

Isosorbide Mononitrate versus Misoprostol for Cervical Ripening

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Abstract

Objective: To compare the efficacy and safety of isosorbide mononitrate (IMN) versus misoprostol used to induce labour for overdue pregnancy.

Setting: A prospective randomized clinical study conducted at AL-Elwiya Maternity Teaching Hospital in Baghdad from Jan. 2008 to Dec. 2008.

Method: One hundred and fifty women with over due pregnancy (past date and posterm pregnancy) referred for induction of labour with Bishop scores ≤ 5 were randomly allocated to receive either forty mg isosorbide mononitrate (IMN) tablet as a single vaginal dose (n=75) or fifty mcg misoprostol vaginally (n=75) every six hrs for a maximum of three doses. Amniotomy and/or oxytocin infusion is considered when Bishop scores frankly progressed (augmentation) or used when no improvement achieved after 24 hour (induction). Adverse effects of medications, induction - delivery interval, mode of delivery and neonatal outcome were recorded and subjected to statistical analysis.

Results: Isosorbide mononitrate was associated with less adverse effects than misoprostol especially

regarding uterine tachysystol (0 with isosorbide mononitrate vs 12% with misoprostol, $P < 0.01$) and hyperstimulation (0 with isosorbide mononitrate vs 16% with misoprostol, $p < 0.01$) but the induction - delivery interval with isosorbide mononitrate group was significantly longer compared with misoprostol (26.3 ± 7.3 hrs vs 15.4 ± 5.4 hrs, $p < 0.01$). Oxytocin was added to 70 women (93.3%) used isosorbide mononitrate while to 15 women (20%) used misoprostol ($p < 0.001$). Caesarean rate was not significantly different between the two groups, but the indications were different, dystocia is the major cause (73.3%) with isosorbide mononitrate while persistent non-assuring fetal heart rate pattern (64%) in the misoprostol group.

Conclusion: Cervical ripening and induction of labour using isosorbide mononitrate resulted in fewer adverse effects but it was less effective than misoprostol.

Key words: Misoprostol, isosorbide mononitrate, cervical ripening, induction

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Introduction

Cervical ripening usually begins prior to the onset of labour and it is necessary for cervical dilatation and subsequent passage of the fetus.⁽¹⁾

The cervix consists primarily of connective tissue in which collagen fibers are embedded in ground substance. Collagen is inelastic and highly tensile (strong), while ground substance is a gel of proteoglycan complexes linked to a hyaluronic acid chain tightly. Its physical properties can be changed rapidly depending on its chemical composition and physical attributes.^(2,3)

Nitrous Oxide (NO) system has been postulated to have a regulatory role in the myometrium and cervix during pregnancy and parturition. Previous studies showed that NO generating system is present in the cervix and is up regulated towards term as well as during labour.⁽²⁾ NO donors are vasodilator i.e. isosorbide mononitrate, they can also used to induce cervical ripening after their local application through stimulation of cyclo-oxygenase activity via increasing production of PGF₂ within the cervix.^(2,3,4,5) While Misoprostol is a synthetic analogus of prostaglandins E₁^(1, 6, 7), with longer duration of action and better safety profile compared with PGE₁^(8,9,10).

Aims of the study are to evaluate the efficacy of Intravaginal isorbide mononitrate and misoprostol

in cervical ripening and induction of labour and to assess their adverse effects.

Methods

This prospective randomized control trail study was conducted at AL-Elwiya Maternity Teaching Hospital in Baghdad between Jan. 2008 and Dec. 2008.

The study sample consisted of 150 primigravidas with singleton uncomplicated pregnancy (no obstetrical, gynecological or medical problem). They were admitted for induction of labour for past-date (pregnancy beyond 40 completed weeks of gestation) or post-term (pregnancy beyond completed 42 weeks).

Demographic and obstetric data were recorded on a special form for each participant and gestational age determination was based on a precisely recalled menstrual date and further confirmation by their first and/ or second trimester ultrasound.

A formal consent was obtained from the participants after explaining to them the idea of the study, types of drugs used and their possible side effects and after assessing their obstetrical and general condition they were admitted to the observation room for treatment and regular review.

They were randomly allocated to receive either:

1. 40 mg IMN tablets, two tablets of 20 mg administered into the posterior vaginal fornix by the obstetrician as a single dose. (Group 1, n=75)

2. 50 mcg misoprostol (1/4 of 200 mcg of oral tablet "cytotec") administered into the posterior vaginal fornix by the obstetrician and repeated every 6 hours if Bishop score didn't improve for a maximum of three doses. (Group 2, n=75)

Uterine contractions and fetal heart rate (FHR) were checked every 30 mins by sonic aid and continuous fetal heart monitoring used when necessary and the symptoms and vital signs were monitored 2 hourly.

The participants were asked to report or inform us when they had uterine contraction, pain or any abnormal symptoms such as headache, palpitation, dizziness, fainting or gastrointestinal symptoms.

Aminiotomy and /or Oxytocin was given when Bishop score showed good improvement after the medication (> 6) in order to augment labour or used for induction of labour when both medications fail to achieve a noticeable progress in cervical condition (Bishop score remain < 6) after 24 hours of commencing IMN or Misoprostol.

The maternal status, labour-delivery characteristics, adverse effects and neonatal outcome were reviewed and recorded on the forms.

Failed induction was defined as (inability to achieve active phase of labour despite of adequate oxytocin stimulation for 6 hrs after amniotomy). Regular uterine contractions were defined as (at least three uterine contractions in 10 minutes, lasting for 45-50 seconds). Ripening of the cervix occur when Bishop score become more than 5.

Caesarean delivery was done for obstetric indications which include secondary arrest of dilatation or arrest of descent (dystocia) or persistent non-assuring FHR pattern and failure of induction .

Statistical Analysis

Data were arranged in tables and analysed using descriptive statistical (tables, graphs, frequency and percentages) and Inferential statistical (Chi square test and unpaired t-test) were used to find the association between the related variables. Data was entered and analyzed by Mini Tab soft ware, P-value < 0.05 was considered significant.

Results

The mean of maternal ages were 25.6 (± 2.1) years in IMN group and 26.3 (± 2) years in the misoprostol group which is not statistically different. The mean of gestational ages were 42.1 (± 0.6) weeks in both groups.

Table.1 shows induction-delivery intervals, time from start of medication to onset of labour was significantly longer in group 1 (15.6 \pm 4.8 hr vs 8.6 \pm 2.4 hr in group 2 $p < 0.001$).

The time from start of ARM and/or oxytocin to the active phase of labour was also significantly longer in group 1 (3.9 \pm 1.5 hr vs 2.3 \pm 1 hr in group 2 $p < 0.001$).The duration of 1st stage of labour was also significantly longer among group 1(10.4 \pm 2.6 hr vs 6.5 \pm 1.2 hr in group 2 $p < 0.001$) while the duration of second and third stages of labour was not significantly different between both groups.

The time from start of medication to complete vaginal delivery was significantly longer in group 1 (26.3 \pm 7.3 hr vs 15.4 \pm 5.4h in group 2 $p < 0.001$)

Table. 1 Induction- delivery intervals

Induction-delivery intervals	IMN	misoprostol	p.value
Time from start of medication to onset of labour (h)	15.6 \pm 4.8	8.6 \pm 2.4	< 0.001
Time from start of ARM and / or oxytocin to the active phase of labour (h)	3.9 \pm 1.5	2.3 \pm 1	< 0.001
Time from start of medication to vaginal delivery (h)	26.3 \pm 7.3	15.4 \pm 5.4	< 0.001
Duration of 1 st stage of labour(h)	10.4 \pm 2.6	6.5 \pm 1.2	< 0.001
Duration of 2 nd stage of labour(min)	31.2 \pm 8.6	30.4 \pm 7.8	0.1
Duration of 3 rd stage of labour(min)	8.3 \pm 3.1	7.5 \pm 2.4	0.2

Data are presented as mean \pm standard deviation

Fig.1 shows number of women needed oxytocin for initiation or augmentation of labour in both groups and women who did not need oxytocin for augmentation or initiation of labour. Higher number of women needed oxytocin for initiation of labour in group 1 (66.6% vs 4% in group 2) while the higher number of women develop regular uterine contraction with group 2 and did not need oxytocin (80% vs 6.6 % in group 1).

Fig.1 Bar chart comparing number of women who needed oxytocin for initiation or augmentation of labour between both study groups.

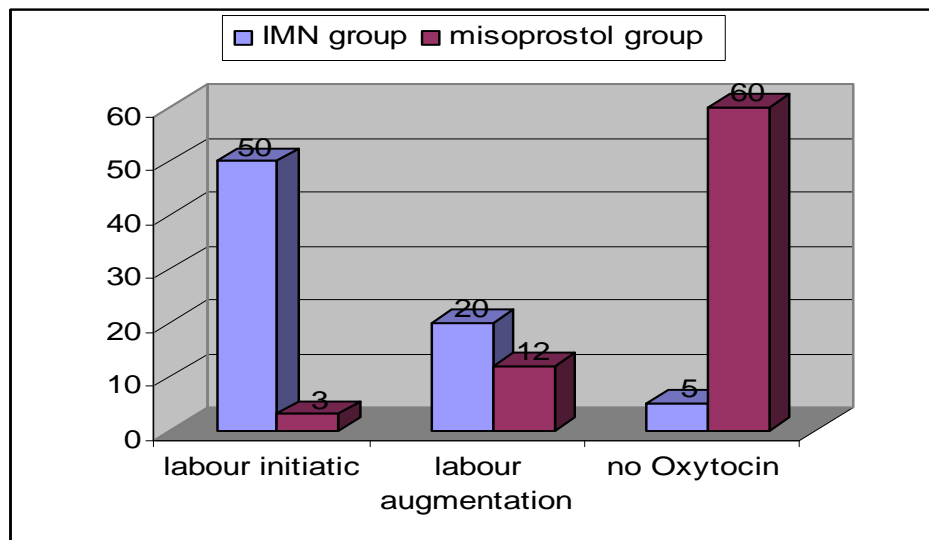


Table 2 show mode of delivery, indications for caesarean section and fetal outcome. Thirty women (40%) in group 1 delivered vaginally compared with thirty-six women (48%) in group 2 which was not significantly different between both groups. While forty-five women (60%) in group 1 delivered by caesarean section versus thirty-nine (52%) in misoprostol group.

The most common indications for caesarean section in group 1 was dystocia (33.73%) but in the group 2 was a persistent non-assuring FHR pattern (25.64%). The number of failed inductions

was significantly lower in the group 2 (20% in group 1 vs 7.6% in group 2 $p < 0.001$).

Fetal outcome was twenty-five newborns (33.3%) in group 2 had an Apgar scores ≤ 7 at 1 min compared with two newborns (2.6%) in group 1 ($p < 0.001$).

At 5 min 13.3% of newborns had Apgar scores ≤ 7 in group 2 vs 0% in group 1. From those newborns who had low Apgar scores at 5 min in group 2 just one improved and discharged, the other nine admitted to NICU then improved and discharged after two hours, there were no prenatal mortality.

Table 2. Comparism of mode of delivery, indication for caesarean section and fetal outcome in the study groups.

Maternal and neonatal outcomes	IMN	Misoprostol	p-value
Mode of delivery (%)			
Vaginal	30(40%)	36(48%)	0.2
Cesarean	45(60%)	39(52%)	
Indications for cesarean section (%)			
Dystocia	33(73.3%)	11(28.2%)	<0.001
Failed induction	9(20%)	3(7.9%)	
Persistent non-assuring FHR	3(6.6%)	25(64%)	
Apgar scores ≤ 7			
At 1min	2(2.6%)	25(33.3%)	<0.001
At 5min	0	10(13.3%)	
Admition to NICU	0	9(20%)	<0.001

Data are presented as n(%)

Fig.2 shows frequency of vaginal delivery in both study groups. Total number of women who delivered vaginally was not significantly different between both groups (40% in group 1 vs 48% in group 2) 30.6% vs 2.6% in IMN group) but the deference was in the time required for those deliveries to occur ,(2.6% of

women in group 1 vs 30.6% women in group 2) delivered vaginally within 12 hrs and (16% of women in group 1 vs 13.3% of women in group 2) delivered vaginally after 12 hrs and within 24 hrs, while the remaining (21.3% in group 1 vs 4% in group 2) delivered after 24 hrs

.Fig.2 Bar chart comparing frequency of vaginal delivery in both study groups

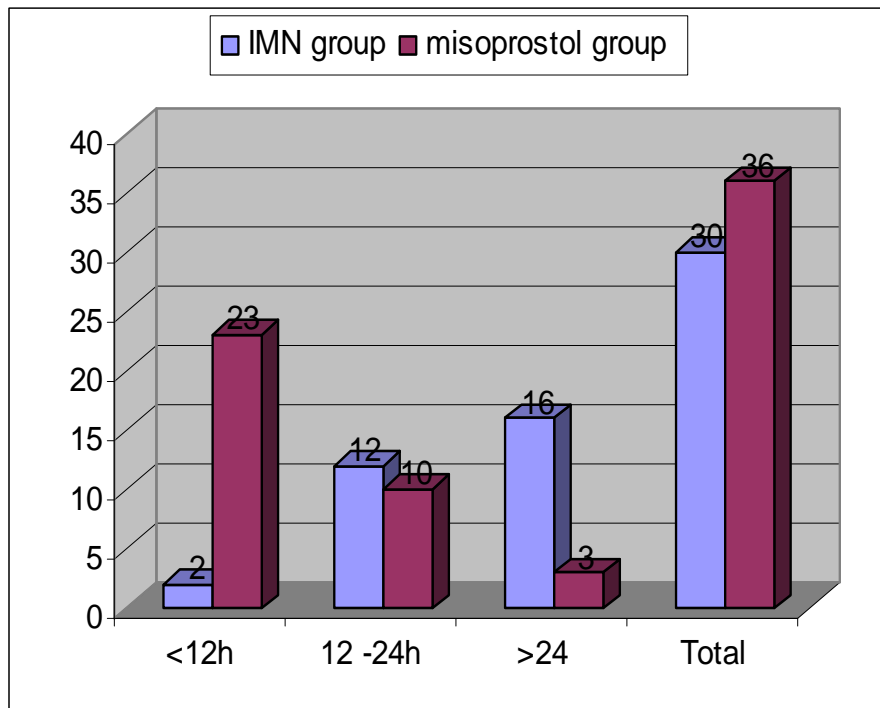


Table.3 Adverse effects of medication used in study groups

Adverse effects	IMN	misoprostol	p-value
Tachysystole	0	9(12%)	0.002
Hyper stimulation	0	12(16%)	<0.001
Post partum hemorrhage	7(9.3%)	6(8%)	0.2
Nausea and vomiting	7(9.3%)	2(2.7%)	0.2

Data are presented as n %

Although misoprostol is effective for cervical ripening, it is associated with various adverse effects especially uterine hyperstimulation and Tachysystole that occurs in (12%) and (16%) respectively of women in group 2 in our study and none of the women in group 1 had these two complications.

None of the women who develop these two complications need tocolytics to relieve their symptoms, just turn the women to left lateral position and I.V. fluid (hydration) and removal of the remnant of misoprostol tab with irrigation of vagina was enough. The other adverse effects noted more frequently in group 1 were nausea and vomiting 9.3% compared with group 2 just 2.7% but statistically the difference was not significant, no one of them needed medication to relieve symptoms. Postpartum hemorrhage

was recorded in our study in both groups, with non significant difference (9.3% in group 1 vs 8% in group 2).

Discussion

Induction of labour is indicated when it is agreed that the fetus and / or the mother will benefit from a higher probability of a healthy outcome than if the birth is delayed.⁽¹¹⁾ Therefore whenever possible, cervical ripening is advised before induction of labour whatever the indication when the cervix is unripe.⁽¹⁾

In this prospective study, the effect of misoprostol in labour induction was evaluated by Bishop score and compared with (IMN). The time required by misoprostol to cause cervical ripening was significantly shorter than IMN ($p < 0.001$) this in agreement with Ivy L, et al.⁽¹²⁾ Regarding oxytocin need there is a significant decrease in using oxytocin for

initiation or augmentation of labour if misoprostol was used for cervical ripening as it is lead to development of uterine contractions this in agreement with Chanrachakul B., et al.⁽¹³⁾, Shrikant B., et al 2006⁽¹⁴⁾, Lauric B., et al.⁽¹⁵⁾ While with use of IMN the need for oxytocin was increase for initiation or augmentation of labour as the IMN relax the myometrium while inducing cervical ripening and this in agreement with Chanrachakul B., et al.⁽¹³⁾, Filomena P., et al.⁽⁴⁾ Time from start of medication to complete vaginal delivery was significantly longer in IMN group than misoprostol group $p < 0.001$ which goes with Chanrachakul, et al study⁽¹³⁾. Total number of women who delivered vaginally were not significantly different between both groups but the deference was in the time that required for those deliveries to occur that just two women (2.6%) in IMN group had vaginal delivery within 12hrs of treatment and twelve women (16%) of them delivered vaginally after 12hr and within 24h and the remaining sixteen women (21.3%) delivered after 24h. while in the misoprostol group the majority of women (23, 30.6%) delivered vaginally within 12h and ten women (13.3%) delivered vaginally after 12hr and within 24hr and the remaining three women (4%) delivered after 24h after starting of medication. Part of this result agreed with chanrachakul B, et al,⁽¹³⁾ who also found that there was no significant difference in number of vaginal delivers between both groups. But not agreed with him that he found none of the women in IMN delivered within 12h of treatment and (20%) of them delivered after 24h. also not agreed with him regarding misoprostol group that he found just (35%) of women delivered vaginally within 12h while the majority (58%) delivered after 12h. and within 24h of start of treatment.

Regarding the total number of caesarean section there was no significant difference between both groups but the significance was in the indication of caesarean section, the most common indication in the IMN group was dystocia this in agreement with the studies of chanrachakul B, et al,⁽¹³⁾ and Shrikant B. et al.⁽¹⁴⁾ while in the misoprostol group the most common indication was a persistent non-assuring FHR. The number of failed induction was significantly lower in the misoprostol group than IMN which may be due to its non-uterine stimulating effect these result was statistically significant $p < 0.001$.

About the side effects of each medication, although misoprostol is effective for cervical

ripening, it is associated with various adverse effects especially uterine hyperstimulation (which can compromise the fetus) and tachysystol this result in agreement with Chanrachakul B, et al.⁽¹³⁾ and Lauric B., et al⁽¹⁵⁾. Even with the higher incidence of these two complications none of the women need tocolytics to relive symptoms, these result disagree with Chanrachakul B, et al.⁽¹³⁾ who found that (3.8%) of women who develop these two complications need B2 agonist to relieve their symptoms.

These adverse effects of misoprostol especially hyperstimulation negatively effect on fetal outcome which was (33.3%) in the misoprostol group had Apgar score ≤ 7 at 1 mint compared with (2.6%) in the IMN group. Which as statistically significant $p < 0.001$ and the number of babies admitted to neonatal intensive care unit (NICU) was significantly different nine of babies in the misoprostol group admitted while no newborns admitted in IMN group.

These results in agreement with Chanrachakul B.⁽¹³⁾, but our result not largely agreed with him regarding the number of newborns with low apgar score ≤ 7 in misoprostol group that in Chanrachakul B, et al.⁽¹³⁾ study (13.5%) had Apgar score ≤ 7 at 1 mint and just (5.8%) admitted to NICU. Other adverse effects noted were nausea and vomiting but there were no significant difference between both groups which agreed with results obtained by Ivy L, et al.⁽¹²⁾.

Conclusion

Misoprostol is more effective than IMN when used to improve Bishop score of the cervix in overdue pregnancy with unripe cervix while IMN had less side effects than misoprostol .

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