Italian Journal of

Gynæcology & Obstetrics

December 2020 - Vol. 32 - N. 4 - Quarterly - ISSN 2385 - 0868

Combination of mechanical and pharmacological methods for induction of labor in women with unfavorable cervices

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ABSTRACT

Objective. This study aimed at improving care of labor in women with unfavorable cervices.

Methods. A randomized clinical trial was conducted at the Department of Obstetrics and Gynecology, Suez Canal University Hospital in the period from from September 2016 to December 2018. All primigravid women with full-term pregnancies and fulfilled the inclusion criteria were included. Sixty patients were enrolled in the study. They were divided into two groups, 30 patients each, involving the different induction techniques.

Results. There was significant reduction in duration to active phase with a mean + SD of 324.52 ± 88.092 *vs*. 545.73 ± 49.787 min (p = 0.0001), shorter mean total length of induction (643.96 ± 162.755 *vs*. 1037.27 ± 145.933 min, p = 0.0001), and more successful induction of labor and delivery in less than 12 h (14 (60.9%) *vs*. 2 (9.1%), p = 0.0001), with the use of Foley catheter & vaginal misoprostol.

Conclusions. Foley catheter combined with vaginal misoprostol was more effective but less safe than a Foley catheter combined with vaginal IMN for induction of labor in term and post-term pregnancy.

SOMMARIO

Obbiettivo. Questo studio mira a migliorare la cura del travaglio nelle donne con cervici sfavorevoli.

Metodi. È stato condotto uno studio comparativo presso il Dipartimento di Ostetricia e Ginecologia dell'Ospedale Universitario Canale di Suez nel periodo dall'1 Gennaio 2016 a Gennaio 2017. Sono state incluse tutte le donne primi-gravide con gravidanze a termine e che soddisfacevano i criteri di inclusione. Sessanta pazienti sono state arruolate nello studio. Sono state divise in due gruppi, 30 pazienti ciascuno, coinvolgendo le diverse tecniche di induzione.

Risultati. È risultata una significativa riduzione della durata della fase attiva con una media + DS di 324,52 ± 88,092 *vs.* 545,73 ± 49,787 min (p = 0,0001), una lunghezza totale media più breve dell'induzione (643,96 ± 162,755 *vs*. 1037,27 ± 145,933 min, p = 0,0001), e un'induzione più efficace del travaglio e del parto in meno di 12 ore (14 (60,9%) contro 2 (9,1%), p = 0,0001), con l'uso del catetere di Foley e del misoprostolo vaginale.

Conclusioni. Il catetere di Foley combinato con misoprostolo vaginale è più efficace, ma meno sicuro, di un catetere di Foley combinato con IMN vaginale per l'induzione del travaglio in gravidanza a termine e post-termine.

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DOI: 10.36129/jog.32.04.02

Key words:
Cervical ripening; Foley catheter; isosorbide mononitrate; labor induction; misoprostol; pregnancy.

INTRODUCTION

Induction of labor is the stimulation of uterine contractions before the spontaneous onset of labor, with or without ruptured membranes to deliver the fetoplacental unit. The frequency of induction varies by location and institution (1). The number of women whose labors are induced has risen dramatically over the past two decades. Rates in the USA and the UK now exceed 20% of all births (2). Data on the magnitude or pattern of labor induction in Egyptian facilities or other developing countries are scarce.

One of the most frequent indications for induction of labor is prolonged pregnancy, and there is evidence from related Cochrane review in 2003 that for pregnancies that have continued beyond 41 weeks, induction of labor may reduce perinatal mortality (3).

Several factors influence the choice of the induction method. These include parity, the bishop score, membrane status, and presence or absence of a uterine scar (usually from previous cesarean section). In 2009 an observation al study, nulliparous women with an undilated cervix whose labors were electively induced, had a 50% cesarean rate (4).

The state of the women's cervix can be assessed by vaginal examination and scored to make a semi-quantitative prediction of favorability for labor induction. Induction tends to be more comfortable if the cervix is soft, dilated, and short (favorable/high cervical score) and more difficult if firm, closed, and lengthy (unfavorable/low cervical score) (5).

Several effective cervical ripening methods can be applied to increase the success rates of vaginal delivery in women with unfavorable cervices. These include mechanical and pharmacologic options. Mechanical options include Foley catheters, either alone or combined with another procedure. It acts by causing pressure on the internal OS of the cervix and stretching of the lower uterine segment, increasing the release of local prostaglandins (PG). When used alone, it resulted in less tachysystole with fetal heart changes than PG and misoprostol with no difference in cesarean section (CS) rates. However, when compared with oxytocin alone, the CS rate was reduced significantly (6).

Misoprostol is a synthetic prostaglandins E1 (PGE1) analog that has been approved for the prevention and treatment of gastric ulcers associated with the use of non- steroidal anti-inflammatory drugs (7).

A 2010 Cochrane review concluded that vaginal misoprostol was also superior to other induction agents (vaginal prostaglandin, intra-cervical prostaglandin, and oxytocin), with less epidural use and fewer failures to achieve vaginal delivery within 24 hours, but more tachysystole with fetal heart rate (FHR) changes (8).

Nitric oxide is thought to be a fundamental mediator of cervical ripening (9). Previous studies have hypothesized that nitric oxide (NO) donor, such as isosorbide mononitrate (IMN), may prove to be an agent that can be administered without causing uterine contractions or other adverse effects of clinical importance during the ripening process (10).

This study aimed to assess & compare the combination of Foley's catheter & misoprostol versus the combination of Foley's catheter & isosorbide mononitrate to achieve successful cervical ripening and hence facilitate the induction process. Also, we evaluated complication rates as well as patients' satisfaction using either method.

PATIENTS AND METHODS

The present study was conducted as a randomized clinical trial at the emergency department of Obstetrics and Gynaecology, Suez Canal University Hospitals, Ismailia, Egypt. The study started from September 2016 to December 2018. It included all primigravid women with full-term pregnancies and fulfilling the inclusion criteria: a) primigravida pregnant women, b) full term (37-41 weeks gestation), c) women with a viable singleton gestation, d) vertex fetal presentation, e) no previous uterine scars, and f) with Bishop Score of 5 or less. The recruited patients had induction of labor for different obstetric causes as prolonged gestation, hypertensive disorders with pregnancy, oligohydramnios, and premature rupture of membranes with no evidence of chorioamnionitis. All the recruited patients were of the same ethnic group.

Eighty patients were eligible for the study. Fifteen patients refused to participate in the study while another five refused the treatment after enrollment. This resulted in sixty patients enrolled in the study. They were randomly divided into two groups, 30 patients each. The participants were allocated to two groups involving the different induction techniques. They were subjected to obstetric history, complete general and obstetric examination, and abdominal ultrasound. Patients were randomized to either group using simple randomization generated by computer programs. Only patients were blinded to

the procedure. Each recruited woman was assigned an order number and received the medication with the same number. The allocation sequence was concealed using sealed envelopes that were opened when it was time to allocate the intervention. The senior researcher opened these envelopes.

Step 1: in-patient procedure

-For both groups: A single-balloon Foley catheter 18-Fr was inserted above the internal cervical OS and filled with 50 mL of normal saline. The catheter was strapped to the inner aspect of one leg after tension. The catheter was left in place until either it falls out spontaneously or 12 hours have elapsed.

Step 2

-In group 1: 50 mcg of misoprostol (2 Vagiprost 25 Mcg vaginal tablets, ADWIA Co, Egypt) was inserted in the posterior fornix of the vagina after application of one drop of sterile water to moisten it by gloved fingers while the patient was lying down for half an hour. The dose was repeated every 6 hours for a maximum of four doses until cervical ripening achieved.
-In group 2: 40 mg of IMN (Monomak 40 mg, October pharma, Egypt) was inserted in the posterior fornix of the vagina after application of one drop of sterile water to moisten it by gloved fingers while the patient was lying down for half an hour and repeated after 12 hours until cervical ripening achieved or for a total induction time of 24 hours.
If the membranes ruptured spontaneously, the balloons were deflated, and the catheter was removed to facilitate active labor management. In this case, the patient was excluded from the study.
The insertion difficulty of the catheter was evaluated in both groups. It was considered difficult with the presence of pain interfering with catheter insertion or the need for excessive manipulation to achieve successful insertion. If none of the above mentioned was present, insertion was categorized as easy.
All participants rated pain associated with the catheter insertion procedure using a visual analog scale (VAS) (0-10: 0 = no pain, 10 = worst possible pain) (11).
A none stress test was conducted after catheter insertion. For both groups, the catheter was removed at approximately 12 hours after insertion, if spontaneous expulsion had not occurred. Artificial rupture of the membranes and oxytocin infusion was started if cervical dilation reached 3-4 cm either after removal or spontaneous expulsion of the catheter. If not, induction was continued using either medication for 24 hours, after which failed induction was declared. Continuous electronic fetal monitoring was done for all cases in established labor. Labor progress abnormalities were diagnosed and managed according to the recommendations of the American College of Obstetricians and Gynecologists (12).

The dose of oxytocin

At 3-4 cm cervical dilatation, amniotomy was done for both groups. Oxytocin was used to augment labor if the arrest of dilatation occurred for more than 2 hours at dilatation of at least 4 cm. Oxytocin was diluted five units in a 500 mL isotonic solution for an oxytocin concentration of 10 mU/mL. Starting dose was six mU oxytocin, then infusion continued at a rate of 3-6 mU/min. The FHR and uterine contractions were monitored closely. In cases of uterine hyperstimulation, oxytocin infusion rates were reduced to 3mU/min and further reduced to 1 mU/min with recurrent hyperstimulation (12).
Uterine activity was monitored after the application of medications, after the beginning of regular uterine contractions, and during all the active phase and second stage of labor by Cardiotocography. Maternal blood pressure and pulse rate were assessed every 30 minutes for 2 hours after initiation of medication. All maternal & fetal adverse effects were documented. After 6 hours of initial application, patients were re-evaluated and based on clinical response; either no medication or another dose of drugs was decided. The optimal contraction pattern was 3-4 contractions in 10 minutes. Fetal heart rate monitoring was done using Cardiotocography after the application of medication, at the start of regular contractions and was conducted continuously from the start of the active phase of labor. In the end, after delivery, all participants rated their satisfaction with the whole induction process using VAS (0-10: 0 = not satisfied, 10 = maximum satisfaction).

Primary outcomes of the study

The change in Bishop's score found after 12 hours from the initial application or falling of the Foley catheter spontaneously.

Secondary outcomes of the study

Secondary outcomes relate to measures of effectiveness, complications, and satisfaction.

Measures of effectiveness

1. Time interval from initial dose to the beginning of the active phase of labor.
2. Needs for oxytocin augmentation.
3. Route of delivery, either successful vaginal delivery or by C.s.

Measures of complications and satisfaction

It was classified into:

1. maternal outcomes.
   - Adverse effects (nausea, vomiting, and diarrhea).
   - Uterine hyperstimulation without FHR changes.
   - Uterine rupture.
   - Postpartum hemorrhage.
   - Maternal severe complications (e.g., intensive care unit admission, septicemia up to maternal death).
   - Maternal satisfaction.
2. Fetal outcomes.
   - Meconium-stained liquor.
   - Apgar scores less than seven at five minutes.
   - Neonatal intensive care unit admission.
   - Perinatal death.

Ethical approval

This study was carried out after obtaining ethical approval on 15/06/2016 with a research number 2836#. Clinical trial registration number: PACTR201909668132445.

Sample size

A sequential sample size calculation was used (13):

$$n = 2\left[\frac{\left(Z_{\alpha/2} + Z_{\beta}\right) * \sigma}{\mu_1 - \mu_2}\right]^2$$

where:

$\boldsymbol{n}$ = required sample size.

$\mathbf{Z}_{\alpha/2}$ = 1.96 – The critical value that divides the central 95% of the Z distribution from the 5% in the tail.

$\mathbf{Z}_{\beta}$ = 0.84 – The critical value that separates the lower 20% of the Z distribution from the upper 80%.

σ is the estimate of the standard deviation in the study group (10).

$\boldsymbol{\mu 1}$ = mean in group 1(10)

$\boldsymbol{\mu 2}$ = mean in group 2 (10)

E = margin of error

n = 30 patients in each group.

Statistical analysis

Data were statistically described in terms of mean and standard deviation, frequencies (number of cases), and percentages when appropriate. P values of less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 22 for Microsoft Windows. Chi-square test was used for categorical variables and t-test for continuous variables with normally distributed data. Non-normally distributed data were tested using Fisher's exact for categorical variables and Mann-Whitney U tests for continuous variables.

RESULTS

Enrollment

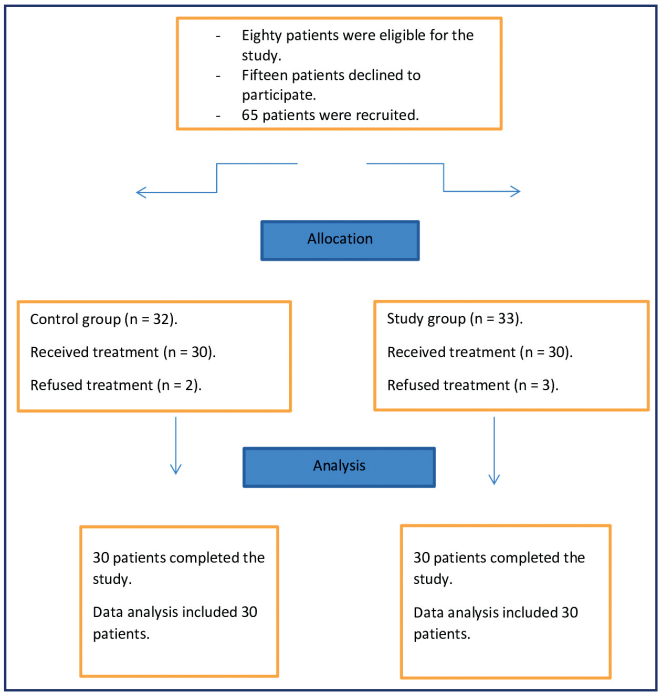

Figure 1. *Patients' flow chart.*

The two groups were not significantly different in the demographic characteristics of the study participants in terms of age, gestational age, or Bishop Score. The majority of the recruited patients had induction of labor because of prolonged gestation (14/30, 46.7%, and 17/30, 56.7% for group I and II, respectively) (**table I**).

Table I. *Demographic characteristics in both the groups.*

		Misoprostol group I (n = 30)	IMN group II (n = 30)	P value
Age, years (mean ± SD)		26.47 ± 3.27	26.2 ± 2.95	0.130
Gestational age, weeks (mean ± SD)		39.37 ± 1.033	39.3 ± 0.988	0.811
Bishop Score (mean ± SD)		3.93 ± 0.785	4.27 ± 0.640	0.087
BMI (mean ± SD)		28.8 ± 2.3	29.0 ± 1.8	0.463
Indication for induction (N%)	Postdate gestation	14 (46.7%)	17 (56.7%)	0.07
	Hypertensive disorders	6 (20%)	7 (23.3%)	
	Oligo-hydramnios	3 (10%)	1 (3.3%)	
	Pre-labor rupture of membranes	7 (23.3%)	5 (16.7%)	
Estimated fetal weight (mean ± SD)		3204.78 ± 435.69	3272.38 ± 447.23	0.067
AFI (mean ± SD)		10.05 ± 5.43	11.53 ± 6.69	0.873

P < 0.05 was considered statistically significant.

Bishop Score, after the balloon catheter expulsion or removal, was significantly higher in group I with a mean of 6.60 ± 0.770 than group II with a mean of 6.03 ± 0.944 (**table II**). In group one, 4 (13.4%), 10 (33.3%), 10 (33.3%), and 6 (20%) patients required 1st, 2nd, 3rd, and 4th doses, respectively. While in group two, 13 (43.3%) and 17 (56.7%) patients required one or two doses, respectively.

Table II. *Bishop Scores before balloon insertion and following expulsion.*

	Group I	Group II	P value
Pre-balloon insertion Median (range)	4 (3-5)	4 (3-5)	0.087
Post-balloon expulsion Median (range)	6 (6-8)	6 (5-8)	0.010*

P < was considered statistically significant. * Statistically significant difference.

Cesarean section rate was not significantly different between both groups (p = 0.766); however, the rate of vaginal delivery within the first 12 hr was considerably higher in group I than in group II (p = 0.0001). Both the duration of induction (p = 0.0001) and the duration to active phase (p = 0.0001) were significantly shorter in group I as compared to group II. There was a significant improvement in the Bishop Score in the Misoprostol group. As regards the indications for the cesarean section, a significant difference was found between both groups regarding failed induction in favor of Misoprostol group and also relating to fetal distress (p = 0.0001). There was no significant difference regarding Dystocia (**table III**).

There were no significant differences between the two groups with regard to neonatal birth weight (g) in group I (mean ± SD, 3375 ± 293.123) versus group II (mean ± SD, 3315 ± 287.12) with (p = 0.553). There were significant differences between the two groups

Table III. *Outcome measures after insertion of catheter.*

		Misoprostol group I (n = 30)	IMN group II (n = 30)	P value
CS		7 (23.3%)	8 (26.7%)	0.766
Vaginal delivery < 12 (hr)		14 (60.9%)	2 (9.1%)	0.0001*
Duration of induction (m)		643.96 ± 162.755	1037.27 ± 145.933	0.0001*
Duration of active phase (m)		324.52 ± 88.092	545.73 ± 49.787	0.0001*
Bishop Scores after catheter expulsion		6.60 ± 0.770	6.03 ± 0.944	0.010*
Indication for CS: **• Failed/induction** **• Fetal distress** **• Dystocia**		 2 (28.6%) 4 (57.1%) 1 (14.3%)	 6 (75%) 1 (12.5%) 1 (12.5%)	0.0001*
Rates of spontaneous expulsion		22 (73.3%)	18 (60%)	0.273
Rates of ROM	**Spontaneous**	6 (20%)	7 (23.3%)	0.156
	Artificial	19 (63.3%)	18 (60%)	

P < 0.05 was considered statistically significant. *Statistically significant difference.

with regard to Apgar score at 1 min group I (mean ± SD, 7.54 ± 0.0696) versus group II (mean ± SD, 7.86 ± 0.439) with (p = 0.001). There were significant differences between the two groups with regard to Apgar score at 5 min group I (mean ± SD, 7.93 ± 0.567) versus group II (mean ± SD, 8.12 ± 0.417) with (p < 0.001). Neonatal distress was significantly higher in group I than in group II (6) 20 %(*versus* 2) 6.7) respectively, p value < 0.011) as well as neonatal intensive care unit admission (6 (20%) *versus* 2 (6.7%) respectively, p value < 0.011) (**table IV**).

Table IV. *Neonatal outcomes.*

	Misoprostol group I (n = 30)	IMN group II (n = 30)	P value
Neonatal birth weight (g) (mean ± SD)	3375 ± 293.123	3315 ± 287.123	0.553
Apgar score at 1 min (mean ± SD)	7.54 ± 0.696	7.86 ± 0.439	> 0.001*
Apgar score at 5 min (mean ± SD)	7.93 ± 0.567	8.12 ± 0.417	> 0.001*
Neonatal distress (No%)	6 (20%)	2 (6.7%)	> 0.011*
Neonatal ICU admission (No%)	6 (20%)	2 (6.7%)	> 0.011*

P < 0.05 was considered statistically significant. *Statistically significant difference.

Uterine hyperstimulation was significantly higher in group I (p = 0.003). There was no significant difference in patients' satisfaction with the whole process of induction in both groups (**table V**).

DISCUSSION

The perception of pain is one of the troublesome side effects of catheter insertion. The mean pain perception during catheter insertion was 4.7 ± 3.1 to the Foley catheter & misoprostol (group I) and 4.3 ± 2.7 to the Foley catheter & IMN (group II). However, this difference was not statistically significant. This agreed with Mei-Dan *et al*., who reported a non-significant difference in pain perceived during catheter insertions although they used Foley catheters in comparison with Cook cervical ripening balloon (3.3 ± 2.3, 3.4 ± 2.3 respectively with a p value of 0.77) (14). This can be explained by the fact that both catheters were inserted using the same technique; the primary source of discomfort was related to the speculum application before insertion of the catheters.

Table V. *Maternal complications.*

	Misoprostol group (n = 30)	IMN group (n = 30)	
Uterine hyper stimulation	6 (20%)	0 (0%)	0.003*
Maternal nausea	6 (20%)	10 (33.3%)	0.243
Maternal headache	5 (16.7%)	3 (10%)	0.488
Maternal shivering	7 (23.3%)	3 (10%)	0.166
Post-partum hemorrhage	2 (6.7%)	0 (0%)	0.150
Patient satisfaction	23 (76.7%)	20 (66.7%)	0.390

P < 0.05 was considered statistically significant. *Statistically significant difference.

There was an improvement and reduction in the time to active phase with a mean ± SD of (324.52 ± 88.092 *vs*. 545.73 ± 49.787 min, p = 0.0001), shorter mean total duration of induction (643.96 ± 162.755 *vs*. 1037.27 ± 145.933 min, p = 0.0001), and more successful induction of labor and delivery in less than 12 hours (14 (60.9%) *vs*. 2 (9.1%), p = 0.0001], with the use of Foley catheter & vaginal misoprostol for labor induction over the use of Foley catheter plus vaginal IMN respectively in cases of the unripe cervix with Bishop Score less than 5. This was matched with the results of a previous study that compared the efficacy of a Foley catheter and misoprostol in the induction of labor compared with misoprostol alone. The combined use of the Foley catheter and misoprostol was associated with a significant reduction in the induction to delivery interval, duration of the latent phase, and successful vaginal delivery in < 12 hours (15).

There was a worsening in the neonatal Apgar score at 1 min and 5 min score with a significantly increased proportion of fetal distress and neonatal ICU admission (20% & 6.7%, p > 0.011) in group I patients. This could be explained by increased rates of uterine hyperstimulation in these patients. A paramount concern with the use of intravaginal misoprostol for induction of labor is the incidence of excessive uterine contractions. The current study demonstrated a significant difference in contraction abnormality/uterine tachysystole. The study showed that contraction abnormality occurred more frequently in the combination of intra-cervical Foley catheter & misoprostol group than intra-cervical Foley catheter & intravaginal IMN group. This finding was consistent with that of a previous study where they reported higher rates of uterine tachysystole in the group of Foley catheter and misoprostol (15).

Induction of labor with IMN was safer with fewer side effects; however, the duration of induction was significantly longer, which was matched with another study with no significantly different cesarean section rate (16).

Strengths and limitations

This study included primigravid women only. Evaluation of this combined regimen needs to be evaluated in multiparous women with unfavorable cervices. This study is a randomized clinical trial that compares two different regimens of induction of labor. It included sixty patients, while larger samples would be more informative. The exclusion of multiparous women increases the accuracy of the results.

CONCLUSIONS

The combined induction using a Foley catheter and misoprostol is valid but associated with significant unwanted effects. Foley catheter, when used alone, is a safe method of induction, especially in low resource settings. However, when combined with other drugs, the efficacy increased, and this should be tailored according to each patient.

ETHICAL STATEMENT

All procedures performed in the study were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
This article does not contain any studies with animals performed by any of the authors.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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