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ORIGINAL ARTICLE

Dinoprostone versus misoprostol: a randomized study of nulliparous women undergoing induction of labor

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Background. The objectives of the study were to compare the efficacy and safety of intravaginal misoprostol and intravaginal dinoprostone for induction of labor and to quantify the clinical response to suspicious cardiotocographic (CTG) readings.
Methods. One hundred and ninety-one patients were randomized to receive either 50 μg misoprostol initially then a further identical dose 6 h later or 2 mg dinoprostone initially followed by 1 mg 6 h later, over a period of 24 h. If not in labor after 24 h, then both arms of the study would thereafter receive dinoprostone alone as per hospital protocol.
Results. The induction to delivery interval (1047 vs. 1355 min, $p = 0.01$), delivery within 12 h (35.4% vs. 18.9%, $p = 0.02$) and delivery within 24 h (83.3% vs. 63.3%, $p = 0.01$) were all shorter in the misoprostol arm. There were no differences in rates of oxytocin augmentation ($p = 0.47$), tachysystole ($p = 0.32$) and hyperstimulation syndrome ($p = 0.82$). There was an increase in the median number of times a doctor was called to advise on a suspicious CTG in the misoprostol group (1 vs. 2 occasions, $p = 0.052$), but there was no difference in neonatal outcome.
Conclusions. Intravaginal misoprostol led to a shorter, more efficient labor, and although there was more anxiety related to the CTG, there was no increase in neonatal adverse effects.

Key words: misoprostol; dinoprostone; nulliparous; induction of labor

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There has been a great deal of interest in comparing misoprostol (prostaglandin E1) with dinoprostone (prostaglandin E2) over the past decade leading to many prospective randomized trials investigating this notion. Most previously published trials using misoprostol (Cytotec, Searle Pharmaceuticals, High Wycombe, Bucks, UK), recruited both nulliparous and multiparous patients who were referred for induction of labor (1–5). However, our trial restricted recruitment to nulliparous women as the multiparous patients in our unit were offered recruitment into a separate induction of labor study. We also imposed this restriction because nulliparous women are considered more difficult to rouse into labor than multiparous women – as they have never had the obstetric challenge of a previous vaginal delivery.

There are wide variations in dosage and regimens of all prostaglandins used for induction of labor around the world. In addition, it is not clear which initial dose should be used and whether the subsequent dose should be halved. Dinoprostone (Prostin, Pharmacia & Upjohn Ltd. Milton Keynes, UK), intravaginal gel is the routine prostaglandin used for cervical ripening and induction of labor in

Abbreviations:
CTG: cardiotocograph; i.m.: intramuscular; CPD: cephalopelvic disproportion; NVD: normal vaginal delivery; NICU: neonatal intensive care unit.

our unit. Misoprostol is considerably cheaper than dinoprostone, and the meta-analyzes (4, 6–10) conducted on existing comparative trials, show that despite heterogeneity of design structure, misoprostol may reduce the induction to delivery time with no increase in serious maternal or neonatal adverse effects. However, there are concerns over uterine rupture and an increased incidence of tachysystole when using misoprostol. An increased rate of tachysystole may lead to extra clinician input and has manpower implications particularly in busy obstetric units. So with this potential additional use of clinical time to deal with tachysystole and any fetal heart rate aberrations, we constructed this study to not only examine the primary outcome measures considered in the meta-analyzes but also to examine the clinical response to a suspicious CTG.

Materials and methods

The University College Hospitals NHS Trust Ethics Committee approved this study. The study ran from January 1998 to December 1999. Nulliparous women who were at term (between 37 and 42 completed weeks gestation) were eligible. Exclusion factors were previous uterine surgery, abnormal fetal heart rate patterns, malpresentations, an estimated fetal weight of >4500 g or other evidence of cephalopelvic disproportion (CPD), placenta praevia and the presence of any contraindication to prostaglandin therapy. Eligible nulliparous patients referred for induction of labor were given a patient information leaflet at the antenatal clinic or upon admission to the labor ward. Patients undergoing induction of labor due to known fetal abnormalities were included in this study. Their induction was considered 'routine' in our unit, which offers tertiary level neonatal care and a specialist pediatric surgery service from Great Ormond Street Hospital. If the patient agreed to take part in the trial, written informed consent was obtained and then the patients were randomized to receive either intravaginal dinoprostone or misoprostol (see below). The dose of 50 μg misoprostol was chosen on the basis of previously published trials at the time of trial design (1997) and also because it was the smallest divisible dose available to our department at that time (i.e. one-quarter of a 200 μg tablet, divided by a tablet cutter) Randomization was derived from numbers generated from STATA software (Stata corporation, College Station, Texas, USA). The arm of the study was concealed in opaquae numbered sealed envelopes that were opened in a consecutive fashion.

The study was unblinded because of the dissimilar drug preparations used and because the drugs had to be prescribed on a hospital drug chart before administration. The dinoprostone was available as a pre-prepared gel with applicator, but the 200 μg misoprostol tablets had to be divided with a tablet cutter to 50 μg by the clinician or midwife commencing the cervical ripening. The standard hospital regimen of dinoprostone consisted of giving 2 mg if there was no significant uterine activity or cervical dilation that would have usually warranted an amniotomy. A second dose of 1 mg of dinoprostone was given 6 h later if there was no significant uterine activity and/or cervical dilatation and/or fetal heart abnormality. A maximum of 2 prostaglandin doses were given in 24 h. If there was no success within 24 h then this regimen was repeated for a second day. Those women allocated to the misoprostol arm were given 50 μg initially, and then another 50 μg 6 h later if required. If further prostaglandins were required after 24 h then the clinicians were instructed that both arms of the study use dinoprostone (i.e. further misoprostol was not given).

CTG was performed for at least 40 min prior to insertion of the prostaglandin and for 40 min after insertion. The prostaglandin was inserted in to the posterior fornix of the vagina. Oxytocin augmentation was used subsequent to rupture of membranes according to the hospital standard protocol (insufficient uterine activity or poor cervical dilation and descent of the fetal head).

A sample size of 75 patients per arm was calculated from the estimate that a 300 min difference in the induction to delivery time, between the two groups, was considered significant with a 95% power with $\alpha = 0.05$. Induction to delivery time and incidence of suspicious cardiotocographic readings that required clinician action were primary outcome measures. There was no published data to produce a power calculation for the incidence of suspicious cardiotocographic readings and we hoped to produce preliminary data for future studies. Types of clinician action included fetal blood sampling, decision to continue observing CTG, giving oxygen by mask, turning the patient into the left lateral position, rupturing the membranes to detect meconium, and commencing a tocolytic agent. Delivery within 12 h and delivery within 24-h oxytocin augmentation, tachysystole ($\geq$6 contractions in 10 min), hyperstimulation (abnormal fetal heart rate pattern related to excessive uterine activity), mode of delivery, deliveries associated with a suboptimal/suspicious CTG (which included normal vaginal deliveries), operative deliveries

because of a suboptimal/suspicious CTG and failed induction of labor were other obstetric factors examined. The definition of a suspicious CTG has been defined by the National Institute for Clinical Excellence (www.nice.org.uk) clinical guidelines for the induction of labor. The neonatal outcomes measured were 5-min apgar <3, 5-min apgar <7, cord venous pH, cord venous pH < 7.0, cord venous pH < 7.20, resuscitation attempts (oxygen by mask, nasopharyngeal suction, intubation) and admission to the neonatal intensive care unit (NICU) for reasons other than routine management of fetal anomaly. Statistical analysis was performed using an independent sample *t*-test for parametric continuous variables, the Mann–Whitney *U*-test for non-parametric data and Fisher's exact χ^2 test for discrete data.

Results

Two hundred patients were recruited and randomized, but there were nine post-randomization exclusions: seven women due to protocol violations and two patients withdrew from the trial after randomization. There were two cases where a randomization envelope was drawn but after vaginal examination, the patients actually did not need prostaglandin and instead had an amniotomy straight away; two cases were recruited from the exclusion criteria, i.e. had abnormal fetal heart rate patterns; in two cases the midwives and doctors muddled up the prostaglandins, giving both misoprostol and dinoprostone; and one case of severe fulminating pre-eclampsia where immediately after giving prostaglandin, before labor, the decision to induce labor was retracted and a cesarean performed due to dramatic worsening of the maternal condition. One hundred and ninety-one patients were ultimately considered in the analysis. Ninety-five patients received dinoprostone and 96 patients received misoprostol. There were no differences across arms of the study with respect to maternal demographic information (Table I) and indications for induction of labor (Table II). However, the misoprostol group performed significantly better when considering parameters that indicate length of labor, e.g. induction to delivery interval, number of patients delivered within 12 h [risk ratio = 2.8 (95% CI 1.36–5.79)] and 24 h [risk ratio = 2.5 (95% CI 1.22–5.34)] (Table III). There was no significant difference in the rates of oxytocin augmentation, tachysystole, duration of tachysystole, hyperstimulation and the use of tocolytic agents.

The rates of normal vaginal ($p = 0.65$) and abdominal deliveries ($p = 0.23$) were not found to be significantly different across the arms of the study (Table IV). Mode of delivery is

Table I. Maternal demographic data: median (range), or median [SD]

	Misoprostol ($n = 96$)	Dinoprostone ($n = 95$)	*p*-value
Maternal age (year)	30 (16–42)	29 (16–45)	0.45
Gestation (weeks)	40 (36–42)	40 (36–43)	0.64
Height (cm)	165 [6.5]	165 [6.2]	0.74
Weight (kg)	77 (52–115)	77 (50–106)	0.58
Initial Bishops score	4 (0–7)	4 (1–7)	0.91

Two sets of twins in the misoprostol arm. No twins in the dinoprostone arm.

Table II. Indications for induction of labor

	Misoprostol ($n = 96$)	Dinoprostone ($n = 95$)	*p*-value (Fisher's exact test)
Pre eclampsia	7	16	0.48
Diabetes	3	3	1.00
Post dates	51	53	0.56
Essential Hypertension	4	10	0.10
Pre-labor rupture of membranes	8	4	0.37
Intrauterine growth retardation	3	3	1.00
Oligohydramnios	8	9	1.00
Social	0	0	1.00
Reduced fetal movements	9	8	1.00
Advanced maternal age	5	3	0.72
Recurrent antepartum hemorrhage	2	1	1.00
Fetal anomaly	7	1	0.65
Gastroschisis	4	1	0.37
Obstetric cholestasis	4	1	0.37
Twins	2	0	0.50
Anitphosholipid antibody	1	0	1.00
Large for dates	3	1	0.62
Maternal renal stone	1	0	1.00

Table III. Comparison of outcomes in labor {median} [mean]

	Misoprostol ($n=96$)	Dinoprostone ($n=95$)	*p*-value
No. delivered			
After single dose	56	47	0.25
<12h	34	18	0.02
<24h	80	63	0.01
Induction/delivery interval (min)	[1047] {901}	[1355] {1135}	0.01
Oxytocin augmentation	42	47	0.47
Tachysystole	28	21	0.32
Duration of tachysystole	[39] {0.00}	[14.7] {0.00}	0.14
Hyperstimulation	10	12	0.82
Tocolysis	1	3	0.37
Labor commenced	86	88	0.59

Table IV. Delivery factors

	Misoprostol ($n=96$)	Dinoprostone ($n=95$)	*p*-value
Normal vaginal delivery	31	34	0.65
Abdominal delivery	29	37	0.23
Suspected CPD/undefined dystocia	9	19	0.04
1st degree tear	5	7	0.57
2nd degree tear	14	7	0.16
3rd degree tear	0	1	0.50
Episiotomy	28	20	0.24
Retained placenta	2	1	1.00
Estimated blood loss (ml)	240	256	0.93

recorded in Table V. When breaking down the parameters which examine intrapartum well-being (Table VI), our results show an increase in the number of times a doctor was called to advise on a suspicious CTG though there was no overall differences in the total number of medical interventions performed. The results also show that more deliveries (including normal vaginal deliveries) were associated with a suspicious CTG and there were more operative deliveries performed for suboptimal CTGs in the misoprostol arm (Table VI). Also more deliveries in the dinoprostone arm were associated with the diagnosis of (Table IV) CPD/undefined dystocia ($p=0.04$). When analysing the neonatal outcomes, there were no clinically significant differences detected between the two study arms (Table VII). Use of intramuscular (i.m.) pethidine analgesia ($p=0.014$) was greater in the dinoprostone group, but rates of epidural use and side-effects such as nausea, vomiting

Table V. Mode of delivery

	Normal vaginal delivery	Forceps	Ventouse	Cesarean section	Total
Misoprostol	31	12	24	29	96
Dinoprostone	34	6	18	37	95

Table VI. Intrapartum fetal well being [SD], (range)

	Misoprostol ($n=96$)	Dinoprostone ($n=95$)	*p*-value
No. of times seen by a doctor due to suspicious CTG	2.25 [2.04]	1.72 [1.72]	0.05
No. interventions for a suspicious CTG	2.5 [2.35]	2.07 [2.30]	0.21
No.of times fetal blood sampling done	0(0–3)	0(0–3)	0.13
Meconium present at rupture of membranes	19	10	0.10
Delivery associated with suspicious CTG (inc NVD*)	52	30	0.002
Operative delivery for suboptimal CTG	43	26	0.02

*Normal vaginal delivery.

and diarrhea were no different. There were no cases of uterine rupture in this clinical trial.

Discussion

This trial adds to pre-existing published data suggesting that intravaginal misoprostol leads to a shorter labor when compared with dinoprostone preparations. The sample size in this work is adequate for the study's primary endpoints but may well allow for type II errors in secondary endpoints – type II error being the acceptance of a null hypothesis when it is false. However, the primary and secondary endpoints are clearly delineated with primary endpoints concerned with induction to delivery times and secondary endpoints concerned with a variety of maternal and fetal outcomes.

All neonatal outcomes of clinical significance were statistically similar between the two regimens. It is interesting to note that there were no significant differences between mode of delivery,

Table VII. Neonatal outcomes

	Misoprostol [sd] (CI) {range}	Dinoprostone [sd] (CI) {range}	*p*-value
Birthweight	3398 [523]	3386 [589]	0.88
Umbilical vein pH	7.26 (7.23–7.27)	7.28 (7.27–7.30)	0.02
Cord base excess	−5.68	−5.07	0.22
Cord ph <7.20	16	12	0.43
Cord pH <7.0	1	0	
Apgar 1 minute	9 {4–10}	9 {1–10}	0.47
Apgar 5 min	9 {0–10}	9 {2–10}	0.89
1 minute apgar score <3	0	1	
5 minute apgar score <3	1	1	
1 minute apgar score <7	9	16	0.13
5 minute apgar score <7	3	2	1.00
Meconium at delivery	20	12	0.17
Resuscitation required	51	50	0.61
NICU admission	11 (7 fetal anomalies)	4 (1 fetal anomaly)	0.10

yet a greater proportion of assisted/operative deliveries in the misoprostol arm were performed for suspicious cardiotocographic readings and a greater proportion of abdominal deliveries in the dinoprostone group were performed for suspected CPD or undefined labor dystocia. On the other hand, the neonatal outcome data does not indicate any statistical difference in the cord blood samples that show hypoxia/acidosis or in birthweight. There is much still to deduce about the specific mechanics of labor induced by misoprostol and further Doppler studies of the uteroplacental circulation may help to address the issues of intrapartum well being (11).

In the UK, women whose labor is induced, but succeed in going in to normal labor are usually thereafter managed by the midwifery team as long as there is good progress and the CTG remains reassuring. However, our study shows that women allocated to the misoprostol group had more obstetrician visits because of concerns over the CTG even though these anxieties were not validated by the neonatal outcomes. This does have manpower implications in busy units, although these women did have a shorter stay on the labor ward.

In conclusion, this study showed that intravaginal misoprostol led to a shorter, more efficient labor, with more clinician anxiety related to the CTG but there were no greater neonatal adverse effects.

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