A Randomized Clinical Trial of Pre-Induction Cervical Ripening by Isosorbide Mononitrate at Term Prgnancy

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ABSTRACT

Background and Objectives: Induction of labor is deemed successful when it initiates uterine contractions, progressively dilates and effaces the cervix, and leading to the normal vaginal birth of the baby with no maternal or fetal complications . Because the success of induction is related to cervical ripening, artificial cervical ripening before labor induction is used when the cervix is unfavorable to reduce the associated risk of cesarean delivery. to test the efficacy and safety of Isosorbide mononitrate for cervical ripening before the induction of labor at term, from.

Methods: A randomized clinical trial was conducted in maternity hospital in Sulaimani, from the 1st of January 2008 to the 1st of July 2008. Forty six pregnant women with gestational age of (37- 42) weeks, singleton, viable, low risk pregnancy and cephalic presentation with Bishop score of less than 6 were selected for induction of labor for various causes. Forty eight hours before induction, 40 mg IMN (2 tablets of 20 mg) were inserted vaginally up to 3 doses 16 hours apart.

Results: It was found that the mean ± SD Bishop score before IMN administration was (1.95 ± 1.5), while after IMN was (6.65± 3.06) P-value = 0.0001. Sixteen cases (35.6%) went to active labor. The mean ± SD time of admission in labor room was (5.06 ± 3.8) hours.43 cases (93.5%) needed oxytocin for their inductions & eighteen cases (39.1%) were delivered by C/S. There was no significant change in FHR before and after IMN and all women delivered active babies with normal Apgar score. The main side effect was headache which was experienced by 31cases (63.4%).

Conclusions: IMN is an effective and safe agent for cervical ripening which can be used as an outpatient basis.

Key words: Term pregnancy ,Pre-induction cervical ripening, Isosorbide mononitrate.

INTRODUCTION:

Induction of labor: is an intervention designed to artificially initiate uterine contractions, leading to progressive dilatation and effacement of the cervix and ultimately birth of the baby [1] According to Bishop score any score of 5 or less is regarded as being unfavorable for induction of labor .[2] Generally, methods for cervical ripening and induction of labor are divided into pharmacological and non pharmacological routes .[2,3] More recently donors have been under study for cervical ripening before induction. (NO) seems to be a factor in cervical ripening, perhaps under control of progesterone expression of both inducible nitrous oxide (iNOS) and endothelialnitrous oxide (eNOS).[4]Also an interaction between NO and PG synthesis has been suggested to be present in the cervix at term. Such linkage between two pro-inflammatory substances could be important in promoting cervical ripening.[5] (NO) has been found to mediate PG synthesis via induction of cyclooxygenase-

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So together NO and PGE_2 are inducing local vasodilatation, increasing vascular permeability and leukocyte infiltration.[8] Nitro dilators are generally well absorbed across skin, and mucosal surface . [9] Common nitro dilators are isosorbide mononitrate (IMN), glyceryle trinitrate and sodium niyroprusside.[5] Common side effects include: predominantly headache, orthostatic hypotension and tachycardia .[10,11] (NO) donors may be an ideal agent for cervical ripening , since it will induce cervical ripening without causing uterine contractions .The absence of contraction has obviated the need for fetal monitoring, such an agent could be given on an outpatient basis. [10-12]

MATERIALS AND METHODS:

This randomized clinical trial was conducted in maternity hospital in Sulaimani from the first of January to first of July 2008. All women included were informed of the nature and scope of the study, and verbal consent obtained from each prior to participation in the study .55 women were selected, Inclusion criteria were Singleton pregnancy, maternal age (19-42) year,P_0 –P_4 Gestational age (37 - 42)weeks, Bishop score less than 6 and reassuring FHR (which was be tested by cardiotoccograph). Cases with previous C,S or medical diseases that is contraindicated for IMN were excluded from the study. IMN 40 mg (2 tablets 20 mg) was applied in the posterior vaginal fornix then the patient was admitted to the ward. After 16 hr every woman was reassessed for evaluation of blood pressure, pulse rate, FHR, assessment of Bishop score and was asked about head ache. IF the cervix was not ripened by the first dose, another 40 mg IMN was administered vaginally (up to 3 doses were used 16 hr apart), during this 48 hr those who started active labor were admitted directly to labour room and managed according to her partogram regarding augmentation with oxytocin; whereas, those who did not start labor were after 48 hr. was not ripened or changed for at least 4 points[13], they were regarded as treatment failure so they were treated by another route of induction of labour. Statistical analysis was performed by epi-info soft ware for statistic analysis and p-value less than 0.05 was regarded to be significant.

RESULT:

Table (1) shows the demographic characteristics of the cases, mean ± SD of maternal age was 28.2 ± 5.2 year (range: 19-42 years), mean ± SD of gestational age was 40.2± 1.07 (range: 37-41weeks). Twelve of them were primigravida, while 34 cases were multigravida . Mean± SD of Bishop score before drug administration was 1.95 ± 1.5 (range:0-5), with mean ± SD FHR was 137± 6.2 bpm.

Figure(1): shows the Bishop score of the cases before and after IMN administration, before IMN was between 0 and 5 score, while after IMN the range was between 0 and 12.

Table (2) shows the mean ± SD of bishop scores before IMN administration which was 1.95 ± 1.5, with mean ± SD of bishop score after drug administration was 6.65 ± 3.06; mean difference was equal to 4.76.P-value equal to 0.0001. By conventional criteria, this difference is considered to be statistically significant.

Table (3) and Figure B show the frequencies of cases that their Bishop scores showed significant clinical changes after IMN administration. From the total of 46 cases, only 33 (71.1%) had their Bishop scores changed by more than 4 points.

Table (4) shows the mean ± SD of FHR before IMN which was 137± 6.2, while mean ± SD FHR after IMN was 138 ± 4.7. P- value equal o.7 which is not significant.

Table (5**)** shows the mode of delivery, it shows that from total 46 cases 28 (60.9%) of them delivered vaginally while 18 (39.1%)of them delivered by C/S.Table (6) shows mean Apgar score at one minute was 8.2 ± 0.9 SD (range: 7-10), while mean Apgar score at 5

minute was 9.4 ± 0.6 (range: 8-10). Table (7) shows the main side effects which was headache, from total 46 cases, 31 cases (67.4%) complaining of headache .

Table1: Demographic characteristics

Variable	Frequency	Mean ± SD
Age (years)		28.2 ± 5.2
Gestational age (weeks)		40.2 ± 1.07
Parity: Pimigravida (cases) Multigravida (cases) Total (cases)	12 (26.1%) 34 (73.9%) 46 (100%)	
Bishop score before IMN		1.95 ± 1.5
FHR before IMN		137.9 ± 6.2

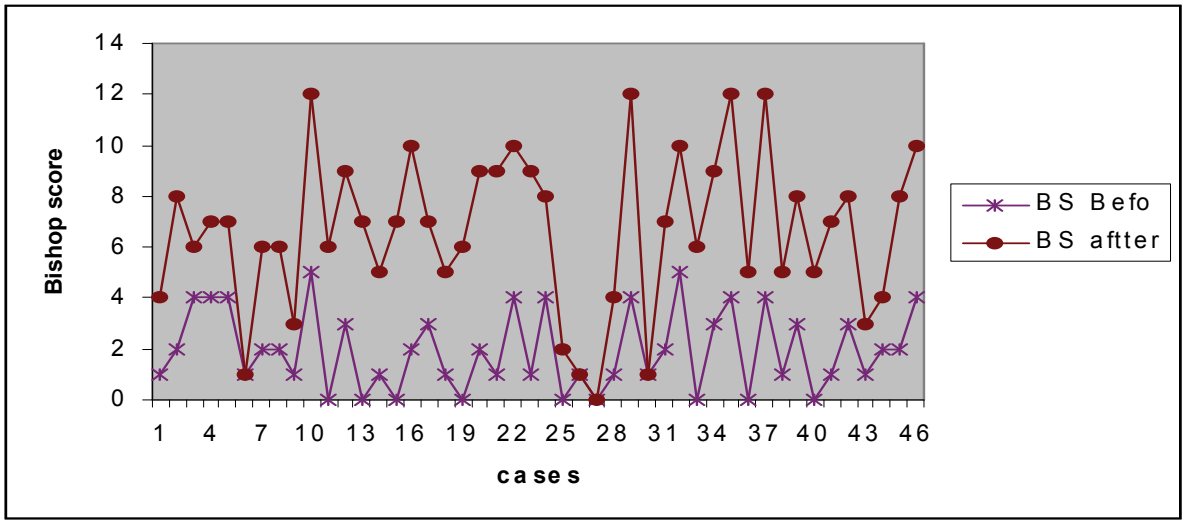

Figure 1: Bishop score before and after IMN

Table 2: Mean and mean difference of bishop score before and after IMN

Mean bishop score before IMN	Mean bishop score after IMN	Mean difference	P- value
1.96 ± 1.55	6.62 ± 3.06	4.76	0.0001 significant

P-value is 0.0001 (statistically significant).

Table 3 : Frequencies and percentages of cases with significant Bishop change.

Bishop score change	Frequency	percent
Change less than 4 points	13	28.3%
Change more than 4 points	33	71.7%
Total	46	100%

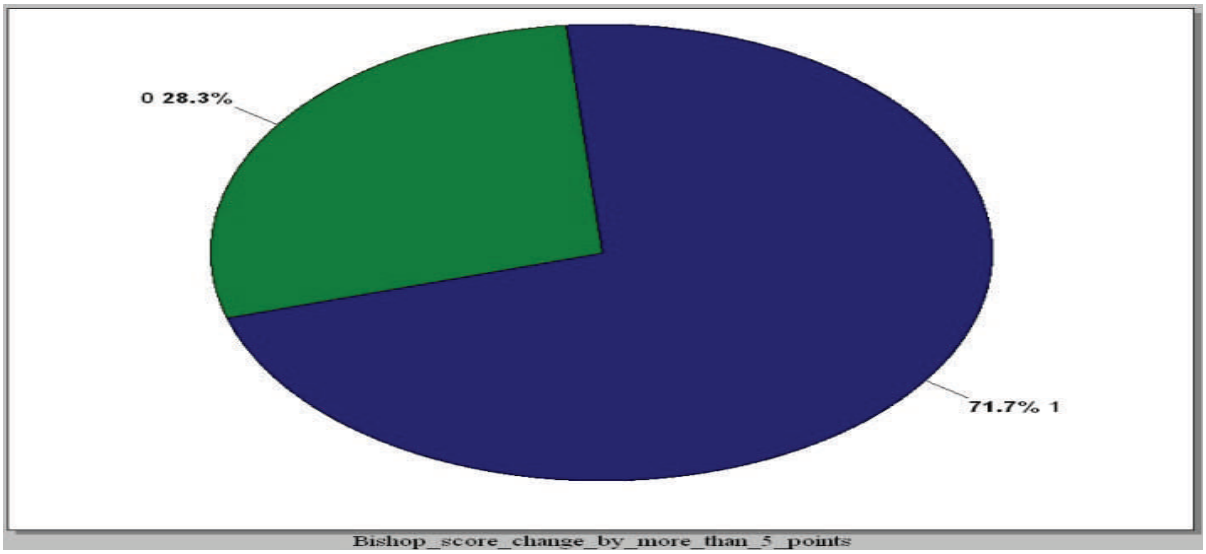

Figure 2: percentages of cases with significant changes in their Bishop score: 28.3% no changes, 71.7% significant changes

Table 5: Mode of delivery .

Mode of delivery	Frequency	percentages
Vaginal	28	60.9%
Cesarean	18	39.1%

Table 6: Mean Apgar score at 1 and 5 minute

	Mean ± SD	Range	Median
Apgar at 1 minute	8.2 ± 0.9	7-10	8
Apgar at 5 minute	9.4 ± 0.6	8-10	9

Table 7: Frequency of cases developed headache

Headache	Frequency	Percent
Yes	31	67.4%
No	15	32.4%
Total	46	100%

DISCUSSION:

In this research IMN was studied in a formulation which is cheap and widely available. Forty six cases were enrolled to take IMN vaginally up to three doses 16 hrs. a part. The primary outcome was a change in the bishop score. Significant changes in the Bishop score was found mean ± SD Bishop Score before IMN was 1.96 ± 1.55, while mean ± SD Bishop Score after IMN was 6.62 ± 3.0, P- value was 0.0001 which is significant. This result was in agreement with study which done in Sweden by Ekerhovd *et al* [14] in a randomized controlled study "Vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at term". Sixty women included in their study, women were randomized to either give 40 mg IMN or placebo vaginally, 4 hr before elective C/S. They found clear effect on the distensibility of the uterine cervix in the study group, the force necessary to dilate the cervix was significantly lower than the placebo group ($p < 0.0001$). The result also agrees with Rameez *et al* study which was "Nitric oxide donor isosorbide mononitrate for pre-induction cervical ripening at 41 weeks .[11] Maria Bullarbo (found in her study "Nitric oxide donors in labor management" that IMN has a clear significant effect on cervical distensibilty (cumulative force to dilate cervix from 5 till 10 mm).[5] In the present study from 28 cases who were delivered vaginally, 24 (85%) of them were those who had favorable cervix after IMN (P=0.012 significant). This mean the rate of C/S will decrease if Bishop score is more than 6. This result disagrees with study done in France by Gabriel *et al* .[15] Their study was conducted prospectively in 179 women who required induction of labor; cervical length was measured before induction. They found that Bishop score was not predictive of the delivery mode, although C/S for failure to progress was more frequent when Bishop score was <6. Among the women with Bishop score 6 and more, the of the induction outcome. However, among the women with a Bishop score <6 but a cervical length <26 mm was associated with a lower C/S rate (20.6 vs. 42.9%; P =0.006), this mean Bishop score alone is not a good predictor of the risk of C/S. this disagreement may be due to small sample in the present study. In this study no significant changes was observed in the FHR before and after IMN. The Mean ± SD before IMN was 137±6.2 while mean ± SD after IMN and before induction was 138 ± 4.7 (P=0.7 not significant). This result agrees with study done in Israel (2002) by Thaler *et al* [16]. They were studied the effect of a nitric oxide donors on FHR patterns in patients with hypertension, they included 20 women with pregnancy induced hypertension, thirty-minute recordings of FHR and fetal movement before and after IMN was done, the baseline FHR was not differ significantly it was 140.9 ± 2.0 bpm and 137.5 ± 2.1 bpm, respectively. In Ekerhovd *et al* (14) study fetal well-being was evaluated intermittently by cardiotocography, FHR being specifically recorded at baseline and after 210 minutes. They found that all cardiotocographics intermittently performed were normal and without any signs of fetal distress, and FHR being within normal range (110-150 bpm) in all participants. In the present study Apgar score was assessed at 1 and 5 minutes which were all with in normal range. At 1 minute mean ± SD was 8.2 ± 0.9 range was 7-10 while median was 8. Five minute mean ± SD Apgar score was 9.4 ± 0.6 with range of 8-10 and median 9. This result is near to Ekerhovd *et al* who reported 9.0 ± 0.6 (7-10), 9.8 ± 0.4 (9-10) and 10.0 ± 0 (10-10) mean ± SD at 1minte, 5 minute and 10 minute respectively. In this study the main side effect was headache which was experienced by 31 cases 67.4%, but nearly all of them had mild headache. This result is lower than what Osman *et al* (10) reported in their thesis: "A randomized comparison of prostaglandin E_2 gel with nitric oxide donors isosorbide mononitrate for cervical ripening

before the induction of labor at term". The IMN group receive 40 mg single dose, they found that from 195 cases who received IMN 172 (88%) developed headache, while prostaglandin group from 188 cases only 19 of them developed headache P- value was less than 0.0001. Ekerhovd *et al* (14) also reported headache in 24 cases from total 30 this mean (80%). Difference in this result between the present and other study may be due to that in these two study mentioned all participating women were informed about possible side effect before giving their informed consent, or may be due to small size sample, difference in the dose regime .

CONCLUSIONS:

IMN seems to be effective, safe, inexpensive, and well tolerated agent for cervical ripening. ((NO) donors are an attractive cervical ripening agent as far as it has no significant maternal side effects and no any fetal effects.

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