus 30% managed

in tertiary care. Our data showed the rate of cesarean section after failed induction was 14.3% compared to 73.7% elective cesarean in the control group. These findings are comparable to other studies.[1,4,7,13] The possible explanation of the high rate of elective abdominal delivery noted in the current investigation is that women with severe preeclampsia near or at term frequently require expeditious delivery. Therefore, in an unfavorable cervix it is easier for the obstetricians to do cesarean operation than to wait the likely longer time of induction with the potential failure in an already compromised pregnancy. However, this high rate suggests that if women were given enough time more than 24 hours, the chance of vaginal delivery might have been more frequent. Certainly, it is important to stress that the benefits of vaginal delivery have to be carefully balanced against serious and progressive maternal and fetal complications.

Our analysis demonstrated that vaginally applied Misoprostol is an effective agent for ripening the cervix in this group of women. There were more than half of women (51.8%) delivered within the first 12 hours. Also there was less need for artificial rupture of membranes and oxytocin augmentation. These findings are comparable to other multiple trials.[9,17] Misoprostol has been administrated in various routes and different regimens have been proposed for labor induction. However, different oral regimens seemed to be less effective than vaginal preparation.[17] This could be related to pharmacokinetic properties which revealed the greater systemic bio-availability of vaginally administered drug. The peak levels are attained more slowly, but sustained for longer periods. In addition, there is probably a direct effect on the cervix.[18] As regards to the safety of 50 microg intravaginal misoprostol, we could speculate that within the limited scope of this study, is safe. The medication adverse effects noted in our investigation were uncommon. Nevertheless, the concern about tachysystole with or without hyperstimulation is still present. These adverse effects have been observed more frequently when misoprostol was compared with placebo or dinoprostone.[19] Paungmora et al[20] found a significantly higher incidence of uterine tachysystole in the vaginally administered group compared to oral group (17.1% versus 5.3%, p=0.032).

In our study 3 cases (5.4%) were complicated by tachysystole, but we could not identify any particular characteristic of those women which might explain their excessive uterine activities. The suggestion is that, these women may have a high sensitivity to the drug resulting in such abnormal response. It is reported that the occurrence of tachysystole did not increase the likely intervention for abnormal fetal heart tracings.[18] Our results in contrast, showed that all 3 cases were having cesarean section. The likely explanation is the higher sensitivity of the obstetricians to this particular effect which undoubtedly led them to move towards cesarean section to avoid unexpected fetal hypoxia. However, further studies in this area are needed to validate our speculation and to better define the safety profile of Misoprotol. No significant differences existed in neonatal morbidity and mortality in term of 1 and 5 min Apgar scores, requirement of resuscitation, admission to NICU and stillbirth. These findings are in the line with other studies that reported no additional major hazards to fetuses undergoing an induction of labor.[7]

The limitations of this study were: effects of Misoprostol in doses of 50 µg every 4 hours empirically and based only on our experience with other groups of women having no preeclampsia. Inability to observe postpartum maternal morbidity apart from the early onset postpartum hemorrhage because of early discharge policy that is followed in this hospital. Further limitation was that this study was hospital-based and therefore, we may not be able to generalize the results to other population. However, our findings reported in this study emphasize that in this high-risk group the vaginal delivery within 24 hours is common when a trial of labor using Misoprostol is attempted.

In conclusion, induction of labor using 50µg Misoprostol intravaginally every 4-hours dose interval for eligible women with severe preeclampsia at or near term when the cervix is unfavorable should be advised. It is frequently successful and could reduce the cesarean section rate in this population.

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