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Mifepristone and misoprostol versus Dilapan and sulprostone for second trimester termination of pregnancy

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Abstract

Objective. To compare two methods for second trimester termination of pregnancy: mifepristone and misoprostol versus Dilapan® and sulprostone.

Methods. This was a randomized study involving 16 patients with a singleton live fetus with congenital malformations or genetic disorders. Eight patients were treated with 200 mg mifepristone orally followed by 200 μg misoprostol vaginally 3 hourly and eight patients received a sulprostone infusion after cervical dilatation with Dilapan.

Results. Mifepristone and misoprostol had a mean induction interval of 17.8 hours and sulprostone and Dilapan 20.9 hours. The mean induction interval did not differ significantly. Mean hospital stay was shorter in the patients treated with misoprostol: 2.1 vs. 3.3 days ($p = 0.02$) with a 95% confidence interval of -2.1 to 0.3.

Conclusion. Mifepristone and misoprostol did not reduce the induction interval significantly compared to the sulprostone and Dilapan treatment for second trimester pregnancy termination. Hospital admission was significantly shorter in patients treated with mifepristone and misoprostol.

Keywords: *Mifepristone, misoprostol, second trimester, sulprostone, termination of pregnancy*

Introduction

The termination of a vital pregnancy in the case of congenital or genetic abnormalities is an emotional experience. The need for several days of hospitalization makes this even harder. Until recently, termination of pregnancy in the Netherlands was performed by sulprostone infusion (a synthetic prostaglandin E2 analogue) with or without cervical dilatation with Dilapan® (GelMed International, spol. S.r.o., Czech Republic), a hydrophilic polymer rod. This treatment includes a three to four day hospital admission. Sulprostone treatment can cause rare but severe cardiovascular complications [1]. Also, incomplete expulsion of placental tissue is common: 38–45% [2,3].

Recently, claims have been made that termination of pregnancy with the use of misoprostol is more effective: 90% delivery within 24 hours [4] and fewer incomplete expulsions (27%) [3]. However, these data have been generated from case series, mostly without controls, or from historic data. To decide whether or not we should change our hospital policy on the use of therapeutic agents, we decided to perform a prospective randomized study.

Materials and methods

From May 2003 to August 2004 we asked all women pregnant with a congenitally malformed or genetically abnormal fetus who requested a termination of pregnancy, to participate in our study. We included only singleton pregnancies with a live fetus at between 14 and 24 weeks amenorrhea. Reasons for termination of pregnancy were diverse. Congenital malformations were established by ultrasound examination and genetic disorders were found by amniocentesis or chorionic villus sampling (Table I). The study was approved by the local medical ethics committee.

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Patients with contraindications for mifepristone or misoprostol were excluded, as were patients with previous cesarean delivery or otherwise scarred uterus. The total number of eligible patients was 28 (Figure 1). Sixteen patients gave informed consent. The other 12 patients included one patient who was not eligible because of two previous cesarean sections. This patient was treated with intra-amniotic instillation of hypertonic saline. Another of these patients with a history of a cesarean section received sulprostone infusion. Ten patients refused to join an experimental study and received standard treatment (i.e., sulprostone).

Table I. Reasons for termination of pregnancy.

Antenatal diagnosis	Misoprostol ($n=8$)	Sulprostone ($n=8$)	Not included ($n=12$)
Trisomy 21	1	4	2
Trisomy 13, 8, triploidy	3	2	0
Other chromosomal abnormalities	1	1	4
Multiple congenital malformations	3	1	6

Randomization took place by opening an opaque envelope containing the prescription for the experimental treatment or for the standard one. The envelopes were prepared by the department of clinical epidemiology of the hospital using random numbers from a random number table.

The experimental treatment consisted of an oral intake of 200 mg mifepristone the first day and an admission to hospital 48 hours later. Then 200 μg misoprostol was applied vaginally every 3 hours until expulsion of the fetus [5]. In the case of no expulsion after 3 days, patients were provided with the standard treatment.

The standard treatment for termination of pregnancy was admission to the hospital on day one to place Dilapan in the cervical canal. One or more of these cervical dilatators made of hydrophilic polymers were used for dilatation of the cervix. The next morning a continuous infusion of 60 μg sulprostone per hour was started until delivery of the fetus. In the case of no expulsion after 3 days, we waited one day, then started a further 3 days with the same infusion. In the rare case that labor had not started after two 3-day cycles we used other modalities of termination

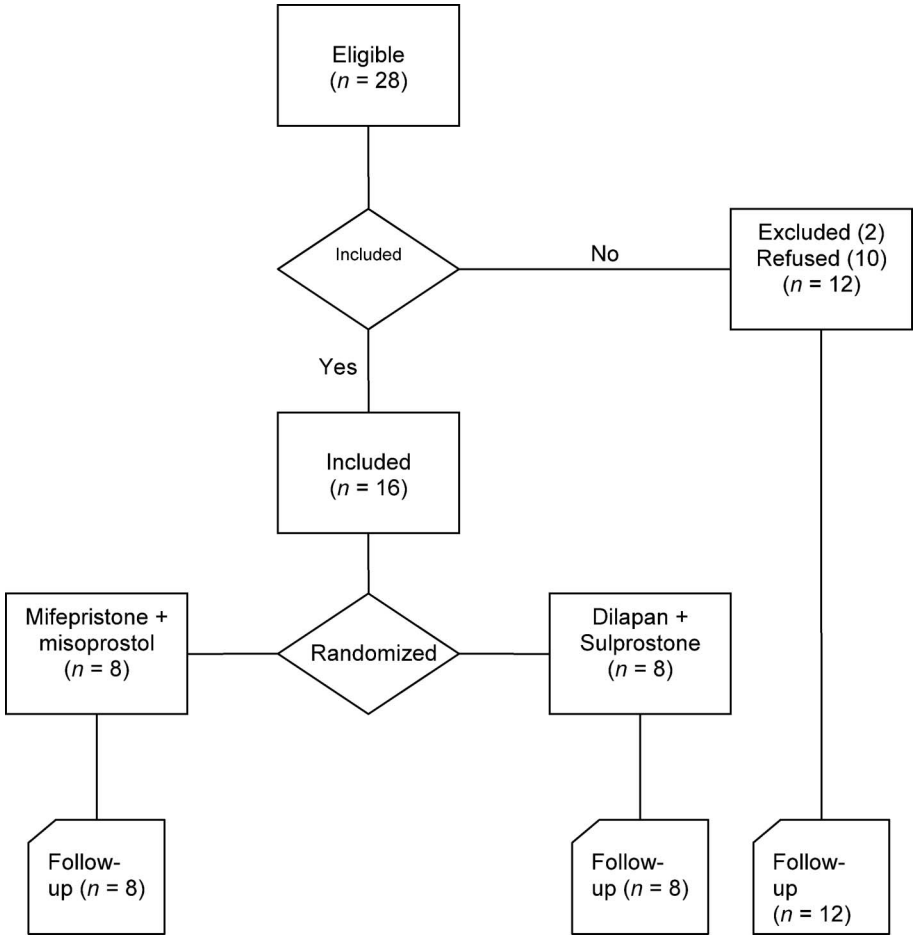

Figure 1. Patients requesting termination of pregnancy (May 2003–August 2004).

including intra-amniotic instillation of hypertonic saline or dilatation and evacuation.

Data for all patients were noted on a case record form. Data obtained included medical history, indication for termination, time and date of administration of medication, time and date of delivery, amount of blood loss, complete expulsion of the placenta, need for analgesia, and time and date of admission to the hospital.

The primary outcome measure was the induction to expulsion interval, measured from the start of misoprostol or sulprostone until delivery of the fetus. Secondary outcome measures were the number of incomplete placental expulsions necessitating surgical evacuation of the uterus, the duration of hospital stay, amount of blood loss, and the need for analgesics.

We estimated an induction interval of 36 hours with sulprostone infusion, based on historical data from our own hospital obtained during the time-period before the use of Dilapan in combination with sulprostone for pregnancy termination. Power analysis at the time of the design of the study showed that a reduction of 50% in induction interval, from 36 hours to 18 hours only, required a sample size of eight patients in each arm for an alpha of 0.05 and a beta of 80%.

Statistical analysis was performed with SPSS. The *t*-test and Mann–Whitney U-test were used as appropriate. Fisher's exact test was used to compare the patients who delivered within 24 hours in each treatment group.

Results

Groups were defined by randomization and were similar with regard to baseline characteristics (Table II). No statistically significant differences were found when we compared mean age, parity, and gestational age in the misoprostol group to those in the sulprostone group. Termination of pregnancy took place in all patients who were randomized into the two different treatment groups. There were no crossovers. All patients received the treatment they were allocated to by the randomization process.

Table II. Baseline characteristics.

	Misoprostol ($n=8$)	Sulprostone ($n=8$)	Not included ($n=12$)
Mean maternal age in years (SD)	33.9 (3.8)	35.9 (5.1)	32.9 (6.0)
Nulliparity	5	4	4
Median gestational age in weeks$^{+\text{days}}$ (SD)	18^{+5} (2.9)	17^{+6} (1.7)	20^{+6} (3.2)

SD, standard deviation.

The mean induction interval for the patients receiving misoprostol was 17.8 hours (SD 15.9). The mean interval for the sulprostone group was 45.1 hours (SD 69.3). The difference did not reach the level of significance ($p=0.30$). The large difference in the mean induction time resulted completely from one treatment failure in the sulprostone group. This patient received two treatments of 72 hours of sulprostone infusion after which labor still did not start. This patient was finally treated with intra-amniotic instillation of hypertonic saline to induce labor. Excluding this patient with the treatment failure, the mean induction interval in the sulprostone group was 20.9 hours (Table III).

Out of eight patients treated with misoprostol, six (75%) delivered within 24 hours after the first dose of misoprostol was administered. Four out of eight patients (50%) treated with sulprostone delivered within 24 hours after the start of sulprostone infusion ($p=0.61$). Figure 2 shows that after 25 hours all except for one patient have delivered in the misoprostol group. Furthermore it shows that the time interval from start of medication until delivery was shorter for patients treated with misoprostol.

Incomplete expulsions occurred in three patients in each group. Blood loss varied between estimated amounts of 100 mL and 500 mL. The mean blood loss in the misoprostol group was 275 mL and in the sulprostone group 380 mL. One patient in the sulprostone group lost an estimated 750 mL of blood.

Patients treated with misoprostol stayed an average of 2.1 days in hospital, while patients who received sulprostone infusion were admitted for an average of 4.3 days ($p=0.06$) with a 95% confidence interval of -4.4 to 0.1. The patient who was eventually treated with intra-amniotic instillation of saline after two episodes of 72 hours of sulprostone infusion stayed in hospital for a total of 11 days. Without this patient, the mean hospital stay in the sulprostone group was 3.3 days ($p=0.02$) with a 95% confidence interval of -2.1 to 0.3 (Table III).

The maximum dose of misoprostol was 3000 μg given over a two and a half day period, four patients received 1000 μg and three patients received 400 μg. No side effects were noted except for contractions of the uterus. Four patients, two in each group received epidural analgesics. The other patients received analgesia including pethidine or tramal, both opiates.

Discussion

In second trimester termination of pregnancy a prolonged hospital stay is undesirable for the patient, who has to cope with a difficult and emotionally burdening experience. Support of these patients is

Table III. Induction to expulsion interval.

Mean induction interval	Misoprostol ($n=8$)	Sulprostone ($n=7$)	p-Value	95% CI
Total group excluding one treatment failure (hours)	17.8	20.9*	$p=0.67$	−18.48 to 12.31
Nullipara (hours)	22.5	17.5	$p=0.33$	−22.79 to 32.92
Multipara (hours)	9.8	23.4	$p=0.18$	−35.86 to 8.73
Hospital stay				
Hospital stay total group excluding one treatment failure (days)	2.1	3.3**	$p=0.02$	−2.1 to 0.3

CI, confidence interval.
*Including the treatment failure, the mean induction interval is 45.1 hours, $p=0.30$, 95% CI −81.22 to 26.57. **Including the treatment failure, the mean hospital stay is 4.3 days, $p=0.06$, 95% CI −4.4 to 0.1.

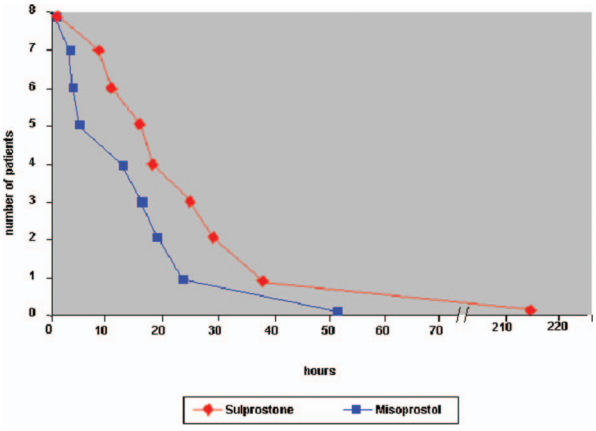

Figure 2. Induction intervals.

intensive and emotionally consuming for the attending staff. Also from the point of view of health economics, reducing the hospital stay is considered worthwhile. As we learned from uncontrolled studies, a reduction in hospital stay might be achieved by altering our method of induction. We put this question to the test: is the combination mifepristone and misoprostol really so much more effective than our traditional scheme of Dilapan and sulprostone?

We report in this randomized study that the induction to expulsion interval was an average 3.1 hours shorter in patients treated with misoprostol (17.8 h) than in patients treated with sulprostone (20.9 h). However, given the relatively small numbers, the difference did not reach statistical significance. Historical data from our own hospital show a mean induction interval of 36 hours in patients treated with sulprostone. So, at the time of the design of the study, we estimated sulprostone infusion to take approximately 36 hours and a reduction of 50% in induction time to be achievable. However, the study supports a sulprostone induction time (after Dilapan) of only around 20 hours. Our explanation is that the additional use of Dilapan preparation of the cervix before termination of pregnancy with prostaglandins is responsible for this shorter induction interval [6]. The expected 18 hours induction interval with misoprostol was indeed found.

Our results in this small, randomized trial do not support the claim that the misoprostol protocol we used is superior in effectivity, measured by induction interval, to sulprostone.

De Heus et al. [7] showed a median induction interval of 13 hours and 88% of deliveries occurring within 24 hours in their study. This was a retrospective study with inclusion of second and third trimester pregnancies with a higher dosage of misoprostol being employed. This higher dosage may explain the shorter interval. Furthermore, the shorter interval can be explained by the fact that in third trimester termination of pregnancy, less misoprostol is required.

Langer et al. [8] described a mean interval of 12.7 hours and an abortion rate of 90% within 24 hours. That study also used a higher dose regimen and included pregnancies at 13 to 30 weeks of gestation. Indications for termination were fetal intra-uterine death, premature rupture of membranes, and fetal anomaly. Feticide was realized in pregnancies of over 24 weeks. All are facts that influence the abortion interval positively and need less misoprostol. Our study contains a homogeneous group of patients all in the second trimester with a live fetus. This group is characterized by longer induction intervals.

A lot of different studies have used different dosages. Tang and Ho [9], in their review article, showed that in second trimester abortion the mean induction to abortion time could differ by 13.8 to 45 hours depending on the regimen used. Our study used a low dose regimen. Although rare, with high doses of misoprostol treatment, uterine ruptures have been described even in an unscarred uterus [10]. Although our study describes the induction intervals of a small group of patients, it also illustrates that in a low dose regimen, the majority of patients deliver in 24 hours.

In our study, hospital admission was significantly shorter in patients treated with misoprostol (2.1 days) than in patients treated with sulprostone (3.3 days). This hospital stay also included the time between

placement of the Dilapan until the sulprostone infusion was started. In some settings, Dilapan is employed on an ambulatory basis thus reducing hospital stay.

Although it was not formally evaluated in the study, we had the impression that treatment with a vaginal tablet instead of medication by intravenous infusion was more comfortable for the patient.

Considering the fact that even treated with a low dose of misoprostol the majority of the cases delivered within 24 hours, patients had a significantly shorter hospital stay, and patients seemed more comfortable, we did adopt this new policy in our hospital for second trimester termination of pregnancy in cases of congenital malformation or genetic disorders. We realize that studies including more patients are needed to show stronger statistical evidence for termination of pregnancy with the mifepristone and misoprostol regimen.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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