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Maternal and neonatal outcome of labour induction at term comparing two regimens of misoprostol

Abstract

Aim: To compare the efficacy and safety of two misoprostol dosing regimens for induction of labour in primiparous (1P) and multiparous (>1P) women.

Methods: Retrospective study of induction of labour using vaginal misoprostol 25 μg vs. 50 μg every 6 h in 942 women at a tertiary centre. The main outcome variables are induction-to-delivery interval, latency period duration, vaginal delivery within 24 h, and maternal and foetal safety outcome.

Results: With the 50 μg regimen, induction-to-delivery intervals were significantly shorter: 18.4 h vs. 24.6 h (1P) and 14 h vs. 17.9 h (>1P), as was latency period duration (by 5.4 and 4 h, respectively). Vaginal delivery within 24 h was significantly more frequent, as were non-reassuring foetal heart rate (1P: 20% vs. 14%) and tachysystole (1P: 31% vs. 11%; >1P: 21% vs. 7%). No uterine rupture was reported. Neonatal outcomes were similar except for significantly more frequent infant referral to neonatal intensive care in the >1P group receiving the 50 μg regimen (11% vs. 4%).

Conclusion: Vaginal misoprostol 25 μg seems to maintain efficacy with more acceptable maternal and neonatal safety. As induction of labour is an off-label use for misoprostol, safety should be prioritised with the lower dosage regimen despite the longer induction-to-delivery interval.

Keywords: Foetal outcome; induction of labour; maternal outcome; misoprostol; off-label use.

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Introduction

Labour is often induced in order to reduce the risk of maternal or neonatal morbidity and mortality. One of the most commonly used agents is misoprostol [11], a synthetic prostaglandin structurally related to prostaglandin E1. Originally licensed as an oral treatment for gastric ulcers [27], it is used off-label worldwide in obstetrics [28]. Misoprostol binds selectively to prostanoid receptors, increases intracellular calcium and contracts myometrium [5, 22], while also softening the cervix by collagen disintegration and dissolution [7]. As a result, it shortens the induction-to-delivery interval compared to placebo, oxytocin or other induction agents in women with an unfavourable cervix [14]. Misoprostol can be applied by various routes and at various doses [6, 12, 24]. Because of its efficacy, cost-effectiveness, easy storage at room temperature and easy administration, misoprostol is listed as an essential medication by the World Health Organization [25, 29, 30].

However, complications when using misoprostol for induction of labour have aroused frequent debates resulting from its off-label use [28]. They include uterine tachysystole or hyperstimulation syndrome, uterine rupture, need for instrumental vaginal delivery or caesarean section and low Apgar scores or umbilical artery (UA) pH with referral to a neonatal intensive care unit. The risk of adverse effects seems to be dose-related and increases with repeated doses of 50 μg or above [14]. Furthermore, parity appears a major outcome determinant, with not only induction intervals, including latent and active phases, being significantly longer in primiparous (1P) women, but also labour itself usually being longer [12], with higher rates of instrumental vaginal delivery and caesarean section than in multiparous (>1P) women [15].

We performed this study to compare the efficacy and safety of a 25 μg vs. 50 μg regimen of intravaginal misoprostol for induction of labour at term and to evaluate the clinical outcome in 1P and >1P women.

Materials and methods

We based this retrospective study on a review of the medical records of all women with induced labour at a Swiss tertiary hospital between January 2007 and December 2011, identified using PERINAT, an in-hospital patient record system, version 5.0 (University Hospital Zurich, Switzerland) [32]. Demographic and obstetric data of all women induced with misoprostol were collected [maternal age, body mass index, parity, gestational age (GA) at delivery, birth weight, and reasons for induction]. Inclusion criteria were term gestation (≥37 weeks), singleton foetus in vertex presentation, and absence of active labour. Exclusion criteria were multiple pregnancy, previous uterine surgery (e.g., caesarean section and myomectomy), changes in regimen for induction of labour or incomplete data. Patients were informed about the induction procedure including the off-label use of misoprostol and its potential risks (hyperstimulation syndrome, uterine rupture and caesarean section).

Until mid-2010 our hospital administered misoprostol 50 μg vaginally every 6 h until labour onset in women with an unfavourable cervix (Bishop score ≤7). Cardiotocography was performed 30 min before and 60 min after each dose. The procedure was repeated after 6 h in the absence of contractions and if the Bishop score was ≤7. No further dose was given if contractions exceeded 2 per 10 min or if there were foetal heart rate abnormalities. In the presence of >2 contractions per 10 min, failure of cervical dilatation (<1 cm/h) or failure to progress during the active first and second stage of labour, management required initiation of intravenous oxytocin by infusion pump at increasing doses from 0.002 international units per minute (IU/min) to a maximum of 0.018 IU/min beginning >6 h after the last dose of misoprostol. Cardiotocography was continuous in the active phase of labour (cervical dilatation >3 cm with regular uterine contractions) and after initiation of the oxytocin infusion.

Since mid-2010 there is a population bias as we have followed a procedure that was identical in every respect except in giving 25 μg misoprostol instead of 50 μg doses. But this change allowed us to compare the efficacy and safety between the two regimens.

Outcome parameters were the induction-to-delivery interval (from insertion of first misoprostol tablet to delivery), latency period duration (from insertion of first misoprostol tablet to onset of the active phase of labour), duration of labour, vaginal delivery within 24 h, mode of delivery, uterine tachysystole (>5 contractions per 10 min), hyperstimulation syndrome (uterine tachysystole with non-reassuring foetal heart rate), uterine rupture, 5-min Apgar score <7, UA pH <7.15 and neonatal intensive care referral rate.

Patients exhibiting tachysystole were monitored closely. Tachysystole >20 min was treated by reducing the oxytocin infusion. Hyperstimulation syndrome was managed by terminating the oxytocin infusion, changing maternal position, giving oxygen by face mask and/or administering hexoprenaline in 5–10 μg doses intravenously.

Further outcomes were the total dose of misoprostol required, the requirement for oxytocin and epidural anaesthesia (EDA), and the presence of meconium-stained amniotic fluid. Complications such as shoulder dystocia, retained products of conception, postpartum bleeding (difference between pre- and postpartum haemoglobin, Hb) and third or fourth degree perineal tears were also recorded.

The data analysis used SPSS (version 20, SPSS, Zurich, Switzerland). Results were reported as means±standard deviation, median, interquartile range and percentage. The groups were compared using contingency table and chi-squared (Fisher's exact test) analysis for categorical and binary values. Quantitative variables were tested for normality by Kolmogorov-Smirnov and Shapiro-Wilk tests. Differences in medians of quantitative variables between groups were tested by a nonparametric Mann-Whitney test. Two-sided P-values were reported for all tests. Values ≤0.05 were regarded as significant.

Ethical approval was given for the retrospective study using anonymised data.

Results

Between January 2007 and December 2011, 1435 women were induced at term with vaginal misoprostol at the University Hospital Zurich. The exclusion criteria reduced the final sample size to 942 (Figure 1) – 437 of whom received 25 μg doses and 505 received 50 μg doses.

Baseline demographics and indications for induction were similar in both groups (Table 1).

Outcome parameters (Table 2) showed that regardless of the mode of delivery, 73% of all women (1P: 66.7%; >1P: 84.1%) had an induction-to-delivery interval <24 h, and 95% and 99.1%, respectively, had an interval <48 h.

The latency period and the induction-to-delivery interval were both significantly shorter in both parity groups receiving 50 μg vs. 25 μg. For the latency period: 11.2±7.2 vs. 16.6±14.3, P<0.001 (1P) and 9.7±6.8 vs. 13.6±15.6 P<0.01 (>1P). For the induction-to-delivery interval, 18.4 h vs. 24.6 h, P<0.001 (1P) and 14 h vs. 17.9 h, P<0.01 (>1P). Significantly more women given 50 μg delivered within 24 h: 77.6% vs. 54.7%, P<0.001 (1P) and 89.9% vs. 76.7%, P<0.01 (>1P). Rates of vaginal delivery within 24 h were significantly higher with 50 μg: P<0.001 and P<0.01, respectively. The 25 μg and 50 μg groups did not differ in the mode of delivery.

In the 50 μg group, non-reassuring foetal heart rates were significantly more frequent in 1P women (19.6% vs. 13.6%, P=0.05) as was uterine tachysystole in both 1P and >1P women (30.9% vs. 10.8%; 20.8% vs. 7.3%, both P=0.001). There were no cases of uterine rupture in any group.

There were no significant intergroup differences in 5-min Apgar score <7 or UA pH <7.15. In >1P women significantly more infants were referred to the neonatal intensive care unit in those given 50 μg (11.2% vs. 4.2%, P<0.05).

Total dosage requirements (Figure 2) showed that with the 50 μg regimen 83% and 87% of 1P and >1P women delivered after a single dose; with the 25 μg regimen 81% and 88%, respectively, required ≤50 μg of misoprostol.

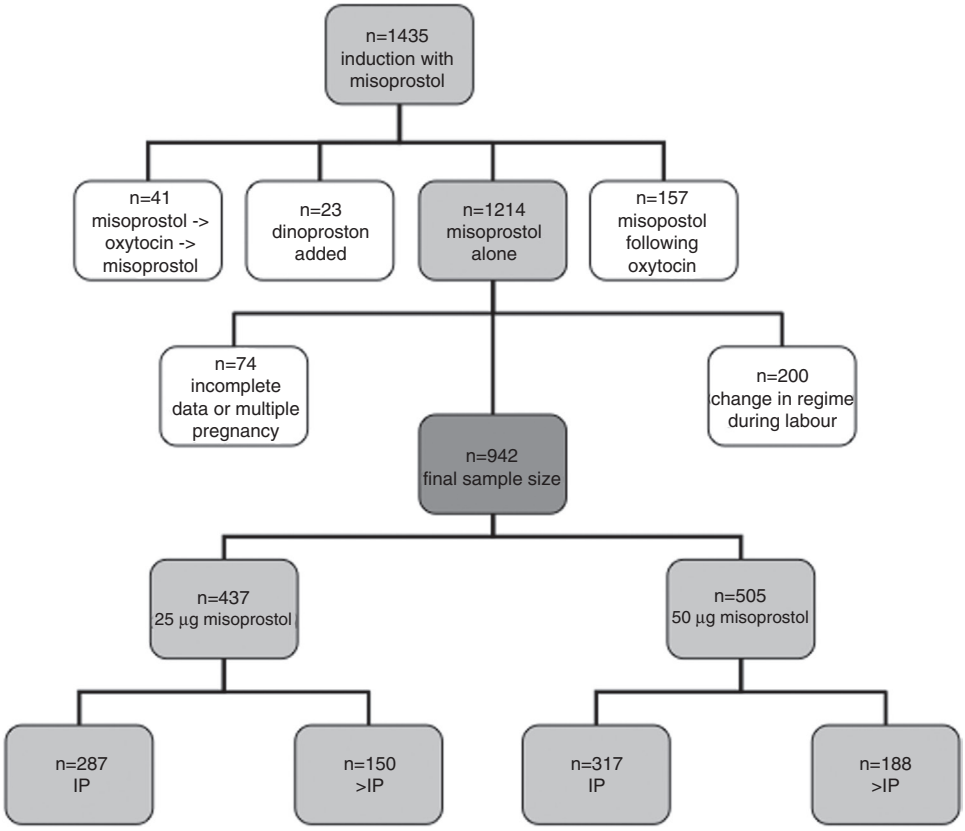

Figure 1 Breakdown of all women being induced with misoprostol between 2007 and 2011 at term.

In 1P women, the requirement for additional oxytocin (84.2% vs. 73.5%, P=0.001) and EDA (61.4% vs. 51.1%, P<0.01) were significantly greater with the 25 µg regimen.

Rates of other clinical outcomes, such as meconium-stained amniotic fluid, shoulder dystocia, retained products of conception or third or fourth degree perineal tears, were similar in both groups, except for greater postpartum haemorrhage in 1P women given 25 µg vs. 50 µg (Hb difference 1.9±1.6 g/dL vs. 1.4±1.4 g/dL, P<0.001).

Discussion

Our results show that a 25 µg regimen of vaginal misoprostol is safe for induction of labour. In 1P women, it reduced the side effects of tachysystole by two-thirds and hyperstimulation syndrome by one-third compared to a 50 µg dose regimen. However, it significantly lengthened the latency period (by about 6 and 4 h in 1P and >1P women) and, therefore, lengthened the induction-to-delivery interval (by 6 and 4 h, respectively).

These results support the 75% decrease in tachysystole (12% vs. 3%) reported in 147 women given 25 µg instead of 50 µg misoprostol vaginally every 4 h, together with a similar prolongation of the induction-to-delivery interval (+4 h) [8]. A 2002 meta-analysis of 5 randomised clinical trials also reported an almost 5 h shorter induction-to-delivery interval in women receiving 50 µg misoprostol instead of 25 µg [21]. Rates of abnormal contractility pattern, tachysystole (21% vs. 9%) and uterine hyperstimulation syndrome (9% vs. 4%) were higher with the 50 µg regimen. One study in the meta-analysis showed a 50% reduction in tachysystole in the 25 µg group (32.8% vs. 15.6%; P<0.001) but no reduction in hyperstimulation syndrome [9]. Unfortunately, the study did not test for the effect of parity, in which case it may have concluded differently, bearing in mind the one-third reduction in hyperstimulation syndrome that we found exclusively in 1P women (19.6% vs. 13.6%, P=0.05).

Meydanli et al. found no significant increase (P=0.09) in induction-to-delivery interval with the 4-h 25 µg regimen in a population of 120 1P and >1P women [18]. Rates of tachysystole, hyperstimulation syndrome and oxytocin requirement were also similar with both the regimens. However, the exclusion criteria were excessive, EDA was not performed and only women with GA >41

Table 1 Baseline characteristics of the study population.

Characteristics	IP		>IP	
	25 µg (n=287)	50 µg (n=317)	25 µg (n=150)	50 µg (n=188)
Age (years)				
(mean±SD)	30.1±5.9	29.6±5.6	31.7±5.4	32.5±5.0
(median, IQR)	30.0, 10.0	30.0, 8.0	32.0, 8.0	33.0, 7.0
BMI (kg/m²)				
(mean±SD)	22.8±4.4	23.3±4.4	24.5±4.5	24.4±4.3
(median, IQR)	21.8, 3.9	22.3, 5.0	23.8, 6.1	23.4, 5.5
Gestation (weeks)				
(mean±SD)	40.4±1.3	40.2±1.4	39.9±1.4	39.8±1.5
(median, IQR)	40.6, 1.9	40.6, 2.4	40.1, 2.7	39.9, 2.8
Birth weight (kg)				
(mean±SD)	3.4±0.5	3.4±0.5	3.5±0.5	3.5±0.5
(median, IQR)	3.4, 0.7	3.4, 0.7	3.5, 0.8	3.5, 0.7
Bishop Score				
(mean±SD)	2.4±1.5	1.9±1.3	2.5±1.5	2.2±1.4
(median, IQR)	2.0, 2.0	2.0, 2.0	2.0, 2.0	2.0, 2.0
Indication for induction of labour, n(%)				
Rupture of membranes	75 (26.1%)	71 (22.4%)	26 (17.3%)	25 (13.3%)
Post date	102 (35.5%)	111 (35.0%)	42 (28.0%)	51 (27.1%)
Foetal malformations	12 (4.2%)	15 (4.7%)	5 (3.3%)	15 (8.0%)
Oligohydramnion	29 (10.1%)	34 (10.7%)	14 (9.3%)	14 (7.5%)
Preeclampsia	10 (3.5%)	16 (5.1%)	6 (4.0%)	7 (3.7%)
On request	16 (5.6%)	14 (4.4%)	21 (14.0%)	26 (13.8%)
Gestational diabetes	8 (2.8%)	18 (5.7%)	10 (6.7%)	16 (8.5%)
Diabetes mellitus	3 (1.1%)	9 (2.8%)	5 (3.3%)	5 (2.7%)
IUGR	7 (2.4%)	5 (1.6%)	3 (2.0%)	4 (2.1%)
Cholestasis of pregnancy	9 (3.1%)	6 (1.9%)	4 (2.7%)	3 (1.6%)
Others[a]	16 (5.6%)	18 (5.7%)	14 (9.4%)	22 (11.7%)
		(P=0.41)		(P=0.76)

[a]Examples: infection, suspect foetal heart rate pattern, macrosomia, vaginal bleeding, blood group incompatibility, maternal indication (each below 2%). BMI=body mass index (kg/m²), IQR=interquartile range, IUGR=intrauterine growth restriction, IP=primiparous women, >IP=multiparous women, SD=standard deviation.

weeks were included, which may have compromised the data.

Loto et al. [16] reported also a significantly shorter induction-to-delivery interval with the 50 µg regimen than with 25 µg (8.2±1.5 h vs. 9.09±2.7 h). In that study, however, the induction of labour was conducted in patients with a favorable cervix (Bishop Score >7), which could explain the shorter interval compared to our results [16].

Uterine hyperstimulation has been accused of increasing the caesarean section or other operative delivery rates [10]. At least one study has shown a decrease in section rates with the 25 µg regimen [23]. We could confirm neither a decrease in section rates nor an increase in vaginal operative delivery rates, in line with other studies showing that high- and low-dose regimens were equally effective in inducing labour [18, 21]. We even found that about 15% more women delivered vaginally within 24 h of induction with the 50 µg regimen. The 50 µg dose is considered more effective in its direct effect on the cervix [18] and it is presumably quicker to reach the threshold plasma misoprostol acid concentration. However, plasma misoprostol concentrations have been reported to decline to a mean 61% of peak levels 4 h after vaginal administration [18, 31]; so repeated 25 µg doses may initiate contractions by reaching the threshold level at a later stage. Thus it is not surprising to observe more women with the 50 µg regimen delivering vaginally after a single dose of misoprostol and within 24 h of induction. The significantly higher number of 1P women requiring oxytocin with the 25 µg regimen also points to the stronger uterine stimulation achieved by higher misoprostol doses.

A serious complication of abnormal uterine contractility due to labour induced with misoprostol is uterine rupture, especially after previous caesarean section (≤5.6%) [19, 20]. It can also occur in an unscarred uterus after a single dose of

Table 2 Outcome after induction of labour with either 25 or 50 µg of misoprostol for primi- (1P) and multiparous (>1P) women.

	IP			>IP		
	25 µg	50 µg	P-value	25 µg	50 µg	P-value
Latency period (h)						
(mean±SD)	16.6±14.3	11.2±7.2	<0.001	13.6±15.6	9.7±6.8	<0.01
(median, IQR)	12.6±12.1	9.9, 8.4		10.5, 10.0	7.9, 6.1	
Induction-to-delivery interval (h)						
(mean±SD)	24.6±15.2	18.4±8.9	<0.001	17.9±16.1	14.0±8.9	<0.01
(median, IQR)	20.8, 14.8	6.6, 10.9		14.3, 12.1	12.0, 8.7	
Length of labour (h)						
(mean±SD)	7.7±4.8	6.8±4.1	0.16	4.3±4.3	4.4±4.4	0.89
(median, IQR)	7.4, 6.1	6.0, 5.5		2.8, 4.6	3.0, 3.9	
Delivery <24 h (%)	54.7	77.6	<0.001	76.7	89.9	<0.01
Vaginal delivery <24 h (%)	43.6	58.1	<0.001	72.0	85.6	<0.01
Vaginal delivery (%)	42.5	50.8		86.7	88.9	
Vaginal operative delivery (%)	28.6	21.8		6.0	6.9	
Caesarean delivery (%)	28.9	27.4	0.08	7.3	4.3	0.46
Uterine tachysystole (%)	10.8	30.9	<0.001	7.3	20.7	0.001
Uterine hyperstimulation (%)	13.6	19.6	0.05	8.7	9.6	0.85
5-min Apgar score <7 (%)	1.0	1.9	0.51	1.4	1.2	1.00
Umbilical artery pH <7.15 (%)	7.1	9.4	0.36	5.5	6.7	0.82
Admission into neonatal unit (%)	5.9	6.3	0.87	4.2	11.2	<0.05
Oxytocin augmentation (%)	84.2	73.5	0.001	56.7	52.7	0.51
EDA (%)	61.4	51.1	<0.05	30.2	35.1	0.39
Meconium-stained liquor (%)	24.5	18.4	0.19	16.2	13.5	0.78
Shoulder dystocia (%)	0.3	0.9	0.63	2.7	0.5	0.18
Retained placenta (%)	3.8	3.8	1.00	5.3	4.3	0.80
Third or fourth degree perineal tears (%)	1.0	0.9	1.00	0.7	0.5	1.00
Postpartum haemorrhage (Hb difference)						
(mean±SD)	1.9±1.6	1.4±1.4	<0.001	1.2±1.3	1.2±1.2	0.42
(median, IQR)	1.6, 1.8	1.2, 1.7		1.0, 1.7	1.0, 1.6	

EDA=epidural anaesthesia, Hb=haemoglobin.

either 50 µg or even 25 µg, but few cases have been reported [4, 17, 26]. None occurred in our study.

Despite the increased rate of uterine contractile abnormalities associated with the 50 µg regimen in our study, overall neonatal outcomes were similar, with comparable Apgar scores and UA pH, as in other studies [16, 18, 21]. However, in the >1P group referral rates to neonatal intensive care were significantly higher with the 50 µg regimen (11.2% vs. 4.2%). One explanation could be that more women in the 50 µg group (n=15, 8% vs. n=5, 3.3%) were induced for foetal malformation. These infants were automatically referred to neonatal intensive care for safety reasons or for further treatment caused by their known malformations.

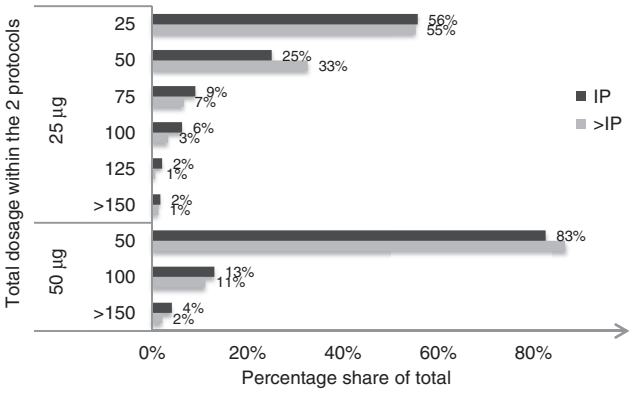

Figure 2 Dosage requirements within the two different protocols (25 vs. 50 µg misoprostol) for primi- and multiparous women.

Our results concur with the 2010 Cochrane review of seven studies comparing vaginal misoprostol 25 µg vs. 50 µg 3–6 h [11] which showed less tachysystole and hyperstimulation syndrome, more failure to achieve delivery within 24 h and significantly more use of oxytocin with the lower-dose regimen. It also found no differences in mode of delivery, meconium-stained liquor or maternal side-effects.

The 25 µg regimen extends the induction-to-delivery interval, which can be exhausting for the women. It is

recommended for reducing side effects such as tachysystole and hyperstimulation syndrome [2, 30], although an optimal dosage regimen has not been firmly established. An alternative could be to combine pharmacological and mechanical techniques such as an intracervical Foley catheter or double-balloon catheter to shorten the latency period while avoiding tachysystole or hyperstimulation syndrome. Hence, there are recent studies evaluating the role of adjuvant interventions to shorten the overall duration of induced labour and also to improve the outcome by using lower dosages of misoprostol [1, 3, 13].

Our study is one of the largest to compare the efficacy and safety of inducing labour with a 25 μg vs. 50 μg regimen of vaginal misoprostol in the two parity groups. But it also has its limitations: it is a retrospective non-randomised study subject to confounding bias. We plan a randomised controlled study using combinations of techniques for induction of labour.

Conclusion

The 25 μg regimen of vaginal misoprostol appears to maintain efficacy with more acceptable maternal and neonatal safety. Given that induction of labour is an off-label use, safety should be prioritised despite the longer induction-to-delivery interval. More research is required to optimise misoprostol management, potentially with adjuvant interventions that shorten the induction-to-delivery interval while securing safe maternal and foetal outcomes.

Conflict of interest statement: The authors certify that there are no conflicts of interest in relation to this article.

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