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Isosorbide Mononitrate and Misoprostol for Cervical Ripening in Induction of Labor

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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.

Objectives: The aim of this study is 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 outpatient 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.

Results: Group I showed better significant improvement than Group II in Bishop Score after 6 hour (7.9 vs 6.6, $P=0.001$), shorter duration of active phase (8.2 vs 10.9h, $P=0.001$), as well as the duration of labor (12 vs 17.1h, $P=0.001$) in group I comparing to group II. The main side effect of IMN was headache.

Conclusion: The addition of Isosorbide mononitrate to misoprostol is safe and increases the effectiveness of pre-induction cervical ripening in comparison to misoprostol alone.

Keywords: Isosorbide mononitrate, Misoprostol, Cervical ripening, Induction of Labor.

Introduction

Induction of labor has increased dramatically over the past two decades[1]. Indications for induction of labor are either maternal (pre-eclampsia, pregnancy-induced 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].

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.

Justification of the sample size

Using 90 %power, α 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, Egypt) in addition to misoprostol (50 mcg), Group B included 60 patients induced by placebo in addition to misoprostol (misoprostol 50 mcg, SEGMA, Egypt) 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 examples: diabetes mellitus, renal or hepatic dysfunction, fetal malpresentations, multiple pregnancies, and intrauterine growth retardation ($<5^{\text{th}}$ 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 Table 1.

For all patients, sonar examination was done to exclude any

Table 1: Bishop score (points assigned)

Factors	Rating			
	0	1	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

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 cervix (Bishop's score ≥ 6 with cervical dilation ≥ 4 cm) were subjected to artificial rupture of membranes (AROM) and according to the presence or absence of meconium the following interventions were performed:

- If liquor was clear (i.e. no meconium), induction of labor was started by oxytocin drip using titration method with fetal heart rate monitoring
- If liquor was stained with thin meconium (i.e., mild degree), fetal heart rate monitoring was done for 30 minutes
- If liquor was deeply stained (i.e., severe 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 administering 10 units oxytocin in 500 ml Ringer solution.

Assessment of uterine contractions was done every 30 minutes to ensure adequate contractions (3-5 contractions in 10 minutes each lasts for 45-60 seconds).

Both groups were compared regarding:

- Age, parity, gestational age.
- Time from start of medication to first contraction pain.
- Time from start of AROM \pm oxytocin to active phase of labor.
- Duration of 1st, 2nd and 3rd stage of labor, and mode of delivery.
- Maternal complications e.g., hyperstimulation, postpartum hemorrhage, headache, nausea, vomiting and dizziness.
- Neonatal outcome including Apgar score at 1 and 5 minutes and Neonatal Intensive Care Unit admission were recorded.

Statistical Methods

On Statistical analysis retrieved data were recorded on an investigative report form. The data were analyzed with SPSS® for Windows®, version 15.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables was performed in form of mean, standard deviation (SD) and range. Description of qualitative (categorical) data was performed in the form of numbers and percent. Analysis of numerical variables was performed by using student's unpaired t-test (for two groups) or ANOVA (for more than two groups). Analysis of categorical data was performed by using Fischer's exact test and Chi-squared test. Logistic regression analysis was performed to calculate association between variables and their odds ratios. Association between variables was estimated using Pearson's correlation coefficient (for parametric variables) and Spearman's correlation coefficient (for non-parametric variables). Significance level was set at 0.05.

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 requirements or 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

Table 2: Comparison between both groups as regard the descriptive data

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

Table 3: Comparison between both groups as regard the mode of delivery and requirement for oxytocin

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)		

Table 4: Comparison between both groups as regard drugs side effects

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
Retained placenta	1 (1.8)	0 (0)	1.042	0.307
ICU admission	5 8.3	5 8.3	0.0	1.0
Hypersystole	3 5.0	2 3.3		
Tachysystole	5 8.3	4 6.7	0.3	0.9
Hyper stimulation	1 1.7	1 1.7		

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.

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 I versus group II was statistically significant. The interval from the beginning of induction to the time of delivery was shorter in group I 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±2.62P ≤ 0.001)., and agreed with another study 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 labor.

In the current study, the difference in Bishop score after 6 hours of medication in group I 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 disagreed 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.

Conclusion and Recommendations

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

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