Comparative study of Misoprostol and Isosorbid mononitrate versus Misoprostol in induction of labour in full term pregnancy.

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Abstract: Background; different methods of cervical ripening have been used including non-pharmacological methods as Brest stimulation, membrane stripping and amniotomy,pharmacological methods including estradiol, oxytocin, prostaglandin and prostaglandin analogues have been used. Many trials have investigated the possible use of nitric oxide donor in induction of cervical ripening, **Objective:** to compare the effectiveness and safety of isosorbid mononitrate plus misoprostol versus misoprostol alone for induction of labour in the full term pregnancy. **Sitting:** Sayed Galal University hospital. **Patients:** 120 full-term pregnant women were recruited in the period from October 2010 to November 2011,the patients were divided into two groups; group A(60 patients) received 40 mg isosorbid mononitrate intravaginal plus 25 µg misoprostol intravaginal.Group B received misoprostol 25 µg intravaginal plus placebo. Oxytocin was used according to hospital protocols for induction of labour. **Methods:** the outcome measures were, preinduction bishop score, follow up of bishop score every 2 hours, time of initiation of active phase, time of labour, incidence and, indications of C/S,neonatal outcomes. **Results:** There were significant differences in bishops score recorded after 2,4,6,8 hours in the two studied groups being better in ISMO plus misoprostol group. There were no significant differences regarding the mode of delivery whether vaginal or Caesarean section in both groups, furthermore the time of delivery were significantly shorter in the ISMO plus misoprostol if compared with misoprostol alone. As regard maternal side effects, there were no significant differences between both groups, but there was high incidence of headache in the ISMO plus misoprostol, also there were no significant differences regarding fetal heart pattern in the both groups as regard neonatal outcome, there were higher Apgar score in the ISMO plus misoprostol if compared with misoprostol alone. **Conclusion**: Isosorbid mononitrate plus misoprostole was more effective and safer than misoprostole alone for induction of labour.
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1. Introduction

There are many indications for induction of labour in obstetric practice, of which prolonged gestational age stand as most common cause. It has been recognized that with unripe cervix induction may be difficult and often unsuccessful. The use of an agent to ripen the cervix before conventional methods of induction of labour is acceptable in the modern obstetric. (1)

Cervical ripening is associated with an increase in cyclo oxygenese enzymes, which lead to increase prostaglandin secretion in the cervix. This in turn led to series of important changes associated with progressive cervical ripening. (2)

Misoprostol is prostaglandin E1 analogue which is indicated for prevention of gastric ulcer in patient taken anti-inflammatory drugs. Some researchers suggested that, the drug might be effective for induction of labour, so there has been great interest in safety and efficacy of drug compared to prostaglandin E2 agent for cervical ripening prior to induction of labour (3-4)

Multiple studies documented clinical advantages and cost benefits of intravaginal misoprostol (PGE1) compared with other prostaglandin preparation for cervical ripening and induction of labour However some reports found high incidence of abnormal uterine contraction with this agent(5).

The ideal cervical ripening agent would induce cervical romedeling without stimulating uterine activity. Nitric oxide donor is such agent. Nitric oxide donor relaxing the myometrium while induce the cervical ripening. (6) Nitric oxide releasing drug are a novel class of effective and safe agent for cervical ripening

In human local application of nitric oxide donor (Isosorbid mono nitrate and glyceryl trinitrate can effect cervical ripening in the first trimester. It is also hypothesized that there possible role for nitric oxide donor in cervical ripening before induction of labour. (7)

Nitric oxide donor could be used as an alternative to prostaglandin to induce cervical ripening

before induction of labour, thereby avoiding side effects associated with prostaglandin.(8)

Isosorbid mono nitrate is inorganic NO donor which can be used for cervical ripening with minimal side effects, but was found to be less effective if compared with prostaglandin.(9)

It has been postulated that combined therapy with nitric oxide donor and prostaglandins for cervical ripening and labour induction at term, would result in improved clinical effectiveness and fewer side effects. (10)

So our aim to compare the effectiveness and safety of isosorbid mononitrate plus misoprostol versus misoprostol alone for induction of labour in the full term pregnancy.

2. Patients and methods

This prospective double blind randomized trial carried out at Sayed Galal University hospital in the period of October 2010 to November 2011,in which 120 full-term pregnant women admitted for induction of labour were recruited for this study. The patients were randomly selected into two groups

Group A: This includes 60 full term pregnant females who received 25 µg misoprostol(Vagiprost® tablets, Adwia pharm,Tenth of Ramadan) and placebo tablets (Sigma pharm, Kusina) in the posterior vaginal fornix.

Group B: This includes 60 full term pregnant females who received vaginal 25 m µg isoprostol (vagiprost® tablet) plus 40 mg isosorbid mononitrate(Effox® Mina pharm, Licsen Schwartz Germany) in the posterior vaginal phornix.

Inclusion criteria: singletone term pregnancy, Bishop score ≤ 4,full term pregnancy, reassuring CTG. The exclusion criteria were patients with PROM, multiple pregnancy, polyhydramnios, non cephalic presentation, previous uterine scar., cephalopelvic disproportion, previous cervical operation, medical disorders necessitating termination of pregnancy by C/S.

Methods

This study was approved by Al Azhar University, and consent were taken from every patient after explanations the details of study and possible risk of medications. The drugs of trial were available in a dark envelope and an attending nurse was select the envelop for each group.

All patients were submitted to complete history taken with special emphysis on the LMP to determine the exact gestational age.General examination included vital signs (pulse, BPr temperature, respiratory rate), chest and heart examination. Abdominal examination that include; fundal level, fetal size, detection of fetal heart rate, fundal, pelvic and umblical grip.The pv examination was done for all patients for evaluation of the bishop score which include; degree of cervical dilatation, degree of cervical length, degree of cervical consistency, cervical position, head station. in addition to condition of membrane and pelvic capacity. All patients had ultrasonography to confirm EDD, number of fetuses, presentation, amount of liquor, placental site,biophysical profile and to exclude abnormalities. The NST was done to exclude fetal distress.

For both group evaluation of initial modified score were done, followed by revaluation of modified Bishop score after 2,4,6,8 hours respectively.

For cases with favourable modified bishop score ≥ 8,the artificial rupture of membrane was done, if the liquor was clear and NST was reassuring, induction of labour using oxytocin in the titrated dose according the department protocol if active labour not initiated one hour after rupture of membrane. If the NST was not reassuring or patient had thick meconium, in this situation c/s was done.

The outcome measures were preinduction cervical ripening assessed by bishop score, induction delivery interval, neonatal outcome, incidence of complications or side effects.

Statistical methods

Analysis of data was done by IBM computer using SPSS version 19 as follows; Description of quantitative variables as mean, SD and ranges, description of qualitative data as number and percentage. The Chi-square test was used to compare qualitative variable between groups.while unpaired t test was used to compare two groups as regard quanaitave variable.

3. Results:

Table 1 shows the descriptive data of both groups.

Table 1. Descriptive data of both groups;

Variables	Group A (N= 60)	Group B (N= 60)	*P* value
Maternal age	26±4	24±7	> 0.05
Gestational age	40.1±0.6	41.1±0.7	> 0.05
Parity PG P1 P2	 40(66.7 %) 15(25%) 5(8.3 %)		> 0.05

The table 2 shows that modified Bishop score was higher among group B compared to group A,the differences were found to be significant, there were 20 patients and 18 patients from group A and B respectively underwent C/S excluded from this table.

Table 2. Comparison between both groups as regard modified Bishop Score

Modified Bishop score	Group A N=40	Group B N=42	T test	*P* value	Significant
Initial score	2.8±0.7	3.3±0.8	1.3	> 0.05	NS
After 2 hours	3.9±1.8	4.6±0.7	1.9	> 0.05	NS
After 4 hours	4.1±2	5.8±2	2.9	< 0.01	HS
After 6 hours	5.1±1.5	6.6±3	3.3	< 0.01	HS
After 8 hours	5.9±2.3	7.8±2.3	4	< 0.01	HS

Table 3 shows that group B had significantly shorter time than group A.

Table 3 Comparison between both groups as regard time from given Dose to beginning of active phase

Time from given medication	Group A N= 40	Group B N=42	t	*p*	Sig
Time until active phase of labour	6.3±2	4.5±2	2.3	< 0.05	S
Time until vaginal delivery from start of cervical ripening	6.2±1.6	6.0±1.4	1.9	>0.05	NS
Time until vaginal delivery from start of induction	12.5±5	10.5±3.6	2.5	<0.05	S

The table 4 shows that headache is more common among group B, the difference was found to be significant.

Table 4 Comparison between both groups as regard side effects

Variables	Group A N=60	Group B N=60	*P* value	
Fever	5 (8.3 %)	3(5 %)	> 0.05	NS
Hot flushes	5(8.3 %)	6(10 %)	> 0.05	NS
Palpitation	4(6.7 %)	7(11.7 %)	>0.05	NS
Nausea	8(13.3 %)	6(10 %)	>0.05	NS
Headache	20(33.3 %)	30 (50 %)	<0.05	S
Vomiting	3(5%)	4(6.7%)	>0.05	NS
Diarrhoea	2(3.3 %)	3(5%)	>0.05	NS

Table 5 shows that there was no significant difference between both groups.

Table 5 Comparison between both groups as regard uterine contraction abnormalities

Uterine contraction abnormalities	Group A N=60	Group B N=60	*P* value	Sig
Tachysystole	6(10%)	5(8.33 %)	> 0.05	NS
Hypersystole	1(1.6 %)	2(3.3 %)	> 0.05	NS
Hyperstimulation	1(1.6 %)	0	> 0.05	NS

The table 6 shows no significant difference between both groups, regarding, the mode of delivery.

Table 6 Comparison between both groups as regard mode of delivery

Mode of delivery	Group A N=60	Group B N=60	*P* value	Sig
VD	39(65 %)	40(66.66%)	>0.05	NS
Instrumental	1(1.66 %)	2(3.3 %)	>0.05	NS
Caesarean section	20(33.3%)	18(30 %)	>0.05	NS

The table 7 shows no significant differences between both group regarding indication of C/S.

Table 7 Comparison between both groups regarding indications of C/S

C/S indications	Group A N(20)	Group B N=18	*P* value	Sig
Fetal distress	11(55%)	10(55.55%)	> 0.05	NS
Arrest of cervical dilatation	6(30 %)	5 (27.77 %)	> 0.05	NS
Failure of induction	3(15 %)	3(16.66 %)	> 0.05	NS

The table 8 shows significant differences between both groups regarding the Apgar score after 1 and 5 minute.

Table 8 Comparison between both groups as regard neonatal outcome

	Group A N=60	Group B N=60	t test	*P* value	Sig
Apgar 1 minute	5.3 ±2	6.8 ±1.9	2.2	< 0.05	S
Apgar 5 minute	7.2 ±2	8.6 ±1.4	2.6	< 0.05	S

4. Discussion

Induction of labour is a common indication for the use of prostaglandins. However in the last years, there has been considerable interest in the use of nitrous oxide donors for cervical ripening and labour induction. In the our study The sample size according the available resources and equipment, variability of group. α errors 5 %, and confidence interval 95 %, the estimated sample size was 120 cases. In this study we found that modified Bishop score was significantly higher in group B if compared with group A, the differences were found to be significance (Table 2).The favourable effects of isosorbid mononitrate could be explained by interaction of nitrous oxide with various matrix metalloproteinase. (10).These findings agreed with study done on two hundred and ninety women scheduled for labour induction were recruited and assigned randomly to IMN or placebo followed by misoprostol 50 ug, they found that women receiving ISMO plus misoprostol showed significant changes in the bishop score 6 h after administration as compared to misoprostol plus placebo.(11)

This our study disagreed with study whose conducted among 120 nulliparous women at term who were admitted for induction of labour of various obstetrics indications, they were randomly assigned to receive ISMO or placebo in addition to prostaglandin, they found that no significant differences between both group regarding the mean time from initial dose to beginning of active phase of labour and delivery, the differences in the result with our study and may attributed to higher and frequent dose of ISMO which has relaxing effect on the myometrium which in turn affect the efficacy of prostaglandin. (12) In the present study we found no significant difference as regard mode of delivary, there were 20 patients who underwent caesarean section in misoprostol group while in the combined group there were 18 patients(Table 6),these findings was in agreement with other findings (12 who found no significant differences regarding the mode of delivery).

As regard incidence of side effects of drugs, we found that no significant statistical differences between both group regarding patients who developed fever, hot flushes, palpitation, vomiting and dirrhoea, but there was highly significant differences in patients who developed headache(50 % in group B vs 30 % in group A). The high ncidence of headache in group B could be explained by vasodilator effect of NO, this finding disagreed with other research (10),,whose found that, addition of vaginal ISMO to oral misoprostol for vaginal

ripening and labour induction did not reduce time to vaginal delivery and was associated with greater incidence of headache, this negative findings may be due to reduced efficacy of oral misoprostol if compared with vaginal misoprostol who was used in the our study, the higher incidence of headache could be explained by higher dose of ISMO,50 mg instead of 40 mg used in our study.(13) Also we found that no significant differences between two groups regarding uterine contraction abnormalities (table 5), furthermore there was no significant differences between both groups regarding fetal heart rate abnormalities or meconium passage during induction of labour.

In our study we found that, significantly higher Apgar score in group B if compared with group A,(Table 8) which could explained shorter period of delivery in the group B which in turn improving the Apgar score.

We concluded that ISMO plus misoprostol is safer and more effective in the induction of labour than misoprostol alone.

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