Original Article

Oral versus vaginal Misoprostol for labour induction

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Abstract

Objective: To compare the safety and efficacy of oral versus vaginal misoprostol for induction of labour.

Methods: Three hundred and ten live singleton term pregnancies with medical or obstetric indication for labour induction were randomly assigned to receive 50 microgram (µg) misoprostol orally or vaginally every 4 - 6 hours to a maximum of six doses. Main outcome measures were time of intervention to vaginal birth and number of doses required. Secondary outcome measures included frequency of tachysystole/ hyper stimulation, maternal side effects, caesarean section (LSCS) rate, instrumental delivery rate and neonatal outcome (apgar score, need of neonatal intensive care). This study was conducted at Kharadar General Hospital; Karachi. Data was collected on a Performa and analyzed using software SPSS (version 10.0) and p-value was used to test the statistical significance.

Results: The mean induction to delivery interval was significantly shorter in the vaginal group compared with the oral group (13.5hrs vs. 20.6hrs p<0.010). In the vaginal group fewer doses of misoprostol were required (1.93 VS 2.52 p<0.001) and there was reduced need for additional oxytocin 65 (44.8%) vs. 89 (53.9%) p< 0.19, but there was an increased incidence of hyperstimulation and tachysystole (8.3% vs. 1.8%).

The modes of delivery were similar in the two groups. A higher incidence of neonatal intensive care unit (NICU) admission in the vaginal group was mainly due to respiratory distress syndrome (RDS).

Conclusion: In this study Misoprostol proved to be a safe and effective drug to use for induction of labour (IOL). Vaginal route was more efficacious compared to the oral route. A slightly higher number of patients in the vaginal group had hyper stimulation and neonates required NICU admission (JPMA 57:404:2007).

Introduction

Induction of labour (IOL) at term is a common obstetric intervention with many indications e.g. postdate pregnancy, Pre-eclampsia, Prelabour rupture of membranes (PROM), oligohydradmnios, intra uterine growth restriction (IUGR) and even for social reasons. With > 15% of all gravid women requiring aid in cervical ripening at the time of labour induction, there is widespread interest and demand for an effective and safe method for labour induction.[1-6]

Dinoprostone, a prostaglandin E2 (PGE2) has been the agent of choice for labour induction and cervical ripening for the past decade. It is the only pharmacological agent approved for this purpose, but is expensive.

Misoprostol [Cytotec (Searle)], a synthetic PGE1 analogue though used internationally for cervical ripening and IOL, is not yet licensed for this indication[3,4] in the majority of countries, and is approved solely for prophylaxis against gastric ulcers in association with nonsteroidal anti-inflammatory drugs (NSAID). Misoprostol is relatively cheap and available as a 200 µg tablet in Pakistan. As misoprostol is heat stable there is no need to maintain the cold chain and hence remains effective when stored at room temperatures. Given the hot conditions prevailing in Pakistan, with frequent power outages the efficacy of Dinoprostone and other oxytocics is sometimes questionable. Misoprostol provides an alternative for IOL in our setup if found to be safe and effective, as it is very cheap and heat stable when compared with Dinoprostone.

Studies have shown that vaginal misoprostol when compared with the oral route, resulted in significantly more women delivering within 24 hours of induction, less number of doses were required, with less requirement of augmentation with oxytocin,[2,7-11] but with significantly higher incidence of uterine hyperstimulation and tachysystole.[8,10,11]

The aim of this study was to generate local experience and to compare the safety and efficacy of misoprostol when administered in equivalent doses orally or vaginally.

Subjects and Methods

This study was conducted in a busy obstetric unit with more than 5000 annual deliveries and on site facilities for emergency caesarean section, and neonatal intensive care. All patients (Nulliparous and multiparous but not more than para 4) requiring IOL at term (37-42 completed weeks of gestation with ultrasound confirmed dates) and with a live singleton foetus of cephalic presentation were included in the trial. Women with previous uterine surgery including a previous caesarean section, non-reactive foetal heart rate

(FHR) tracing, moderate to severe abruption or placenta praevia were excluded. Women who required induction were randomly allocated to receive misoprostol either orally or vaginally. The allocation was done by opening sequentially numbered folded forms with already stamped route of administration.

From Dec 2002- Nov 2003, a total of 310 women were recruited in the trial and were randomized into two groups, one group to receive misoprostol orally and other vaginally. 50µg of misoprostol was given every 4 to 6 hours. A maximum of 6 doses were given if required. The 50µg dose was prepared by dividing a 200µg tablet of misoprostol into 4 pieces manually. Foetal well being was confirmed by cardio tocography (CTG) on admission and prior to administration of each dose of misoprostol. The next dose of misoprostol was withheld if cervix was suitable for amniotomy (ARM) or if the patient was in active labour or if there was evidence of foetal distress, tachysystole or hyper stimulation. Oxytocin was used for augmentation of labour after 4 hours of administering the last dose of misoprostol, if required.

If a woman was not in labour after receiving 6 doses of misoprostol it was categorized as failed induction. The need for labour induction was then reassessed and subsequent decision was taken by the respective consultant.

Besides standard management of patient in labour, uterine contractions, pulse and FHR were monitored hourly in latent phase and ½ hourly in the active phase of labour. CTG was repeated earlier than the scheduled time in patients who were categorized as high risk (e.g. bad outcome in previous pregnancy or conditions associated with increasing likelihood of foetal compromise like IUGR, decreased liquor etc) or were in active labour or showed evidence of foetal distress. Labour was managed according to standard labour ward protocol.

Out of 310 women oral misoprostol was given to 165 women and 145 received it vaginally. There were more patients in the oral group as the drug was already being used in the department by oral route prior to the study. So in the initial 3 months more patients received misoprostol orally according to routine and these patients though not randomized were included in the study as the protocol of induction and monitoring were the same. Out of 25 non-randomized patients, 21 (12.72%) were in the oral group and 4 (2.75%) in the vaginal group.

Indications for labour induction included post dates, PROM, IUGR, pre-eclampsia/eclampsia/essential hypertension (HTN), oligohydramnious, prolonged latent phase, mild antepartum haemorrhage (APH) without placenta praevia, small for dates(SFD),non reactive CTG with a repeat reactive CTG, bad obstetric history(BOH),fever, unstable lie, social reasons, previous still birth at term, precious pregnancy, large baby with adequate maternal pelvis(trial of labour), diminished foetal movement, polyhydramnious, with suspected congenital heart block and sickle cell anemia. Labour was induced in 35 women due to more than one indication.

Patients were considered booked if they had 3 antenatal visits and numbered 300 (96.7%) in this study. There was post randomization protocol violation in parity and gestational age, as 4 patients in the non-randomized group were Para 5 and 18 patients with pregnancies less than 37 completed weeks of gestation (35-36+6 weeks of gestation) who required labour induction for obstetric indication. The indications for labour induction in these patients were PROM (11), severe IUGR (03), impending eclampsia (02) and high-grade fever due to falciparum malaria (02).

The primary outcome measure was time of intervention to vaginal birth and number of doses of Misoprostol required. Secondary outcome measure included frequency of tachysystole, (exaggerated uterine contractions i.e. >5/10 minutes or sustained uterine contraction lasting for 2 minutes), hyper stimulation (exaggerated uterine contractions with late foetal heart decelerations or foetal tachycardia >160bpm). Other secondary outcome measures included maternal side effects e.g. febrile illness, nausea / vomiting, diarrhoea, abdominal pain and shivering, cesarean delivery rate, instrumental delivery rate, apgar score less than 6 at 5 minutes, and requirement for neonatal intensive care. The demography of the two groups was also compared in terms of maternal age, parity, gestational age and bishop's score.

Results

Of the 310 patients enrolled 193 (62.3%) were primigravida. There was no difference in maternal demographic characteristics e.g. age, parity, gestational age and bishop's score (Table 1) or in the indication for labour induction, with post dates being the most frequent indication in both the groups; 48 (29.09%) in oral group and 42 (28.96%) in the vaginal group. Unfavourable Bishop's scores (0-6) were encountered in 83.5% patients in each group. There were four (1.29%) failed inductions, all belonged to the oral group and all of whom were primiparous. LSCS was done in 2 of these patients and 2 patients were left for 24 hours without intervention. One of these patients went into labour with single dose of vaginal misoprostol in the second cycle of labour induction, ARM was done after one dose, augmented with oxytocin and then emergency LSCS was required due to non progress in second stage of labour. The other patient was induced with

Table 1. Patient demographics and outcome measures.

Characteristics	Oral (n=165)	Vaginal (n=145)	P-value
Age (Years)	24.76 ± 4.48	23.99 ± 4.03	0.118
Parity	0.98 ± 1.48	0.73 ± 1.14	0.10
Gestational Age (Weeks)	41.07 ± 4.45	40.86 ± 3.84	0.667
Bishop score	4.52 ± 2.03	4.63 ± 2.18	0.638
Duration of Labour	20.64 ± 31.32	13.53 ± 9.02	0.010*
Number of Doses	2.52 ± 1.48	1.93 ± 1.21	0.001*
Weight of Baby (Kgs)	3.016 ± 0.47	3.008 ± 0.48	0.890

Data are presented as mean ± SD
* Statistically significant

Table 2. Mode of delivery and indications for LSCS according to route of administration (%)

Mode of delivery	Misoprostol Administration		Total
	Oral N = 165	Vaginal n = 145	310
Vaginal delivery	135 (81.8)	121 (83.4)	256
SVD*	122 (74)	115 (79.3)	237
FVD+	9 (5.45)	3 (2.06)	12
Vaccum	4 (2.42)	3 (2.06)	7
LSCS++	30 (18.1)	24 (16.5)	54
Indication for cesarean section:			
Foetal distress	16 (53.3)	13 (54.2)	29
NPOL	11 (36.6)	08 (33.3)	19
Failed IOL	02 (6.7)	NIL	02
Impending eclampsia /	01 (3.3)	01(4.2)	02
Pt's request	00	02 (8.3)	02

*Spontaneous vertex delivery
+Forceps vaginal delivery
++ Lower Segment Caesarean Section

Table 3. Relationship of parity to mode of delivery.

Parity	Total patients (acc to parity)	Outcome		Instrumental
		SVD	LSCS	
0	193	130	47	16
1	40	36	02	02
2	34	30	03	01
3	17	16	01	-
4	22	21	01	-
5	4	4	-	-
	310	237	54	19

intracervical Foley's catheter and augmented with ARM and oxytocin. She had a forceps delivery. There was no failed induction in the vaginal group.

The mean induction to delivery interval in those who delivered vaginally was significantly shorter in vaginal misoprostol group (13.53 hrs vs. 20.64 hrs p<0.010) and vaginal group required less number of doses (1.93 VS 2.52 p<0.001). Overall 155/193 (80%) primigravida required 3 or less doses of misoprostol (Table 1). Fewer women required oxytocin augmentation in the vaginal group 65 (44.8%) vs. 89 (53.9%) in oral group, (p<0.19). There was no difference in mode of delivery between the two groups (Table 2). There was no significant difference in the caesarean section and instrumental delivery rates (Table 2).

Colour of liquor was observed in all the patients, 250 (80.6%) had clear liquor, 136 (82.42%) in the oral group and 114 (78.6%) in the vaginal group while meconium was found in only 39 (12.5%) patients [19 (11.51%) in oral group and 20 (13.79%) in the vaginal group (p<0.52)], 5 (1.61%) had blood stained liquor, 4 (2.42%) in oral and 01 (0.68%) in vaginal group and liquor was not obtained at ARM in 15 (4.83%) patients, 05 (3.03%) in oral and 10 (6.89%) in vaginal group.

Majority of babies had apgar scores >6 at 5 minutes in both the groups, only 6 babies (2 %) had apgar scores < 6 at 5 minutes. Fifty (30.3%) babies were admitted to the neonatal observation unit in oral and 47 (32.41%) in vaginal group. Eighty-two (26.4%) of these babies were admitted in nursery for observation and were discharged within twenty-four hours in both groups cumulatively. The reason for admission being transient tachypnoea of newborn (TTN), instrumental deliveries, meconium stained liquor, prolonged rupture of membranes, cleft lip, meningocele, low birth weight and infant of diabetic mother. Of the admitted babies 4 (2.42%) in oral and 10(6.89%) in vaginal group required intensive care. The main reason for neonatal intensive care admission was respiratory distress syndrome (RDS), which was more in vaginal group (5 vs. 1). Ventilatory support was required by one baby in each group and 2 babies had birth asphyxia in oral and 3 in vaginal group. No neonatal death was recorded in oral group while there were 2 neonatal deaths in vaginal group. One baby died after 3 days due to aspiration after feeding in the postnatal ward and 1 baby was diagnosed to have meconium aspiration syndrome (MAS), did not require ventilatory support and died of unexplained cause.

Maternal side effects were observed in 5 patients only, 4 had vomiting (2 in each group) and 1 patient had low-grade fever. Incidentally 1 patient had post partum haemorrhage (PPH) due to cervical tear. Hyperstimulation was recorded in 6 women, 5 (3.44%) in vaginal group (two primiparous and 3 multiparous), 1 of them required caesarean section due to NPOL after receiving 6 doses, 4 others achieved vaginal deliveries while 1 multiparous patient in the oral group had Emergency LSCS due to NPOL having received 3 doses. 9 patients had tachysystole, 7 of them were in the vaginal group (5 primiparous and 2 multiparous), all delivered vaginally and 1 required vacuum delivery. In oral group 2 women (1 primiparous and 1

multiparous) had tachysystole, both had assisted vaginal delivery with vacuum; of these two, one was given sublingual Nifedipine to control tachysystole. No case of uterine rupture was recorded in the study. No difference was noted in both the groups in terms of gastrointestinal side effects. As these side effects were small in number statistical analysis was not possible therefore the two groups were compared with percentage only.

Discussion

Misoprostol although not licensed for use in pregnancy, is widely used for obstetric and gynaecological indications worldwide. It has proven to be a safe drug to use for termination of first and second trimester pregnancies, for preventing and treating PPH and increasingly for IOL.[12-13]

Our study supports the safety and efficacy of 50 ug of Misoprostrol for induction of labour.

Misoprostol is being used by both oral and vaginal routes to induce labour. The vaginal route, in our study was found to be more efficacious in terms of quicker induction to delivery time, fewer doses required and reduced need for additional use of syntocinon to augment labour. This has been reported by other authors as well.[2,7-11] when used by vaginal route there are increased chances of tachysystole and hperstimulation. This was true in our study also.[7-11,14] In our study however the risk of uterine rupture was not increased and there was no difference in neonatal outcome and maternal side effects. This has also been noted by others.[9,10]

Misoprostol is especially relevant for a country like ours where economic resources are scarce and high temperatures prevail. This drug is cheap as compared to other prostaglandins licensed for pregnancy termination, induction of labour and treatment and prevention of post partum haemorrhage. It is heat stable so is easily stored at room temperatures with few systemic side effects. Although formulated for oral usage it is rapidly absorbed via sublingual, oral, vaginal and per rectal route.[6,15]

More supervised trials are required in local hospitals to prove the efficacy and safety of the drug. Subsequently smaller doses e.g. 25 g can be tried for IOL, to see if it is equally effective and thereby increasing the safety margin.[10,13]

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