Research Article

Nitric Oxide Donors Combined with Misopristol Versus Misopristol Alone in Induction of Labour in Postterm Pregnancy

Mahmoud H. Ibrahim MD, Hashem F. Mohammed MD and Ahmed M. Abdelghany MD
Department of Obstetrics and Gynecology,
Minia Maternity and Pediatric University Hospital, Minia, Egypt .

Abstract
Objectives: To evaluate the role of Nitric Oxide donors combined with misopristol versus misopristol alone in induction of labour in postterm pregnancy **Study Design:** Patients were randomly allocated into two groups (fifty patients for each group) using computer generated tables and sealed envelops according to the method of termination. These two groups were as follows: Group A (Misoprostol-only group): ١\٤ tablet of misoprostol "٥٠ micrograms" (Misotac; Sigma ,Co, Cairo, Egypt) was put every ٤ hour sublingual with a maximum dose of ٦٠٠ micrograms "٦ doses" . Group B (Glyceryl trinitrate- Misoprostol group): One tablet of glyceryl trinitrate "٥٠٠ micrograms" (Angised; Welcome Co; London, UK) was put every ٤ hours in the posterior fornix with a maximum dose of ٣ milliograms "٦ doses" in the same time of giving ٥٠ ug (١\٤tablet) misoprostol every four hours for a maximum of (٦٠٠ug) ٦ doses. **Results:** The results of this study indicated that the NO donor, glycery trinitrate, cause cervical ripening effect because it increase the softness, and the dispensability of cervix and did not affect the diameter and length of the cervix. **Conclusions**: NO donor can induce more cervical ripening by local application of gel or paste intra-cervical. This may produce more significant changes in Bishop score and be more effective as cervical ripening agent .

Key Words: Nitric Oxide**,** labour**,** NO donor

Introduction
Induction of labour is a common obstetric problem and is considered as a greet challenge to obstetricians. The condition of the cervix is almost always related to the success of the process of termination and its duration, so the cervix should be adapted (ripened) before beginning of termination.[١]

Misoprostol is a synthetic prostaglandin El analogue used originally for the prevention and treatment of peptic ulcer caused by the prolonged use of NSAIDs[٢]**.** It has been used as a cervical ripening agent and for induction of labour many years ago[٥]**,** many studies have been conducted ever since in order to evaluate its use with a living fetus.

Nitric oxide donor, glyceryl trinitrate,is a free radical which involved in the process of cervix ripening[٦]**.** Its involved in the acute inflammatory response and also know to stimulates matrix metalloproteinase that breakdown collagen of the cervix[٧]**.**

Patients and methods
This study was done in the Department of Obstetrics and Gynecology, Minia maternity and pediatric University Hospital, Minia, Egypt from February ٢٠١٣to may ٢٠١٤. The study included one hundred apparently healthy postterm pregnant patients eligible for induction of labour, admitted through the emergency room or out patient clinic. The duration of pregnancy was thoroughly calculated from the last reliable menstrual period and early ultrasonography scanning (<٢٢weeks).

All patients included in this study were postterm pregnancy (١٠ days after the EDD)

The exclusion criteria of these patients were:

١. Previous scarred uterus.
٢. Grandmultipara (Gravida ٥ and more)
٣. Patients with Bishop score >٤.
٤. Premature rupture of membranes.
٥. Transverse lie (>٢٠weeks).
٦. Multiple pregnancies.
٧. Placenta previa (>٢٠weeks).
٨. Patients with known contraindications to the used drugs e.g history of allergy to the used drugs.
٩. Patients with any medical problem such as chronic liver disease, chronic renal disease, chronic hypertension, diabetes, history of bronchial asthma, known cardiac disease, chronic headache such as migraine
١٠. History of any drug intake except vitamins and iron.

All patients were subjected to:

A) History taking: included personal, obstetric, menstrual and past history

B) Clinical examination: included general, obstetric and vaginal examination for assessment of Bishop score on admission to the study.

C) Investigations:

١ - Laboratory:

- Hemoglobin level and platelets count.
- Coagulation profile (clotting time, prothrombin time and concentration, PTT).
- Renal function tests (urea, creatinine).
- Random blood sugar.

٢- Ultrasonography examination:

- Estimation of the gestational age.
- Localization of the placenta.
- Diagnosis of major congenital anomalies.

All patients included in this study were informed about the details of the procedure before starting termination of their pregnancy and informed oral consent was taken.

Methodology:

Patients were randomly allocated into two groups (fifty patients for each group) using computer generated tables and sealed envelops according to the method of termination. These two groups were as follows:

Group A (Misoprostol-only group):

١\٤ tablet of misoprostol "٥٠ micrograms" (Misotac; Sigma ,Co, Cairo, Egypt) was put every ٤ hour sublingual with a maximum dose of ٦٠٠ micrograms "٦ doses" (Ho et al., ١٩٩٧).

Group B (Glyceryl trinitrate- Misoprostol group):

One tablet of glyceryl trinitrate "٥٠٠ micrograms" (Angised; Welcome Co; London, UK) was put every ٤ hours in the posterior fornix with a maximum dose of ٣ milliograms "٦ doses"[٧] in the same time of giving ٥٠ ug (١\٤tablet) misoprostol every four hours for a maximum of (٦٠٠ug) ٦doses.

Bishop score pattern were recorded throughout the procedure at ٠ hour (on admission to the study), ١٢ hour and ٢٤ hour after drugs intake in both groups.

Patients were examined every ٤ hours for:

١. Occurrence of uterine contractions, its frequency and duration.
٢. Formation of bag of fore water in patients with uterine contractions.
٣. Changes in the Bishop score.

The following parameters were calculated and recorded in both groups throughout the procedure:

Induction - maximum Bishop interval (In hours): The interval that lapses from the time of the misoprostol insertion to the time of achievement of maximum Bishop.

Induction – termination interval (In hours): The sum of the duration of misoprostol insertion plus the duration of any complementary procedure (if any).

Maximum Bishop- termination interval (In hours): The time from maximum Bishop achieved till the time of complete termination.

- Complications of induction of labour such hyperstimulation syndrome of the utrerus, fetal distress, and rupture of the uterus.

Side effects of the used drugs such as:

Headache, hot flushes, palpitation, dyspnea, fever, G I T symptoms (nausea, vomiting and diarrhea).

- Changes in maternal pulse and B.P. (recorded every ٢ hours)

Follow-up:

The patients were followed after termination for detection and management of any immediate post termination complications (if any).

Statistical analysis:

The data were collected and tabulated on a statistical package for social sciences (SPSS) program, version ٩ for windows resulting in:

- Descriptive statistics:

- Mean (X).
- Standard deviation (SD).

- Analytical statistics:

- Unpaired "t" was used to compare between two independent means.
- Paired "t" test to compare within the same group.
- Chi-square test to compare between different groups in qualitative data.
- P-Value of <٠.٠٥ was considered significant.

Results

Table (١): Patient's characteristics on admission.

The parameter	Group A (Misoprostol-only group) (n=٥٠)	Group B (Glyceryl trinitrate-Misoprostol group) (n=٥٠)	Significance
Age (years)			
Range	١٧-٤٠	١٧-٤٠	NS
X± SD	٢٥.٠٨±٥.٧٢	٢٦.٧١±٥.٧	
Weight (Kg)			
Range	٦٠-٩٧	٦٠-٩٥	NS
X± SD	٧٩.٠٨±٨.٦١	٧٧.٨±١.١٩	
Number of deliveries (no)			
Range	٠-٤	٠-٤	NS
X± SD	١.٣٦±١.٢	١.٧٤±١.١٦	
Number of abortions (no)			
Range	٠-٤	٠-٤	NS
X± SD	٠.٧٢±٠.٩٩	١.٠٢±١.٨	

Kg = Kilograms **NS= Non Significant**

There was no statistically significant difference between the two groups on admission regarding the age, weight, number of deliveries, number of abortions, gestational age calculated by LMP and gestational age calculated by ultrasonography scanning (P> ٠.٠٥) (Table ٦ and figure ١)

Table (٢): Bishop Score pattern throughout the procedure.

	Group A (Misoprostol-only group) X ± SD (n=٥٠)	Group B (Glyceryl trinitrate-Misoprostol group) X ± SD (n=٥٠)	Significance
At ٠ hour (on admission)	٢.٢٤ ±١.٣٩	٢.٢±١.٣	NS
At ١٢ hour (after beginning of termination)	٣.٧٤±٢.٠٢	٣.٧٨±١.٦١	NS
At ٢٤ hour (after beginning of termination)	٦.٢٦±٢.٧٦	٦.٣٤±١.٧٢	NS

There was no statistically significant difference between the two groups regarding Bishop score pattern throughout the procedure (P > ٠.٠٥)

Table (٣): Comparison of Bishop Score pattern at different time intervals throughout the procedure within each group.

	Bishop score at ٠ hour X ± SD	Bishop score at ١٢ hour X ± SD	Bishop score at ٢٤ hour X ± SD
Group A **(Misoprostol-only group)**	* ٢.٢٤±١.٣٩	** ٣.٧٤±٢.٠٢	٦.٢٦±٢.٧٦
Group B **(Glyceryl trinitrate-Misoprostol group)**	*** ٢.٢±١.٣	****٣.٧٨±١.٦١	٦.٣٤±١.٧٢

* = Bishop score at ٠ hour versus Bishop score at ١٢ hour in group A
** = Bishop score at ١٢ hour versus Bishop score at ٢٤ hour in group A
*** = Bishop score at ٠ hour versus Bishop score at ١٢ hour in group B
**** = Bishop score at ١٢hour versus Bishop score at ٢٤hour in group B

In both groups:
There was statistically significant improvement in Bishop score at ١٢ hour and at ٢٤ hour compared to that at ٠ hour (P<٠.٠٥)

Table (٤): Efficacy indicators in both groups.

Indicator	Group A (Misoprostol-only group) X ± SD (n=٥٠)	Group B (Glyceryl trinitrate-Misoprostol group) X ± SD (n=٥٠)	significance
Induction –maximum Bishop interval (in hours)	٢٧.٦٦±٣.٦٤	٢٤.١٢±٤.٨٨	NS
Induction- delivary interval (in hours)	٣١.٧١±٣.٩٦	٢٨.٠٢±٦.١١	NS
Maximum Bishop- termination interval (in hours)	٤.١±٢.٦	٣.٧±٣.٠٥	NS

There was no statistically significant difference between two groups regarding the induction – maximum Bishop Interval, induction- termination interval and maximum Bishop- termination interval (P > ٠.٠٥)

Table (٥): Side effects recorded in the studied groups.

	Group A (Misoprostol-only group) (n = ٥٠)		Group B (Glyceryl trinitrate-Misoprostol group) (n = ٥٠)		Significance
	n	%	n	%	
Symptom free	٣٧	٧٤٪	٣٠	٦٠٪	S
Headache	٠	٠٪	٢٠	٤٠٪	S
Hot flushes	٠	٠٪	٠	٠٪	NS
Nausea	٥	١٠٪	٠	٠٪	S
Vomiting	٣	٦٪	٠	٠٪	S
Fever	٥	١٠٪	٠	٠٪	S
Palpitation	٠	٠٪	٠	٠٪	NS

The percentage of asymptomatic patients in group A was statistically lower than that in group B (P<٠.٠٥).

Nausea,vomiting and fever were recorded in a higher percentage in group A than that in group B) (Table ١٢).

Table (٦): Frequency of combined side effects in both groups.

	Group A (Misoprostol-only group) (n = ٥٠)		Group B (Glyceryl trinitrate-group) significance (n = ٥٠)		Misoprostol
	n	%	n	%	
Nausea and vomiting	١	٢٪	٠	٠٪	NS
Vomiting and fever	٠	٠٪	٠	٠٪	NS
Nausea and fever	٢	٤٪	٠	٠٪	NS

There was no statistically significant differences between the two groups regarding the frequency of combined side effects (P>٠.٠٥)

Table (٧): Mean maternal blood pressure and pulse during the procedure.

	Group A (Misoprostol-only group) X ±SD (n=٥٠)	Group B (Glyceryl trinitrate-Misoprostol group) X ±SD (n=٥٠)	Significance
Systolic BP			
At ٠ hour	١١٤.١±١٢.٣٥	١١١.٧±١١.٨٤	NS
At ١٢ hour	١١٢.٤±١١.٨٣	١١١.١±٩.٧٥	
At ٢٤hour	١١٢.٤±١١.٨٢	١١١.٧±١١.٨٩	
Diastolic BP			
At ٠ hour	٧٤.٨±٧.٨٢	٧٢.٧±٧.٥	NS
At ١٢ hour	٧٩.٨٢±٧.٤٢	٧٣.٤±٦.٠١	
At ٢٤hour	٨١.٣٤±٦.٠٢	٧٣.٤±٦.٠١	
Maternal pulse			
At ٠ hour	٧٩.٨٢±١٠.٩٢	٨٣.٦٤±٩.١١	NS
At ١٢ hour	٧١.٨±٧.٩٢	٨٧.٥±٨.٤٤	
At ٢٤hour	٨١.٣٩±٩.٢	٨٧.٧٤±٨٨١	

There was no statistically significant difference between the two groups as regard the Changes in the maternal systolic BP, maternal diastolic BP and maternal pulse during the procedure. (P>٠.٠٥) (Table ١٤).

Table (٨): Complications of termination in both groups.

	Group A (Misoprostol-only group) (n= ٥٠)		Group B (Glyceryl trinitrate-Misoprostol group) (n=٥٠)		Significance
	n	%	n	%	
Severe vaginal bleeding	٠	٠٪	٠	٠٪	**NS**

Rupture of the uterus	٠	٠٪	٠	٠٪	**NS**
Incomplete evacuation of the intrauterine contents	١٠	٢٠٪	٤	٨٪	**S**

Only ١٤ (٢٨٪) cases in the study were complicated by retained produces of conception (incomplete evacuation of the uterus), ١٠(٢٠٪) of them were in group A and ٤ (٨٪) in group B. This difference between the two groups was statistically significant (P<٠.٠٥)

Discussion

The results of this study indicated that the NO donor, glycery trinitrate, cause cervical ripening effect because it increase the softness, and the dispensability of cervix and did not affect the diameter and length of the cervix. These Bishop Score changes are significant. The induction –termination interval and induction -maximum Bishop interval was shorter in NO donor group (B) but it's not statistically significant.

The need for complementary procedure such as Foleys catheter, oxytocin or both and D&C was ٥(١٠٪), ١٥(٣٠٪), ٤(٨٪) and ١٠(٢٠)% in group A respectively and ٢(٤٪), ٧(١٤٪), ٣(٦٪) and ٤(٨٪) in group B. So There significant decrease in the need of the complementary procedure group B

As regard maternal B.P. and pulse change during the proceed there was change in the maternal B.P in the form of decrease in BP and increase in pulse rate but these changes are not statistically significant.

As far as the total side effects were occur in the misoprostol induced group (A) was ٢٦٪ ,of them there was nausea ٣٧٪, vomiting ٢٦٪, fever ٣٧٪ ,compared with ٤٠٪ in group B ,all of them were complain of headache[٢].

No serious obstetric complications such as sever vaginal bleeding and rupture uterus had done in both groups whoever retained products of conception was occur in ١٠(٢٠٪) patients in group A and in ٤ (٨٪) patients in group B.

From the results of the present study we can reach the following conclusion:

١. Misoprostol is less effective drug in induction of second trimester pregnancy termination in patients with unfavourable cervix (Bishop Score < ٤) because of nearly half cases need complementary procedures and only ١/٢ of these patients completed termination of their pregnancy without any complementary procedure.
٢. NO donor glyceryl trinitrate was effective drug concerning cervical ripening as regard it improves the Bishop score on repeated doses

Recommendations:

١. NO donor can induce more cervical ripening by local application of gel or paste intra-cervical. This may produce more significant changes in Bishop score and be more effective as cervical ripening agent.
٢. Use of other systemic preparations of NO donors as Isosorbid mononitrate instead of glyceryl trinitrate for higher doses
٣. Glyceryl trinitrate can be used with higher doses to produce more cervical ripening effect.
٤. The NO donor can be also used for produce more softness of the cervix before suction evacuation of vesicular mole

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الملخص العربي

" معطيات عقار النيتريك أوكسيد مع ميزوبروستول مقارنة بال ميزوبروستول فقط فى تحفيزالولادة بعد انتهاء فترة الحمل "

أجريت هذه الدراسة بقسم أمراض النساء والتوليد بمستشفى المنيا الجامعي في الفترة من فبراير٢٠١٣حتى مايو ٢٠١٤ . احتوت هذه الدراسة على ١٠٠ حالة من السيدات الحوامل بدواعي واضحة لإنهاء الحمل . تعتبر هذه الدراسة مقارنه عشوائية لتحديد دور معطى أوكسيد النتريك وهو ثلاثي نيترات الجلسرول (الانجسيد) في تهيئة عنق الرحم قبل إنهاء الحمل فى هذه الفترة وتم تقسيم هذه الحالات إلى مجموعتين:

المجموعة الأولى (أ) :

تم إعطاؤهن عقار الميزوبروستول(الميزوتاك) بجرعة ٥٠ميكرو جرام كل ٤ ساعات(نصف قرص) بحد أقصى ٦جرعات (٥٠٠ ميكرو جرام) وتم وضعها تحت اللسان .

المجوعة الثانية (ب) :

تم إعطاؤهن عقار ثلاثى نيترات الجلسرول بجرعة ٥٠٠ ميكرو جرام (قرص واحد)) ثم استكمال عملية إنهاء الحمل باعطاؤهن الميزوبروستول (الميزوتاك) بجرعة٥٠ ميكروجرام كل ٤ ساعات بحد أقصى ٦ جرعات

وتم فحص السيدات كل ٤ ساعات لملاحظة التغيير فى نظام البيشوب لتقييم عنق الرحم ولقد كان الانتقال لأى وسيلة أخرى يتم إذا لم تبدأ عملية انهاءالحمل بعد مرور ٢٤ ساعة من بداية إعطاء الميزوبروستول لكل الحالات فى المجموعتين .

وقد تم حساب الوقت الكلى من استخدام عقار الميزوبروستول لكلا من المجموعتين بالإضافة للوسيلة المساعدة حتى حدوث عملية إنهاء الحمل وذلك لحساب الوقت الكلى التى استغرقته عملية إنهاء الحمل فى كل مجموعة على حدة.

تم ملاحظة وتدوين أى من الأعراض الجانبية للأدوية المستخدمة في الدراسة كما تم أيضاً متابعة السيدات لمدة ٢٤ ساعة بعد عملية إنهاء الحمل للاكتشاف المبكر وعلاج أى مشاكل بعد عملية إنهاء الحمل.

ومن هنا خلصت هذه الدراسة الي الاتى :-

(١) عقار الثلاثى نيترات الجلسرول فعال فى تهيئة عنق الرحم وتحسين تقييم بيشوب لتقييم عنق الرحم .
(٢) بالرغم من الفعاليات السابقه للعقار الا نه لا يؤثر على الوقت بين عملية تحفيز انهاء الحمل واستكمال الانهاء .
(٣) تقليل عدد الحالات التى استخدمت عقار الثلاثي نيترات الجلسرول الى حالات التى استخدمت وسائل اضافية (استكماليه) لانهاء الحمل .
(٤) النسبة الواضحة للحالات التى كانت تعانى من الصداع بعد استخدام عقار ثلاثى نيترات الجلسرول .

(٥) لا يوجد تأثير لهذا العقار على النبض والضغط للسيدات المشتركات فى الدراسة .