Isosorbide Mononitrate and Misoprostol for Cervical Ripening in Induction of Labor

Mohamad Elsokary[1]

[1] Ain Shams University

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Abstract

Background: The most favorable method for cervical ripening is not fully agreed upon by practitioners; however, isosorbide mononitrate administration is considered a low-risk method of labor induction for pregnant women at full term.Objective: To evaluate the safety and effectiveness of adding isosorbide mononitrate to misoprostol for cervical ripening in prelabor induction of full term pregnant women in comparison with misoprostol alone. Design: Randomized study.Setting: Ain Shams Maternity teaching hospital. Patients and methods: 120 women were divided randomly into two equal arms of 60 women in each one.Intervention: Patients admitted through the reception room or out patient clinic and they scheduled for induction of labor. Group I were given intravaginal isosorbide mononitrate with misoprostol while group II were given placebo with misoprostol intravaginally.

Index terms— isosorbide mononitrate; misoprostol; cervical ripening; induction of labor.

1 I. Introduction

nduction of labour has increased dramatically over the past two decades 1 . Indications for induction of labor are either maternal (pre-eclampsia, pregnancyinduced hypertension) or fetal (post-term dates, growth retardation, ruptured membranes, diabetes) 2 .

Nitric oxide (NO) is an apocrine hormone, synthesized in the cell by oxidation of L. arginine through the enzyme Nitric oxide synthase 3 . In human, it is involved in many physiological and pathological processes. It stimulates cyclo-oxygenase II which is involved in prostaglandin synthesis 4 .

In contrast to prostaglandins, nitric oxide donors inhibit rather than stimulate uterine contractions, and promote rather than restrict uterine blood flow 3 . Therefore, nitric oxide donors appear to be the ideal cervical ripening agent 5 for outpatient use. It also results in fewer adverse effects like headache, hot flushes, nausea, dizziness and abdominal pain but is less effective than misoprostol 6 .

2 II. Patients and Methods

This randomized, double-blind, controlled study was carried out on 120 full term pregnant women admitted for induction of labor in Ain Shams University Maternity Hospital from January 2011 to December 2012. The study was approved by the research Ethics Committee of Ain Shams University Maternity Hospital, Cairo, Egypt. Informed consent was obtained from each participant, after they were fully informed about the nature and scope as well as the potential risks of the study before the first application of the medication.

3 a) Justification of the sample size

Using 90% power, ? error 0.05, standard deviation 3 and case to control ratio 1:1, a sample size of 60 women was calculated to detect a difference of at least 20% between the two groups.

Patients were divided randomly into two groups, Group A included 60 patients were induced by intravaginal isosorbide mononitrate (Effox 40 mg MINAPHARM) in addition to misoprostol (50 mcg), Group B included 60 patients induced by placebo in addition to misoprostol (50 mcg) administered in the posterior vaginal fornix.

Inclusion criteria included being a Primipara with single viable post-term cephalic pregnancy, Bishop score of ? 5, average liquor, intact membrane, average size of the fetus, and absence of pelvic contraction Exclusion criteria included Bishop's score ?6, rupture of membranes, suspected chorioamnionitis, placenta previa or unexplained vaginal bleeding, uterine scar, hypertonic uterine contraction pattern, soft tissue obstruction, medical disorders eg diabetes mellitus, renal or hepatic dysfunction, fetal malpresentations, multiple pregnancies, and intrauterine growth retardation (<5 th percentile).

All patients were subjected to history taking that included a complete personal, medical, and a detailed obstetric history, in addition to a menstrual, and contraceptive history, with emphasis on the date of the last menstrual period to determine the exact gestational age.

General examination included recording the vital signs as blood pressures, pulse, temperature, respiratory rate, chest and heart examination.

Abdominal examination included estimation of the fundal level, Leopold maneuvers and fetal heart rate.

Vaginal examination was done every 4 hours to all patients to evaluate the Bishop score. For all patients, sonar examination was done to exclude any abnormality of the fetus and to ensure the gestational age, and the amniotic fluid index.

The drugs were available in dark envelopes. An attending nurse selected an envelope that contains the medication for each patient. The patients were assigned to receive intravaginal IMN and misoprostone (Group A) or misoprostol and placebo (Group B). Examination of the patients was done by the residents, Each resident followed up his patient and data were documented on a partogram. For each patient. Preinduction external monitoring by Cardio tocography was done. Uterine contractions and fetal heart rate were checked every 30 minutes. A second and a third dose of the medications were given if the Bishop score was < 6 after 6 hours.

On repeated examinations after giving the medications, cases with favorable cervices (Bishop's score ? 6 with cervical dilation ? 4cm) were subjected to artificial rupture of membranes (AROM) and according to the presence or absence of meconium the following interventions were performed: a. If liquor was clear (i.e. no meconium), induction of labor was started by oxytocin drip using titration method with fetal heart rate monitoring. b. If liquor was stained with thin meconium (i.e., mild degree), fetal heart rate monitoring was done for 30 minutes c. If liquor was deeply stained (i.e., sever degree), cesarean section was done to avoid meconium aspiration syndrome and fetal anoxia. Oxytocin infusion was given when cervical dilatation is 3 cm. IV drip of 5 units in 500 ml of Ringer solution were started. Infusion rate was increased (by doubling drops/min) every 30 min until 3 contractions occurred every 10 minutes and each lasting for 45-60 seconds. If 60 drops/min was reached with no efficient contractions, infusion was increased by administrating 10 units oxytocin in 500 ml Ringer solution.

Assessment of uterine contractions was done every 30 minutes to ensure adequate contractions (

4 b) Statistical Methods

Statistical analysis was done using the SPSS software for windows, version 17 (SPSS, Chicago, IL, USA). The paired t test for independent samples was used for comparisons between means. The Chi-square test (x2 test) was used for analysis of the qualitative variables. $P<0.05$ was considered significant.

5 III. Results

Table (2) shows that, there is no statistical significant difference between the two groups as regards mean age , gestational age, or mean initial bishop score. There is a higher bishop score after 6 hours among cases in group I compared to cases in group II and the difference is statistically significant. There is a shorter duration of the active phase of delivery and labor in group I compared to group II and the difference is highly significant. There is no statistical significant difference between the two groups as regards the mean weight of infants or the Apgar score at 1 and 5 minutes. Table (3) shows that there is no significant difference between the two groups as regards oxytocin requirementsor the indication of C.S There is no statistical significant difference between the two groups as regards indication for C.S. There is a higher percentage of C.S delivery, nausea and shivering in group II compared to group I but the difference is not statistically significant. Table (4) shows that, there is a higher incidence of side effects and headache in group I compared to group II and the difference is statistically significant. There is no statistical significant difference between the two groups as regards the incidence of PPH or retained placenta. There was no need for ICU admission. Higher percentage of uterine contraction abnormalities in group I 15% compared to 11.7% in group II but the difference is not statistically significant.

6 IV. Discussion

Several studies postulated that a combination between misoprostol and IMN might improve induction success rates while reducing side effects associated with misoprostol 7 .

In the current study, the difference in the mean duration of the active phase in group ? versus group II was statistically significant. The interval from the beginning of induction to the time of delivery was shorter in group ? than in group II. These results agreed with another study 8 , which reported that the association of NO donor

glyceryl trinitrate (GTN) (500 mg/kg) with dinoprostone (2 mg) was more effective than dinoprostone alone for cervical ripening and labor induction at term. In agreement with our results, similar study 9 , had found significantly shorter interval from the beginning of induction to the time of delivery in misoprostol and IMN group versus misoprostol group (19.56 ± 3.96 versus 23 ± 2.62 P ? 0.001)., and agreed with a study 10 , which had found the time from start of medication to vaginal delivery in IMN group was significantly longer (25.6±6.1 versus 14 ± 6.9 hrs).

These findings disagreed with another study 11 , which showed that vaginal application of IMN plus dinoprostone appeared to be no more effective than placebo plus dinoprostone for cervical ripening and labor induction at term suggesting a different effectivity of IMN depending on the gestational age in this study, also these results disagreed with a study 7 , which reported that, the time from start of induction to vaginal delivery not reduced when IMN was added to misoprostol, might be due to the relaxing effect of IMN on the uterine fundus. The findings could possibly be explained by the differences in parity of patients, mean gestational age at delivery and the indication for the induction of labour.

In the current study, the difference in Bishop score after 6 hours of medication in group ? versus group II was statistically significant, this coincided with similar study 12 , which found The mean initial modified Bishop's score for Group I was 2.8 then Bishop's score became 3.9, 4.1, 5.1, 5.9 after 2, 4, 6, 8 hours, respectively indicating significant improvement in the modified Bishop's score This improvement may be related either to the inflammatory mechanisms associated with IMN involving vasodilatation, to altered vascular permeability and neutrophils influx into cervical tissues leading to cervical ripening and changes in cervical consistency, but these findings disagreed with another study 13 , which failed to demonstrate an improvement in the mean Bishop score following IMN despite showing clinical effectiveness in shortening labor, also disagreed with a recent study 8 , This may be due to different type and dose of drug to our study.

There is a higher percentage of occurrence of side effects and headache in group I compared to group II and the difference is statistically significant and can be explained by vasodilatation effect of (NO) donors these complications were minimal and self limited and needed no medical interference, this agreed by other studies 5,7,11 .

In the present study both groups were similar with no significant statistical difference regarding mean maternal age, gestational age. Also there was no statistical significant difference between both groups as regard the birth weight, Apgar score at 1 and 5 minutes and the need for neonatal ICU admission, This result coincided with other studies 8,9 . These results were higher in GTN group but did not reach the level of statistical significance.

In the present study, there was no significant difference between both groups as regards the incidence of uterine hypersystole, tachysystole and hyperstimulation. These results coincided with another study 9 , which found no significant difference between 2 groups in the incidence of uterine hypersystole, tachysystole and hyperstimulation. But these results disagreed with similar study 14 , which had found that GTN is safer, but less effective, compared with prostaglandins for pre induction cervical ripening at term.

In the present study as regards the C.S rate there was no significant difference between the 2 groups, This result coincided with a study 7 , which concluded that no significant difference between 2 groups as regards the C.S rate. But this study disagree with another study 10 who found dystocia was more frequent in IMN 9 (45%) versus, 6 (37.5%) in misoprostol group while non reassuring FHR in IMN group was 3 (15%) versus, 9 (56.3%) in misoprostol group.

7 V. Conclusion and Recommendations

Isosorbide mononitrate plus misoprostol is safe and more effective for pre-induction cervical ripening in comparison to misoprostol alone.

8 Global Journal of

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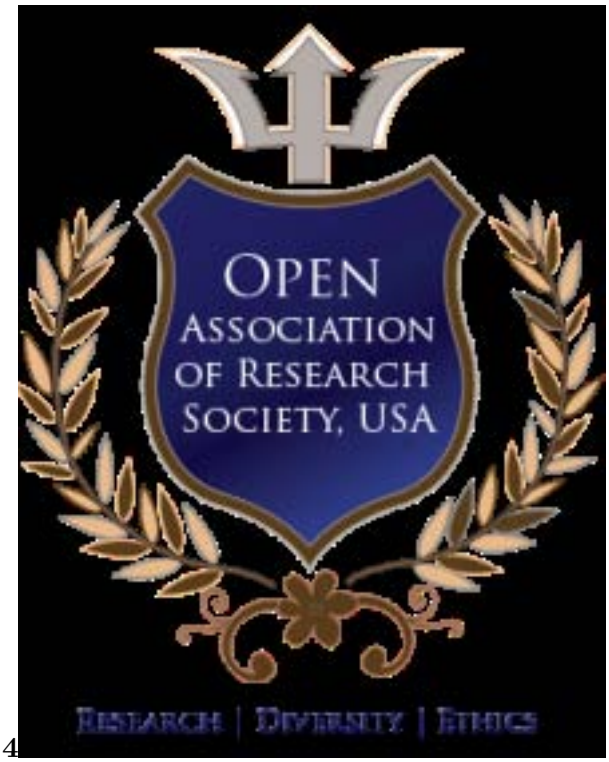

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Figure 1: 4 Volume

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Factors	0	1	Rating	2	3
Dilatation	Closed	1-2 cm	3-4 cm		5 cm
Effacement	0-30%	40-50%	60-70%		80%
Station	-3	-1, -2	-1, 0		+1, +2
Consistency	Firm	Medium	Soft		-
Position	Posterior	Middle	Anterior		-
	Unfavorable cervix Bishop score ? 5				

Figure 2: Table (1

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Variable	Group I n = 60 Mean ± SD	Group II N = 60 Mean ± SD	T	P
Age(years)	22.6 ± 2.0	21.9 ± 2.0	1.7	0.07
Gestational age(wks)	40.1 ± 0.8	40.3 ± 0.3	1.8	0.06
Initial bishop	3.8 ± 0.6	3.5 ± 0.6	1.8	0.06
Bishop score after 6h	7.9 ± 0.6	6.6 ± 0.7	10.6	0.00*
Mean duration of active phase(h)	8.2±1.3	10.9 ± 1.2	12.1	0.00*
Mean duration of labor(h)	12±2.9	17.1± 2.3	10.7	0.00*
Neonatal Weight (gms)	2952.1 ± 173.3	2955.0 ± 236.0	0.07	0.9
Apgar 1 minute	7.5 ± 1.1	7.2 ± 1.2	1.7	0.07
Apgar 5 minutes	9.2 ± 0.5	9.3 ± 0.6	0.4	0.6

Figure 3: Table 2 :

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Variable	Group I n =60 n. (%)		Group II n =60 n. (%)		X2	P
Requirement for oxytocin						
Required	19	(30)	25	(40)	10.3	0.08
Not required	41	(70)	35	(60)		
Mode of delivery Indication for CS						
VD	54	90.0	49	81.7		
CS	6	10.0	11	18.3	1.7	0.1
Arrest of cervical dilatation	3	(5)	5	(8.3)		
Fetal distress	3	(5)	5	(8.3)	2.2	0.5
Failed induction	0	(0)	1	(1.7)		

Figure 4: Table 3 :

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Variable		Group I		Group II	T	P
Adverse side effects	28	(46.7)	17	(28.3)	4.3	0.03*
Headache	22	(36.7)	5	(8.3)	13.8	0.000 *
Nausea	2	(3.3)	7	(11.7)	3.0	0.1
Shivering	4	(6.7)	5	(8.3)	0.1	0.7
PPH	0	(0)	1	(2)	2.041	0.153

Figure 5: Table 4 :

.1 Acknowlegment

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