Misoprostol for cervical ripening at and near term — a comparative study

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Objective. To compare the safety and efficacy of misoprostol with that of dinoprostone for the induction of labour at term, or near term.

Design. Three hundred and ninety-six women with term pregnancies were randomised to receive either oral or vaginal misoprostol, or dinoprostone. Women who had had a previous caesarean section (CS) or those with a malpresentation or who were parity ≥ 5, were excluded. The control group received dinoprostone 1 mg inserted in the posterior fornix and repeated 6-hourly to a maximum of three doses. The study group received either oral misoprostol 20 µg 2-hourly to a maximum of four doses (80 µg), or vaginal misoprostol 25 µg in the posterior fornix with a switch to the oral misoprostol regimen if there was no change in the Bishop's score or no palpable uterine contractions.

Results. There was no significant difference in vaginal delivery rate within 24 hours between the groups (58.1% v. 58%, $p = 0.633$). There were no significant differences in CS rates between the groups; however, more CSs were performed for fetal distress in the misoprostol group than in the dinoprostone group (28% v. 25%). There was a significantly higher incidence of hyperstimulation in the vaginal misoprostol group (21.4%) than in the other two groups (oral misoprostol 16.5%, dinoprostone 8.9%) ($p = 0.004$). The incidence of meconium staining of liquor was comparable between the groups.

Conclusions. In selected women, the efficacy of misoprostol for the induction of labour at term is similar to that of dinoprostone but misoprostol is associated with a higher incidence of hyperstimulation.

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Induction of labour is performed frequently for a variety of obstetric conditions. However, in the presence of an unfavourable cervix, the procedure can be prolonged and result in increased caesarean section (CS) rates. Therefore agents that cause cervical softening and dilatation are used before formal induction of labour. The most common agents used for this purpose are the prostaglandin E_2 (PGE_2) series or dinoprostone (Pharmacia, USA). These agents are expensive and require refrigeration, making their use in poor countries prohibitive. Recently, there has been interest in the off-label (non-registered) use of misoprostol (Cytotec, Searle, USA), a PGE_1 analogue, for cervical ripening and induction of labour.[1,2] Misoprostol is widely used for first- and second-trimester termination of pregnancy and for the management of postpartum haemorrhage.[1] Most centres in South Africa, however, have taken a cautious approach to its use for induction of labour at term, despite the fact that numerous clinical trials and a recent meta-analysis have demonstrated its efficacy.[2-4] Further, the American College of Obstetricians and Gynecologists (ACOG) guidelines recommend that misoprostol, at a dose of 25 µg 3 - 6-hourly, is effective for the induction of labour (level A evidence), and that 50 µg 6-hourly may be appropriate in some situations, although an increased risk of complications has been reported (level B evidence).[5]

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Controversy over the use of misoprostol at term exists because of the risks of hyperstimulation and lack of information about the appropriate dosage and route of administration.[1] We therefore decided to compare the efficacy of misoprostol with that of dinoprostone for induction of labour in near-term and term pregnancies, in carefully selected patients.

Methods

This prospective study was conducted at King Edward VIII Hospital (KEH), Durban. Institutional ethical permission was obtained and 400 women with viable term or near-term pregnancies who fulfilled the criteria for induction of labour were enrolled.

Women who had had a previous CS and those with a malpresentation, a non-reassuring electronic fetal heart rate recording, a Bishop's score of ≥ 6 and parity ≥ 5 were excluded.

On enrolment, women were allocated to two groups by opening sequentially numbered opaque envelopes, which had cards with computer-generated numbers stating the method of induction.

The control group received dinoprostone (Prandin gel). Administration followed standard methods, viz. 1 mg was inserted into the posterior vaginal fornix and repeated 6-hourly for up to three doses if contractions were inadequate. If labour was not established at the end of the third dose, a consultant reviewed the indication for induction and a decision was made

as to whether to perform a CS or initiate induction a few days later.

If uterine contractions were considered adequate, progress of labour was managed by standard methods.

The study group received misoprostol either orally or vaginally. Oral administration consisted of a 200 µg tablet dissolved in 200 ml tap water (1 µg / ml), and administered in a dosage of 20 ml (20 µg) every 2 hours until adequate contractions were achieved or a maximum of 80 ml (80 µg) was given.

Vaginal misoprostol (25 µg) tablets prepared by the hospital pharmacy were inserted in the posterior fornix, and the cervix was assessed after 4 hours for any change in the Bishop's score or palpation of moderate to strong contractions abdominally. If neither was achieved, a switch to oral administration to a maximum of 60 µg (three doses) was initiated. If labour was not achieved, a consultant reviewed the indication as in the control group.

Uterine contractions were observed using a combination of abdominal palpation and uterine cardiotocodynamometry. The hyperstimulation syndrome was defined as a combination of hypersystole and / or tachysystole with abnormal heart rate changes. Management of these conditions followed the standard labour ward procedures at KEH.

The standard labour protocol was used for monitoring of patients. This consisted of pre- and post-misoprostol administration cardiotocographic assessment.

The primary outcome measure was the initiation of labour and delivery within 24 hours.

Secondary outcomes were induction to delivery time, meconium staining of liquor, non-reassuring fetal heart rate patterns, hyperstimulation, mode of delivery, perinatal mortality, and average dose requirements.

Statistics

Statistical methods used included Pearson's chi-square and Fisher's exact tests to measure comparisons. A sample size of 396 achieves a power of 98%, at the significance level of 0.05.

Results

Four hundred women were enrolled. There was incomplete documentation in 4 cases, therefore analysis of the data will show variation in the numbers of cases. Table I shows the characteristics of the women at enrolment. The commonest indication for induction was postdatism (*N* = 131). The groups were all matched in terms of maternal characteristics and demographic data.

Failed induction

Labour was successfully initiated and delivery achieved within 24 hours in 373 (94%) of the 396 patients (inclusion of caesarean sections). Eleven patients (5.7%) from the dinoprostone arm (group 1) and 12 (6%) from the misoprostol arm (group 2), i.e. 23 in total, did not go into labour. Of the 11 failed inductions in group 1, 3 subsequently went into spontaneous labour within 72 hours and the remaining 8 had subsequent re-insertions of dinoprostone and had CSs for failure to progress in labour or fetal distress.

Table I. Demographic details and indications for labour (range)

	Oral misoprostol alone (*N* = 103)	Vaginal + oral misoprostol (*N* = 100)	Dinoprostone (*N* = 193)
Age (years)	26	25	26
Parity	1 (1 - 2)	1 (1 - 2)	1 (1 - 3)
Gestational age (weeks)	38 (28 - 40)	38 (27 - 42)	38 (26 - 42)
Bishop's score at various time intervals (hours)			
Trial entry — 0 h	5 (3 - 5)	4.5 (4 - 5)	5 (4 - 5)
6 h	6 (5 - 7)	7 (6 - 7)	7 (5 - 7)
12 h	9 (7 - 9)	9 (7 - 10)	9 (7 - 10)
24 h	9 (7 - 12)	9 (8 - 13)	9 (8 - 13)
Indications for induction			
Gestational hypertension	26	40	55
Pre-eclampsia	17	20	45
Post dates	41	25	65
PROM	8	7	16
Fetal growth restriction	12	13	37
Intrapartum haemorrhage	0	0	2
Intra-uterine death	2	4	2
Others	2	1	4

PROM = premature rupture of membranes

Of 12 women with failed inductions in the misoprostol group, 4 went into spontaneous labour within 72 hours while 6 had further insertions of dinoprostone; 8 of the 12 had vaginal deliveries and all were delivered within a week of trial entry.

Mode of delivery

Overall, there were 113 vaginal deliveries (58.1%) and 80 CS deliveries (40%) in the dinoprostone group. In the misoprostol group, 118 women (58%) had vaginal deliveries and 81 (40%) had CSs. The overall vaginal delivery rate was 58% (calculated from 231 vaginal deliveries), while the CS rate was 40% (calculated from 161 CS deliveries). The difference was not statistically different, with *p* - values of 0.45 and 0.73 respectively.

Overall, vaginal delivery was achieved in 60.8% of women (*N* = 226) and CS in 142 (38%). There was no statistical difference between the groups, as shown in Table II ($p = 0.633$).

Neonatal outcome

Of the 396 patients in the study, 5 had an intrauterine death, leaving 391 women with a live fetus at term who underwent induction of labour. In 388 cases neonatal outcome was good. Of the 3 perinatal deaths, 2 were in the misoprostol group and 1 in the dinoprostone group. In the misoprostol group a stillborn baby (weighing 850 g) was born to a woman with severe pre-eclampsia who had an induction for uncontrollable hypertension at 28 weeks' gestation; the second stillbirth occurred in a primigravida who underwent caesarean section for a non-reassuring fetal heart rate and cephalopelvic disproportion, approximately 8 hours after insertion of vaginal misprostol. The perinatal death in the dinoprostone group occurred after a caesarean section for delay in the second stage of labour. The baby had poor Apgar scores and despite resuscitation died 3 days later.

There were no significant differences between the two groups in terms of neonatal outcome.

Meconium staining of liquor

Meconium staining was found in 16 women in the dinoprostone group (8.2%) and 22 in the misoprostol group (10.9%) ($p = 0.33$).

CS delivery for fetal distress

Fetal distress accounted for 39 of 80 CSs in the dinoprostone group (0.5%) and 43 of 81 CS deliveries in the misoprostol group (0.52%) ($p = 0.51$).

Hyperstimulation

There were 55 cases of hyperstimulation, 17 in the dinoprostone group and 38 in the misoprostol group. The difference between the two groups was statistically significant ($p = 0.004$); 21.4% of vaginal misoprostol patients had hyperstimulation compared with 16.5% in the oral group, and 8.9% in the dinoprostone group.

Induction to delivery time

The average induction to delivery time was 17 hours in the dinoprostone group and 16 hours in the misoprostol group ($p = 0.493$).

Average dose required

The average dose utilised was 2 mg in the dinoprostone group, whereas in the misoprostol arm of study the average dose was at 60 µg, which is equivalent to three ingestions / insertions.

Other variables inclusive of hospital stay (4 - 5 days), age, Bishop's score, and cervical dilatation at CS were not statistically different.

Table II. Obstetric outcomes

	Oral misoprostol (N = 103)	Vaginal + oral misoprostol (*N* = 100)	Dinoprostone (*N* = 193)	Misoprostol v. dinoprostone (*p*-value)	Vaginal misoprostol v. oral misoprostol (*p*-value)
Vaginal delivery 24 hrs	57	54	104	0.633	0.776
CS rate	41	40	80	0.732	
Number of doses (mean)	3	2	2	0.076	0.000
CS fetal distress	21	23	39	0.517	
Tachysystole	16	21	9	0.004	0.391
Meconium staining of liquor	9	13	16	0.33	0.341
Oxytocin	23	24	60	0.065	0.868
Failed induction	8	4	11	0.517	0.248
Ruptured uterus		-	-	-	
Admit to nursery	12	21	29	0.167	

Maternal morbidity

There were 2 cases of morbidity in the dinoprostone group. One woman developed a postpartum haemorrhage (PPH) following CS and the other had a total hysterectomy for puerperal sepsis which developed following a CS.

There was 1 case of morbidity in the misoprostol group. A hysterectomy was performed for PPH following a CS.

Discussion

Our study, using doses of < 50 µg of misoprostol and conducted in a setting of poor resources and a busy labour ward performing 10 000 deliveries per year, has shown that misoprostol is as effective as the standard method of induction of labour at term, viz. dinoprostone. Labour was successfully achieved in 373/396 women (94%); 58% of patients in the dinoprostone arm and 58% in the misoprostol arm of the study were successfully delivered vaginally. These results confirm recent reports and have positive implications for health services that are poorly resourced as misoprostol is cheap, does not need refrigeration, and is easily administered either orally or vaginally.[6-9]

The higher efficacy of misoprostol after vaginal administration may be due to the greater systemic bioavailability of vaginally administered misoprostol; peak levels are attained more slowly but sustained for longer periods due to avoidance of first bypass hepatic and/or presystemic gastrointestinal metabolism. Moreover, there is probably a direct effect on the cervix leading to uterine contractility.[10,11]

Despite concerns about hyperstimulation with the use of misoprostol for term induction of labour, the regimens utilised have not been associated with an increase in perinatal mortality rates or perinatal asphyxia. We had strict criteria for trial entry. Women with previous uterine surgery, a malpresentation, and 5 or more pregnancies were excluded. We had no cases of uterine rupture. There have been reports on the use of misoprostol to induce labour in women with previous CS and a recent retrospective study found significantly more cases of uterine rupture, or dehiscence after cervical ripening with misoprostol than with oxytocin or prostaglandin E_2.[12]

In our study, the incidence of hyperstimulation was higher in the vaginal misoprostol group (21.4%) than in the oral group (16.5%) and the dinoprostone group (8.9%). The difference between the vaginal misoprostol and dinoprostone groups was statistically significant ($p = 0.004$). The doses used varied from 20 µg to a maximum of 85 µg. An interim analysis after the enrolment of 200 patients did not show any statistical significance between the groups. Larger numbers are required to establish the difference between groups and it has been reported that 4 000 patients would need to be recruited,[13] necessitating a multicentred study.

The incidence of meconium staining of liquor was comparable between the two groups ($p = 0.33$). None of the cases displayed severe grades of meconium staining. Previous reviews have shown a trend towards more meconium passage with misoprostol than with other induction agents.[2] It is not clear whether meconium is due to hyperstimulation or to a direct effect of misoprostol on the gastrointestinal tract. In our study, many women had inductions for postdatism and pre-eclampsia, conditions not uncommonly associated with meconium staining. Furthermore, many women in our setting take traditional herbal medications during late pregnancy to facilitate labour. This has been shown to be associated with a high incidence of meconium.[14] Trials involving larger numbers of patients may answer concerns about meconium staining of liquor and hyperstimulation. The findings of this study, however, did not impact on perinatal mortality or CS rates.

The CS rates in our study were high, but the overall CS rate at KEH is 25%. Invasive monitoring during labour is not practised because of the high prevalence of HIV and this may also account for higher CS rates.

Our study was also designed to address complications associated with misoprostol in our environment and the results are similar to those of studies conducted in other centres with an overall, uniform finding of low complication rates.[6-9]

At the dose described, oral misoprostol is as effective as vaginal and oral administration combined. The cost-benefit ratio of misoprostol (approximately R1 - R2) over dinoprostone (approximately R250 - R350) for the induction of labour at term, is a strong argument for using misoprostol. It should be noted, however, that as uterine hyperstimulation occurred more frequently when misoprostol was used, the fetal heart rate should be monitored electronically and continuously when this drug is used at term. Trials with larger numbers of patients are required to establish optimal and safe doses.

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