Intravaginal misoprostol alone versus intravaginal misoprostol and extraamniotic Foley catheter for second trimester pregnancy termination: an observational study

Dopochwowy misoprostol sam lub w kombinacji z zewnątrzowodniowym cewnikiem Foleya w celu terminacji ciąży w drugim trymestrze: badanie obserwacyjne

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Abstract

Background: *No systematic empirical research exists addressing the question of optimal pregnancy termination method in second trimester pregnancies.*

Objectives: *The purpose of this study was to determine the efficacy and safety of intravaginal misoprostol and extraamniotic Foley catheter combination for second trimester pregnancy termination.*

Methods: *A single center, observational study was conducted in a total of 91 pregnancies. Women who met the termination of pregnancy criteria due to feto-maternal indications between 13 to 26 gestational weeks were included into the study. Study participants received intravaginal misoprostol in combination with Foley catheter (n=46) or intravaginal misoprostol alone (n=45).*

Results: *The efficacy of intravaginal misoprostol and Foley catheter insertion combination was comparable to that of intravaginal misoprostol alone in terms of time to abortion/birth [median (95% Confidential Interval [95% CI]): 14.33 (11.33-17.25) hours and 12.08 (9.50-15.33) hours, respectively. Hazard Ratio: 0.73, 95% CI: 0.47 to 1.12, p= 0.14 (log-rank)]. The only serious maternal event was uterine rupture observed in one woman in Foley combination group.*

Conclusion: *The combination of intravaginal misoprostol and extraamniotic Foley catheter for second trimester pregnancy termination does not provide additional efficacy.*

Key words: **Foley catheterization** / **prostaglandins** / **abortion** / **induced** / **pregnancy** / / **second trimester** / **misoprostol** /

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Otrzymano: **18.02.2013**
Zaakceptowano do druku: **08.03.2013**

Streszczenie

Wstęp: *Nie znaleziono żadnych badań empirycznych dotyczących pytania o optymalną metodę terminacji ciąży w drugim trymestrze.*

Cel: *Ocena skuteczności i bezpieczeństwa zastosowania misoprostolu dopochwowo oraz w kombinacji z cewnikiem Foleya w terminacji ciąży w drugim trymestrze.*

Metoda: *jednoośrodkowe badanie obserwacyjne przeprowadzono na 91 pacjentkach. Do badania włączono kobiety, pomiędzy 13 a 26 tygodniem, które spełniły kryteria matczyno-płodowe terminacji ciąży. U 46 pacjentek zastosowano misoprostol w połączeniu z cewnikiem Foleya a u 45 sam misoprostol.*

Wyniki: *Skuteczność dopochwowego misoprostolu w połączeniu z cewnikiem Foleya była porównywalna do użycia samego misoprostolu w odniesieniu do czasu do poronienia/porodu [mediana (95% przedział ufności [955CI]): 14,33 (11,33–17,25) godzin i 12,08 (9,50-15,33) godzin, odpowiednio. HR: 0,73, 95%CI: 0,47–1,12, p=0,14 (log-rank)]. Jedynym poważnym matczynym powikłaniem było pęknięcie macicy obserwowane w grupie z cewnikiem Foleya.*

Wnioski: *Użycie cewnika Foleya dodatkowo oprócz dopochwowego misoprostolu nie zwiększa skuteczności terminacji ciąży w drugim trymestrze.*

Słowa kluczowe: **cewnik Foleya** / **prostaglandyny** / **aborcja** / **indukowana**/ **ciąża** / / **drugi trymestr** / **misoprostole** /

Introduction

The second trimester pregnancy termination can be performed either by medical or surgical methods including mechanical and pharmacological agents. The medical method recommended by the World Health Organization and the Royal College of Obstetricians and Gynaecologists is the regimen of intravaginal mifepristone followed by a prostaglandin analogue [1, 2]. The induction to abortion/birth interval (the interval between the first dose of prostaglandin and the expulsion of the products of conception) becomes significantly shorter with this combination compared to that with prostaglandins used alone. In many countries, mifepristone is still unavailable and misoprostol has to be used alone.

The application of the extraamniotic balloon catheter (EABC) is a mechanical method aiming the cervical ripening and labor induction by using different techniques such as insertion of a Foley catheter into the intrauterine extraamniotic space and subsequent traction if desired followed by the infusion of extraamniotic solution. With or without saline infusion, EABC is related with rapid improvement in Bishop scores and shortening in labor induction in third trimester pregnancies [3, 4]. It has advantages of simplicity, low cost, reversibility, and lack of systemic or serious adverse effects [3].

Combination of misoprostol with EABC may provide an optimal induction to abortion/birth interval with minimum side effects in pregnancy termination. Although previous studies comparing intravaginal misoprostol-Foley combination with misoprostol alone have failed to demonstrate such an assumed beneficial effect in third trimester pregnancies [5-7], we hypothesize that the uterus may respond differently to pregnancy termination methods through various gestational weeks. To our knowledge, no systematic empirical research exists addressing the question of optimal pregnancy termination method by comparing intravaginal misoprostol-Foley combination with intravaginal misoprostol alone in second trimester pregnancies.

The purpose of our study was to determine the efficacy and safety of intravaginal misoprostol and Foley combination for the termination of second trimester pregnancies.

Materials and methods

Study design and patients

A single center, observational study was conducted between June 2008 and May 2009, at Akdeniz University Hospital, Antalya, Turkey. Patients who met the termination of pregnancy criteria due to feto-maternal indications such as severe preeclampsia occurring before the limit of fetal viability, fetal malformations, chromosomal abnormalities, and intrauterine fetal death (IUFD) between 13 to 26 gestational weeks were included into the study. Exclusion criteria included previous history of prostaglandin allergy, poor general health, preterm premature ruptures of membranes, multiple gestation, and placenta previa.

Each participant provided written informed consent before undergoing any procedure. The study was conducted in accordance with the principles of Good Clinical Practice and approved by the institutional review board.

Procedures

All patients underwent routine laboratory tests and a complete clinical examination before the treatment procedures. As a routine procedure in our institution, patients without a uterine scar receive intravaginal misoprostol (Cytotec®, ARIS, Istanbul, Turkey) at a dose of 400 μg every 3 hours up to 5 doses. Lower doses of intravaginal misoprostol, that is an initial dose of 400 μg, followed by 200 μg every 6 hours up to 5 doses, were used in patients with a history of previous uterine scar. Decision to insert 16 F Foley catheter was at the physician's discretion.

A single dose of antibiotic prophylaxis was administered before the Foley catheter insertion. The vaginal portion of the uterine cervix was exposed with a sterile speculum and cleansed thoroughly with povidone iodine solution. Under direct vision, a 16 F Foley catheter was inserted through the external cervical os, and the balloon was inflated above the internal os by means of 30 cc of sterile saline. Effort was made to avoid contact of the catheter with the vagina or ectocervix and to perform the procedure with sterile technique. At the same time, the induction was started by the application of the initial dose of misoprostol into the posterior fornix. The catheter was checked in hourly periods in order to detect possible spontaneous catheter expulsion. If the catheter expulsion did not occur within the first 24 hours, it was withdrawn in order to prevent infection risk. Misoprostol dose was skipped in patients experiencing severe contractions. If delivery or abortion did not occur at the end of the fifth dose of misoprostol, a second cycle (five doses) of misoprostol was applied 12 hours apart from the last dose of misoprostol. Clinical and vital signs including the characteristics of uterine contractions and status of vaginal bleeding were monitored hourly until the completion of the expulsion of conception products. All adverse events were recorded. A blood sample was taken to determine hemoglobin level before the hospital discharge. Revision curettage was applied to patients with a suspicion of placental retention. All patients were informed about the contraception.

Lack of expulsion of the conception products within the first 48 hours following the initial misoprostol dose was defined as induction failure. In case of induction failure, oxytocin infusion was initiated in patients without uterine scar. Oxytocin infusion was started on the 60th hours of the first misoprostol dose in patients with a history of uterine scar. The pregnancies in which expulsion of the conception products did not occur within the 72 hours from the initiation of the induction were terminated by means of dilatation and evacuation. 10 units of oxytocin diluted in the 500 cc normal saline was infused with a rate of 0.2 to 0.3 units per minute in whom placental expulsion was not achieved within one hour following expulsion of the conception products. If placental expulsion was not achieved at the end of the sixth hour of expulsion of the conception products, manual extraction was applied.

Statistical analysis

The study was designed to show a hazard ratio (HR) of 0.5 with a power of 80% and an overall two-sided type I error of 5%, with use of a two-sided log-rank test. Inclusion of a total of 72 (36 on each arm) patients into this study would allow this power. We intended to evaluate a minimum of 96 patients undergoing second trimester pregnancy termination (assuming that 75% (n=72) of the patients would be eligible to include into the study). Primary aim of this study was to compare the induction to abortion/birth time in misoprostol−Foley catheter combination to misoprostol alone. The secondary aim was to evaluate the occurrence of significant clinical endpoints: uterine rupture, vaginal bleeding, induction failure, placental retention, nausea/vomiting, and diarrhea rates. Induction to abortion/birth interval was defined as the time elapsed between the first misoprostol dose and abortion.

Induction to abortion/birth time functions were estimated by the Kaplan-Meier method and compared by log-rank test stratified by abortion induction regimen. Abortion or birth was defined as event in survival analysis. Normality of distribution was assessed by Shapiro-Wilks test. Continuous data with normal distribution were expressed as mean ± standard error of mean and compared by Student's t test. When distribution was skewed, median followed by interquartile range in brackets was used to define data. Skewed continuous data were compared by Mann Whitney test. Comparison of proportions was performed by Chi-square test with or without continuity correction unless expected cell count was less than 5, in which case we used Fisher's exact test. Two tailed *P* values lower than .05 were considered significant. Stata/SE 11.2 for Macintosh (Stata Corporation, TX, USA) statistical package was used for all calculations.

Results

Participant characteristics

A total of 95 women underwent second trimester pregnancy termination procedure during the study period. Four subjects were excluded from the study because of multiple gestations (n=1) and preterm premature membrane rupture (n=3). Finally, 91 women were included into the study. Study participants received intravaginal misoprostol in combination with Foley catheter (n=46) or intravaginal misoprostol alone (n=45).

Intrauterine fetal death was the most common indication of pregnancy termination accounting for 30% of pregnancies (Table 1). We noted no differences regarding other demographic characteristics including nulliparity (p=0.12) and gestational age (p=0.17) between women who received misoprostol alone or misoprostol plus Foley catheter insertion (Table II).

Induction to abortion/birth interval

The efficacy of intravaginal misoprostol and Foley catheter insertion combination was comparable to that of intravaginal misoprostol alone in terms of time to abortion/birth interval [median (95% Confidential Interval [95% CI]): 14.33 (11.33-17.25) hours and 12.08 (9.50-15.33) hours, respectively. Hazard Ratio (HR): 0.73, 95% CI: 0.47 to 1.12, p= 0.14 (log-rank), (Figure 1).

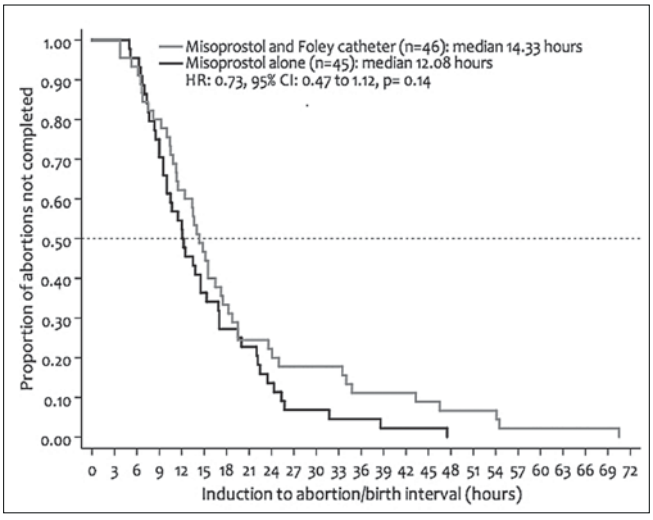

Figure 1. Comparison of induction to abortion/birth intervals of intravaginal misoprostol plus Foley catheter combination and intravaginal misoprostol alone.

Table I. Indications for pregnancy termination.

Indications n (%)	Misoprostol + Foley (n=46)	Misoprostol alone (n=45)
IUFD	13 (28.2)	14 (31.1)
CNS anomalies	10 (21.7)	9 (19.6)
UGS anomalies	5 (10.9)	5 (11.1)
Trisomy 21	5 (10.9)	3 (6.7)
Multisystem anomalies	2 (4.3)	3 (6.7)
Skeletal dysplasia	1 (2.2)	4 (8.9)
Turner syndrome	1 (2.2)	3 (6.7)
Thalassemia major	2 (4.3)	2 (4.4)
Trisomy 18	3 (6.5)	–
Cystic hygroma	2 (4.3)	–
Preeclampsia	1 (2.2)	1 (2.2)
Trisomy 13	1 (2.2)	–
Ring chromosome 21	–	1 (2.2)

IUFD – denotes intrauterine fetal death; CNS – central nerve system; UGS – Urogenital system.

Table II. Demographic characteristics of study population.

Characteristics	Misoprostol + Foley (n=46)	Misoprostol alone (n=45)	P
Age, y, median (range)	27 (17-38)	29 (17-42)	.99[a]
Gravidity, n, median (range)	2 (1-7)	2 (1-8)	.62[a]
Parity, n, median (range)	1 (0-4)	0 (0-5)	.36[a]
Nulliparity, n (%)	16 (34.78)	23 (51.11)	.12[b]
Previous abortion, n, median (range)	0 (0-3)	0 (0-2)	.62[a]
Previous C/S, n (%)	13 (28.26)	13 (28.89)	.95[b]
Gestational age, w, mean ± SD	20.46 ± 3.58	19.49 ± 4.03	.23[c]
Gestational age <20w, n (%)	19 (41.30)	25 (55.56)	.17[b]
Fetal weight, g, median (range)	358 (15-1200)	235 (10-1350)	.35[a]
Placental weight, g, median (range)	165 (40-510)	150 (15-65)	.20[a]
Fetus alive, n (%)	33 (51.56)	31 (48.44)	.77[b]
Total misoprostol dose, x10^3 µg, median (range)	1.6 (0.4-4.0)	1.2 (0.6-4.0)	.29[a]

[a] Mann-Whitney test, [b] Chi-square test, [c] Student's t test

Table III. Side effects and complications.

Side effects and complications, N (%)	Misoprostol + Foley (n=46)	Misoprostol alone (n=45)	P
Nausea-vomiting	13 (28.26)	14 (31.11)	.95[b]
Diarrhea	6 (13.04)	7 (15.56)	.97[b]
Vaginal bleeding[a]	2 (4.34)	2 (4.44)	1.0[c]
Uterine rupture	1 (2.17)	None	1.0[c]
Induction failure	4 (8.70)	1 (2.22)	.40[c]
Placental retention	1 (2.17)	1 (2.22`)	1.0[c]

[a] >5 pads/day, [b] Chi-square test with continuity correction, [c] Fisher's exact test

Potential confounding factors

Pre-emptively, fetal viability (alive vs dead), nulliparity, and gestational age (<20 vs ≥20 weeks) were considered to be the potential confounding factors those might affect induction to abortion/birth interval. We planned to include these variables into the Cox proportional hazard model to adjust the effect of pregnancy termination procedure, if those reach a p-value less than 0.25 in univariate log-rank analysis. However, none of those variables had an impact on induction to abortion/birth interval and fulfill the predefined inclusion criterion to perform a multivariate analysis: Fetal viability (Dead vs alive), median (95%CI) 13.50 (9.00-17.00) vs 13.50 (11.33-15.50) hours, respectively, HR (95% CI): 1.16 (0.73-1.84), p=0.54; nulliparity (Nulliparous vs Primiparous/Multiparous), median (95%CI) 14.50 (12.08-18.25) vs 11.50 (10.00-15.16) hours, respectively, HR (95% CI): 1.21 (0.79-1.84), p=0.39; gestational age (<20 vs ≥20 weeks), median (95%CI) 13.50 (11.50-18.25) vs 12.50 (10.41-15.50) hours, respectively, HR (95% CI): 1.05 (0.69-1.60), p=0.82.

Adverse events

Nausea and vomiting was the most common adverse event in all study population. There were no significant differences between the groups in terms of adverse events and induction failure. Complications were often observed in patients with a history of uterine scar. Only one uterine rupture occurred in a 27-year-old woman, gravida 2, and para 1, at 19 weeks of gestation. She underwent pregnancy termination due to cystic hygroma. She had previous history of caesarean section and received misoprostol plus Foley catheterization. Four out of total five induction failures were seen in patients with a history of uterine scar; three of them have received misoprostol plus Foley catheterization. Two patients had placental retention. Both of those patients had a uterine scar; one in misoprostol group and one received misoprostol-Foley combination. Vaginal bleeding was moderate (<2 pads/day) in the majority of patients. Intense vaginal bleeding (≥5 pads/day) was observed in only four patients. Two of them needed blood transfusions. In one of those, manual placental extraction was performed due to the total placental retention. The other one underwent laparotomy due to the uterine rupture (Table III).

Discussion

Misoprostol, a synthetic prostaglandin E1 analogue, is commonly used for medical abortion because of its uterotonic and cervical softening effect. The latter effect is more likely to be due to the direct effect of misoprostol on extracellular matrix metabolism [8]. Misoprostol induces several enzymatic reactions that promote collagen breakdown and rearrangement of collagen fibers resulting in cervical softening and dilation [9].

A sustained serum misoprostol level, rather than a peak level, is required for the generation of regular uterine contractions [10, 11]. There is no a predefined threshold serum level of misoprostol that provides uterine contractility.

Foley catheter insertion generates pressure and tension on the cervix and lower uterine segment by a direct effect. It also provides separation of chorionic membrane from decidua indirectly. Cervical ripening is ensured via the release of endogenous prostaglandins and other oxytocic mediators as a result of direct and indirect effects of Foley catheterization [12, 13].

In this study, we hypothesized that the local endogenous prostaglandins and other mediators released by means of Foley catheter insertion would have an additive effect on those of local prostaglandin analogue in terms of shortening induction to abortion/birth interval. But our results have failed to demonstrate such a potential beneficial effect.

Previous randomized prospective trials demonstrated that Foley catheter insertion alone was comparable to misoprostol alone in providing the pre-induction cervical maturation and induction of labor in third trimester pregnancies. However, none demonstrated a synergistic or beneficial effect of Foley catheterization-misoprostol combination over misoprostol alone in terms of induction to delivery interval, vaginal and caesarean delivery rates [5-7]. As being the first study comparing intravaginal misoprostol with misoprostol-Foley combination in second trimester pregnancy termination, our results are consistent with those of previous third trimester pregnancy studies.

Comparable efficacy of Foley catheterization plus intravaginal misoprostol and intravaginal misoprostol alone can be interpreted as both of those methods may exert their main effects through the same or similar pathways in a dose independent manner as long as a specific dose threshold was exceeded. Impact of these agents on uterus/cervix was probably not affected during the varied gestational ages. However, it does not go further than being a speculation since our study was not designed to explore causality. In order to clarify this situation, it is necessary to define threshold levels for serum and/or tissue endogenous and exogenous prostaglandin those can induce and sustain uterine contractions.

Our study demonstrated that use of either misoprostol plus Foley catheter combination or misoprostol alone have a similar overall and serious adverse event profile. Uterine rupture is a rare but serious complication of the pregnancy termination in the second trimester. In our study, uterine rupture was observed in a pregnant with a history of one previous caesarean delivery in misoprostol-Foley combination group. In a recent systematic review, use of misoprostol in second trimester pregnancies with previous history of uterine scar has been reported to be safe (the risk of uterine rupture is about 0.3%) [14]. Nevertheless, it is not possible to draw a definite conclusion about the safety of these pregnancy termination modalities. Because none of the studies including our study was powered to test differences in adverse events. The best adverse event data can be achieved by large scaled post-marketing data.

In conclusion, the combination of intravaginal misoprostol and Foley catheter insertion does not provide additional efficacy over intravaginal misoprostol alone in the termination of second-trimester pregnancies.

Authors' Contribution

1. Tayfun Toptas – acquisition of data, analysis and interpretation of data, article draft, corresponding author..
2. Inanc Mendilcioglu – study design, concept, assumtions, analysis and interpretation of data, revised article critically.
3. Mehmet Simsek – revised article critically.
4. Omur Taskin – revised article critically.

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the manuscript has not been published in or submitted to any other journal.

Source of financing:

The study have no need for financial support.

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