Efficacy of Vaginal Misoprostol in Induction of Preterm Severe Preeclampsia

PRETERM AĞIR PREEKLAMPTİK GEBELİKLERDE DOĞUM İNDÜKSİYONU İÇİN VAGINAL MİSOPROSTOLÜN ETKİNLİĞİ

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Summary

Objective *: To assess the efficacy of vaginal misoprostol, when rapid delivery is needed in severe preeclampsia remote from term.*

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Materials and methods: *Randomized clinical trial. Thirty seven preeclamptic cases between 20-24 weeks of gestation were randomized to vaginal misoprostol (19 cases) and oxytocin infusion with cervical PGE_2 gel (18 cases) groups. The outcome of labor induction with different agents were analyzed with menn-withney U-test.*

Results *: Interval between the beginning of induction of labor and delivery was significantly shorter in misoprostol group (593 minutes, median) in comparison with oxytocin-PGE2 group (1277 minutes, median) ($p<0.001$). Duration of magnesium sulfate treatment and indwelling urinary catheterization was significantly shorter In misoprostol group ($p<0.05$). There was no statistically significant change in hospital stay. Endometritis and urinary infection was seen in two cases of oxytocin-PGE? group.*

Conclusion: *Misoprostol application provides safe and rapid vaginal delivery without associated time related morbidity.*

Key Words: Misoprostol, Severe preeclampsia, Labor induction

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Özet

Amaç: Preterm ağır preeklamptik gebelerde doğum indüksiyonu için vaginal misoprostolün etkinliğini değerlendirmek.

Çalışmanın Yapıldığı Yer: *GATA Kadin Hastalıkları ve Doğum Anabilim Dalı*

Materyal veMetod: *Randomize kontrollü çalışma. 20-24 gestasyon haftasındaki 37 şiddetli preeklamptik vaka, servikal PGE-ı jel ile oxytosin infüzyonu (18 vaka) ve vajinal misoprostol (19 vaka) uygulantmı için randomize olarak gruplandırıldı.Farklı ajanlar ile yapılan eylem indüksiyon sonuçları menn-withney U-test ile değerlendirilmiştir.*

Bulgular: Eylem indüksiyonunun başlangıcı ile doğum arasındaki süre misoprostol grubunda (ortalama 593 dk.) oksitosin grubuna (ortalamal277 dk.) göre anlamlı olarak kısa bulundu ($p<0.001$).Magnesyum sülfat tedavisi ve iiriner katater süresi misoprostol grubunda anlamlı olarak daha kısa bulundu ($p<0.05$). Hastanede kalış süresi olarak her iki grup arasında istatiksel bir farklılık bulunamadı. Endometritis ve uriner infeksiyon 2 oksitosin-PGE2 vakasında görüldü.

Sonuç: Misoprostol kullanımı zamanla ilişkili morbiditeden bağımsız olarak hızlı ve güvenilir vajinal doğum imkanı sağlamaktadır.

Anahtar Kelimeler: Misoprostol, Şiddetli preeklampsi, Doğum indüksiyonu

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The most frequently used agents for induction of labor are oxytocin and prostaglandins (PGs) (1). Prostaglandins offer both cervical ripening and myometrial contractions while oxytocin provides only the latter. Therefore, oxytocin is usually combined with prostaglandin E_2 applied cervically (gel form) or vaginally (suppositories).

Misoprostol is a synthetic PGE_1 analogue and currently marketed for the prevention of peptic ulcers (7). Vaginal and oral administrations were reported to induce labor with strong myometrial contractions and cervical ripening simultaneously (2).

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Preeclampsia occurs 6-8% of all pregnancies and carries clinically significant morbidity for the mother and fetus (8).Delivery is the only definitive treatment of preeclampsia and the treatment of choice for the mother. In cases of severely affected mother (3) and fetus, rapid delivery is needed and vaginal route is preferred especially with a previable fetus.

Although with a limited number of such cases, this study was designed as a randomized clinical trial to assess the safety and efficacy of misoprostol to induce labor.

Materials and Methods

Thirty seven preeclamptic cases between 20-24 weeks of gestation were included in this study.

Severity of preeclampsia was assessed by ACOG criteria; 160 mmHg systolic or 110 mrnHg diastolic blood pressure at least, proteinuria of minimum 5 g/24 hours, platelet count below 100 000/ml, elevated serum transaminases, oliguria (less than 400 ml/24 hours), pulmonary edema, epigastric pain or cerebral or visual disturbances.

Age, gravidity, parity, gestational age, weight gain and Bishop scores before induction of the two groups were shown in Table 1.

We decided to deliver the patients when persistent severe hypertension (>160-110 mmHg, systolic-diastolic) despite Nifedipine 90 mg/day (expectant management), persistent oliguria, persistent severe headache or visual disturbances, and intrauterine growth retardation (IUGR) in ultrasound was diagnosed (Table 2).

We haven't faced any criteria of ACOG for severe preeclampsia implicating HELLP syndrome (platelet count<100 000/ml, elevated liver enzymes or hemolysis signs).

The rationale for vaginal delivery was that median gestational age for misoprostol group was 22.6 weeks and 23.1 weeks for oxytocin-PGE_2 group, namely the fetuses were immature or previable. IUGR was diagnosed in 6 (31%) and 6 (33%) of patients in misoprostol and oxytocin-PGE_2 groups respectively.

After ethic commitee permission ,Misoprostol (Cytotec, 200 mg/tablet, Searle Pharmaceuticals - Ali Raif İlaç Sanayi AŞ. İstanbul/TÜRKİYE) was administered 100 mg intravaginally and patients were monitored with electronic cardiotocography. In general satisfactory uterine activity was achieved. Only in one case we added another 100 mg after six hours.

Prostaglandin E_2-gel (Cerviprost gel, 0.5 mg: Organon/TÜRKiYE) was administered 0.5 mg to cervix and with cardiotocographic monitorization 10 IU oxytocin (Synpitan forte 5 IU/ampule: Deva Holding/TÜRKiYE) was infused in 500 ml of 5% Dextrose solution with an increasing rate (2 mU/min X 30 min).

All patients were routinely under intravenous magnesium sulfate prevention against convulsions and urine flow was monitored with indwelling Foley catheterization.

Statistical analysis were made with mann-withney u-test and $p<0.05$ was judged as statistically significant. Randomization was made with sealed envelopes using random number table, and none of the patients were excluded from the study.

Table 1. Characteristics of patients

	Misoprostol (nil 9)	Oxytocin-PGE_2 (n:18)
Age (year)	24.1 (16-39)	23.8 (17-35)
Gravidity	1.9(1-4)	2.1 (1-4)
Parity	1.1 (0-3)	1.3 (0-3)
Gestational age (week)	22.6 (20-24)	23.1 (20-24)
Weight gain (kg)	16.8 (8-23)	17.3 (9-21)
Bishop score before induction	3.2 (2-4)	3.4 (2-4)

Data are presented as median and range in parentheses.

Table 2. Indications for delivery

Indications	Misoprostol group (%)	Oxytocin-PGE2 group (%)
Severe hypertension(*) (>160-110mmHgsys-dias)	19 (100)	18 (100)
Persistent oliguria (less than 400 ml/24 hours)	6(31)	4(22)
Persistent severe headache or visual disturbances	4(22)	4(22)
IUGR in ultrasound (<fifth percentile)	6(31)	6 (33)

IUGR : Intrauterine growth retardation
(*) : Despite Nifedipine 90 mg/day

Table **3.** Main Outcome Variables

	Misoprostol group	Oxytocin-PGE_2 group
Labor room time (*) (min.)	593 (460-753)	1227 (827-1558)
MgS04 time from the beginning of induction (hours)	34.2 (32-35)	44.3 (38-51)
Hospital stay (days)	5.S (5-7)	6.3 (5-7)
Bleeding >500 ml	0	0
Complications Endometritis	0	1 (5.5%)
Urinary infection	0	1 (5.5%,)
Intrapartum fetal death	0	1 (5.5%)
Admission to NICU	19 (100%)	17 (94.5%)
Neonate lived	0	0
Cesarean delivery	0	3 (16.5 %)

NICU : Neonatal intensive care unit
(*) : Time interval from the beginning of induction to delivery

Results

Interval from the beginning of drug administration to delivery was found 593, and 1227 minutcs-median-in misoprostol and oxytocin-PGE_2 groups respectively ($p<0.001$).

All women in misoprostol group were delivered vaginally, and 3 women in PGE_2-Oxytocin group were delivered by Cesarean section because of convulsions.

Magnesium sulfate was administered by first admission. Here we emphasized time interval between active labor and postpartum 24 hours for usage of intravencous $MgSO_4$. $MgSO_4$ time for misoprostol group was 34.2 hours and 44.3 hours for oxytocin-PGE_2 group ($p<0.05$).

We haven't encountered bleeding more than 500 ml intrapartum and postpartum in either groups. Endometritis and urinary infection was diagnosed in 2 patients of oxytocin-PGE_2 group.

None of the newborns lived despite admission to neonatal intensive care unit. There was one intrapartum fetal death.

Maternal hospitalization time from the beginning of induction was 5.8 days -mean- for misoprostol group and 6.3 for oxytocin-PGE_2 group ($p>0.05$). Wc haven't seen any side effects as nausea, vomitting, fever diarrhea and rupture of uterus in both groups. But polysystole (more than 5 contractions in 1 minute) was more frequent in the misoprostol group (19%) than in the oxytocin group (%11).

Comments

Delivery is the treatment of choice for maternal management of preeclampsia (4) and failed induction was signiftciantly more common in the preeclamptic group then non preeclamptic group (8.2% vs 1.7%).

The first report of misoprostol for labor induction was in 1987, and 400 meg was used. Recently in various studies, misoprostol is used 50-100 meg usually (2,6). We used 100 meg as a halftablet, and only in one case we added 100 meg. after six hours.

Margulics et al (2) evaluated misoprostol and oxytocin to induce labor.This study was randomized controlled trial comparing 50 pg misoprostol administered intravagmally and IV oxytocin in labor-induction patients. Delivery occured within 24 hours in 79% of patients in the misoprostol group and in 62% in the oxytocin group.No significant differancies were noted in the induction to delivery interval , made of delivery or incidence of hyperstimulation.

Luis Sanchez- ramos et al compare the safety and efficacy of intravaginal misoprostol (50 pg) vs IV oxytocin infusion for labor induction.They found no statiscially significant differences between the groups for intrapartum complications incluciing hyperstimulation and way of dclivcry.But the interval from induction to vaginal delivery was significantly shorter in the misoprostol group (11 vs 18 hours; P=0.004)

Misoprostol can be used with oxytocin infusion sequentially, but in this study wc tried to show

whether or not misoprostol alone is efficient to induce labor and keep myometrial contractions going on.

One of the major priorities of misoprostol is that it causes very few serious maternal side effects (6). Nausea, vomitting, fever and diarrhea arc the mam side effects of prostaglandins, but we haven't seen any one of these in both groups.

Magnesium sulfate treatment is one of the major concerns in preeclamptic patient. Duration of MgS04 is correlated with delivery and postpartum course of hypertension and other parameters. MgS04 treatment has to be critically monitored for plasma concentrations, and respiratory and neurological side effects. That is why when indicated rapid delivery means rapid witholding of $MgS0_4$.

Endometritis and urinary infection seen in two cases of oxytocin-PGE_2 group may be attributed to extended duration of labor and indwelling bladder catheter.

Our study gives special emphasis to significantly shorter duration of labor. The main objective to use misoprostol in severe preeclamptic cases is to prevent time related morbidity. When vaginal delivery is indicated misoprostol should be the first choice to induce labor safely in such cases that fetal well being is not of concern, but maternal well being is.

REFERENCES

1. American College of Obstetricians and Gynecologists, induction and augmentation of labor. A C O G technical bulletin no: 157. Washington, DC: American College of Obstetricians and Gynecologists, 1991.

2. Margulics **M,** Campos-Perez G, Voto LS. Misoprostol to induce labour (letter). Lancet 1992: 339:64.

3. American College of Obstetricians and gynecologists. Management of preeclampsia. Technical bulletin No:91, Washington,DC: American College of Obstetricians and Gynecologists, 1986.

4. Schiff E, Friedman SA. Sıbaı BM. Conservative management of severe preeclampsia remote from term. Obstet Gynecol 1994; 84:626-30.

5. Mariani-Neto C, Leao EJ, Baretto EM. Kcnj G, Dc Aquino MM. Use of misoprostol for labor induction in stillbirth. Rev Paul med 1987;105:325-8.

6. Sanchez-Ramos L, Kaunittz A M, Del Valle GO, Delke 1, Schroedcr PA, Briones DK. Labor Induction with the Prostaglandin El Methyl Analogue Misoprostol Versus Oxytocin: A Randomized Trial. Obstet Gynecol 1993;81:332-6.

7. Osmanoğlu MA vc ark. 7 hafta ve üzerindeki gebeliklerin sonkmdınlmasmda servikal dilatasyon için oral misoprostol kullanımının etkinliği. Jin Obst Dergisi 1998;8(4): 181-5.

8. Elly et al. Preeclampsia :ls induction of labor more sıicces-ful? Obstet Gynecol 1997 89:600-3.