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Original Scientific Paper

LABOR INDUCTION BY PROSTAGLANDINS: COMPARISON OF THE EFFICACY OF MISOPROSTOL AND DINOPROSTONE

Matija Šego[1], Mirna Došen[1], Petra Glad Štritof[2], Paulo Zekan[2], Marija Gotić Pavasović[2], Vladimir Blagaić[2] and Alenka Boban Blagaić[1]

[1]School of Medicine, University of Zagreb, Zagreb, Croatia;
[2]Department of Obstetrics and Gynecology, Sveti Duh University Hospital, Zagreb, Croatia

SUMMARY – In developed countries, almost every fourth woman in labor is induced with the aim of stimulating uterine contractions before the spontaneous onset of labor. The aim of this retrospective study carried out at the Department of Gynecology and Obstetrics, Sveti Duh University Hospital was to compare the efficacy of using two prostaglandin preparations, misoprostol and dinoprostone, in labor induction. A total of 200 female subjects were divided into 2 groups, a group induced by misoprostol (N=100) and a group induced by dinoprostone (N=100). The criteria for inclusion in the study were women with a live fetus admitted for programmed or indicated induction. The exclusion criteria were the post-cesarean section condition and the fetus in a breech position. The results of the study showed that the use of misoprostol significantly shortened the duration of labor and reduced the risk of cesarean delivery compared to dinoprostone. Finally, the research showed the advantage of using misoprostol in the induction of labor compared to the use of dinoprostone, which along with its stability at room temperature, affordability and wide availability make it a good and safe agent for labor induction.

Keywords: *Labor induction; Misoprostol; Dinoprostone; Duration of labor; Cesarean section*

Introduction

In developed countries, roughly 25% of births are nowadays induced[1,2]. Induction of labor goal is to stimulate uterine contractions before the spontaneous onset of labor. The advantages of labor induction must be evaluated against the potential hazards to both the mother and the fetus[3]. Prostaglandin (PGE)1 (misoprostol), PGE2 (dinoprostone) and oxytocin as pharmacological inducers, along with amniotomy and mechanical dilatation with a balloon catheter are the most commonly utilized techniques for inducing labor. Indications for induction of labor are numerous and depend on the gestational age, diseases of the mother and the fetus, and the most common among them are gestation above 41 weeks, Rh immunization, intrauterine growth restriction, oligohydramnios, polyhydramnios, gestational hypertension, gestational diabetes and other maternal chronic illnesses.

Correspondence to: *Vladimir Blagaić, MD*, Department of Obstetrics and Gynecology, Sveti Duh University Hospital, Sveti Duh 64, HR-10000 Zagreb, Croatia
e-mail: vladimir.blagaic@gmail.com

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Prostaglandins have been used in labor induction since the 1970s[4]. Due to the rapid metabolism of endogenous prostaglandins, synthetic analogs have been created which are characterized by longer bioavailability. Synthetic analogs of PGE1 (misoprostol) and PGE2 (dinoprostone) are important pharmacological agents used in labor induction, causing softening of the cervix (so-called preinduction) and uterine contractions[5]. Although both misoprostol and dinoprostone are commonly used, the best choice is still controversial.

Misoprostol is a synthetic PGE1 analog which was first developed for gastric ulcer treatment and prevention. It is also recognized in gynecology as an effective agent for labor induction, prevention and treatment of postpartum hemorrhage, and induction of abortion. Therefore, it is included in the World Health Organization Model List of Essential Medicines[6]. The mechanism of action includes collagenase activation, remodeling of extracellular matrix, and stimulation of uterine contractions. It can be administered orally, sublingually, vaginally and rectally. Misoprostol is affordable, stable at room temperature, and widely available. Misoprostol, when administered orally, has been demonstrated in multiple studies to be an effective strategy for inducing labor, comparable to PGE2 and oxytocin[7-9].

Dinoprostone is a PGE2 analog. Different formulations for local use of dinoprostone have been developed. The available types are intravaginal tablets or suppositories, intracervical or intravaginal gels in a single-use syringe, and sustained-release intravaginal inserts. Its main pharmacological effect is stimulating the maturing of the cervix and stimulation of uterine contractions. Rapid absorption of dinoprostone can cause uterine hyperstimulation. The effects of applied dinoprostone gel (intravaginal or intracervical) are almost impossible to reverse in case of side effects after its application[10,11].

Possible side effects of misoprostol and dinoprostone

The number of doses, the method of drug administration, and factors related to the mother influence the risk of adverse effects. Tables 1 and 2 show possible side effects related to the use of misoprostol and dinoprostone. The side effects of misoprostol are classified into three groups, i.e., very common (may occur in more than 1 in 10 people), common (may occur in less than 1 in 10 people), and less common (may occur in less than 1 in 100 people)[12].

Table 1. Misoprostol side effects

Very common	Common	Less common
Meconium stained amniotic fluid	Uterine hyperstimulation	Low Apgar index
Postpartum hemorrhage	Diarrhea	Fetal heartbeat disorder
	Nausea	
	Vomiting	
	Chills	
	Fever	

Table 2. Dinoprostone side effects

Very common	Common	Rare	Very rare
• Fetal heartbeat disorder • Newborn stress • Low Apgar index • Nausea • Vomiting • Diarrhea	• More frequent, stronger and longer lasting contractions • Feeling of warmth in the womb • Fever	• Severe blood clotting disorder • Chills	• Hypersensitivity reactions • Sudden separation of the placenta, rapid dilatation of the cervix, rupture of the uterus • Stillbirth, death of a newborn • Pulmonary embolism with amniotic fluid • High blood pressure • Bronchospasm • Asthma • Back pain

Side effects of dinoprostone are classified into four groups, i.e., very common (may occur in more than 1 in 10 people), common (may occur in less than 1 in 10 people), rare (may occur in less than 1 in 1000 people), and very rare (may occur in less than 1 in 10,000 people)[10].

General and specific research goals

The general aim of the research was to determine the effect of applied misoprostol and dinoprostone on the induction and outcome of labor. The specific goals of the research were as follows:

1) to compare the duration of labor between the study groups induced with misoprostol and dinoprostone;
2) to compare the mode of delivery between the groups: vaginal (with or without instrumental completion) or cesarean section; and
3) to compare the frequency of intrapartum occurrence of meconium stained amniotic fluid between the groups.

Subjects and Methods

Subjects

This was a retrospective study conducted at the Department of Obstetrics and Gynecology, Sveti Duh University Hospital in Zagreb. It included pregnant women who gave birth in the period from August 25, 2020 until September 22, 2021. A total of 200 pregnant women were included in the research. Data on pregnant women were collected from the hospital database. The local Ethics Committee approved this research (reg. no. 01-03-285/6 as of February 9, 2022).

The study inclusion criteria were women with a live fetus admitted for programmed or indicated induction. The exclusion criteria were previous cesarean section and the fetus in a breech position. Contraindications to misoprostol use are kidney failure (glomerular filtration rate <15 mL/min/1.73 m^2), suspicion or proof that the fetus is at risk (for example, failed non-stress or stress test, meconium stained amniotic fluid or form of fetal distress or fetal distress in the history), if oxytocin or other labor induction drugs were used before misoprostol administration, hypersensitivity to prostaglandins, disproportion between the size of the child's head and the mother's pelvis, polyhydramnios, multiparous women with six or more pregnancies, previous cesarean section or uterine operations, fetal distress, uterine bleeding during the current pregnancy, toned uterus, and placenta previa[10].

Research design

Study subjects were divided into 2 groups, i.e., the group induced by misoprostol and the group induced by dinoprostone, and each group contained 100 women. The first group of subjects used the magistral preparation of misoprostol (PGE1) as a labor induction agent, which was made in the hospital pharmacy (Mispregnol tablets 400 μg, Nordic Pharma, The Netherlands) in the form of a powder that the women received *per os*. The drug was prescribed as follows: women took 25 μg of misoprostol every 2 hours up to a maximum of 8 doses or until regular uterine contractions appeared. To continue and intensify labor induction, amniotomy and oxytocin infusion were used, which were applied not earlier than 4 hours after the last dose of misoprostol. If regular contractions did not occur even after the administration of misoprostol, amniotomy and oxytocin infusion, cesarean section was performed under the clinical presentation of failed induction.

In the second group of subjects, PGE2 analog, dinoprostone preparations, were used as labor induction agents, i.e., intracervical gel (Prepidil 0.5 mg/3 g endocervical gel, Pfizer Croatia d.o.o.) or intravaginal gel (Prostin E2 2 mg gel for delivery, Pfizer Croatia d.o.o.). The type of medicine was determined by the obstetrician depending on his subjective assessment of the Bishop score (Prepidil in case of lower Bishop score and Prostin in case of higher Bishop score). In all study subjects, dinoprostone was administered every 6 hours until a maximum of 3 doses or the appearance of regular uterine contractions. Amniotomy and oxytocin infusion were used to continue and intensify labor induction, which were not used earlier than 6 hours after the last dose of dinoprostone. If regular uterine contractions did not occur after 3 doses of dinoprostone, amniotomy and oxytocin infusion, cesarean section was performed under the clinical presentation of failed induction.

Table 3. Maternal age

	Misoprostol		Dinoprostone		p-score
	Mean	95% CI	Mean	95% CI	
Age (years)	31.9	30.9-32.9	30.5	29.4-31.6	0.08

95% CI = 95% confidence interval

Measured parameters

The following variables were determined:

- maternal age in years;
- maternal parity (primiparous or multiparous);
- Bishop score at the beginning of induction;
- appearance of meconium stained amniotic fluid during labor as a potential sign of fetal distress;
- duration of labor (time from application of the first agent to delivery) in hours; and
- mode of delivery (vaginal delivery or cesarean section).

Statistical data analysis

Continuous variables were presented as arithmetic mean with a 95% confidence interval (95% CI), and categorical variables as percentages. Student's t-test was used to compare continuous variables, and χ^2-test was used to compare categorical variables. For the purpose of further data analysis, binomial and multivariable regression analyses were used. A p-value of less than 0.05 was considered statistically significant. Microsoft Excel was used for data collection, and Jamovi 2.3.16 was used for statistical processing.

Results

A total of 200 pregnant women were included in the research, 100 in each group. Age, parity and Bishop score at the start of induction for each group are shown in Tables 3, 4 and 5.

Maternal age

Data on maternal age were presented as mean values and 95% CI. Maternal age between the groups was compared by Student's t-test. These results showed that there was no statistically significant age difference between the two groups (Table 3).

Bishop score at the beginning of induction

Data on Bishop score at the start of induction were presented as absolute numbers. Bishop score at the beginning of induction between the groups was compared by χ^2-test. According to the results, there was no statistically significant difference in Bishop score at the beginning of induction between the two groups (Table 4).

Table 4. Bishop score at the beginning of induction

Bishop score	Misoprostol	Dinoprostone
<5	79	77
≥5	21	23
p-score	0.733	

Maternal parity

Data on maternal parity were presented as absolute numbers. Maternal parity was compared between the groups with the χ^2-test. The results showed a statistically significant parity difference between the two study groups (Table 5).

Table 5. Maternal parity

	Misoprostol	Dinoprostone
Primiparous women	67	82
Multiparous women	33	18
p-score	**0.015**	

Due to statistically significant difference in parity between the groups, in further analysis of outcome we used logistic regression analysis for categorical variables and multivariable regression analysis for continuous variables (Tables 6, 7 and 8).

Multivariate regression analysis of labor duration

Table 6 shows coefficient values in the multivariate linear regression model with the associated 95% CI.

Table 6. Multivariate regression analysis of labor duration

Variable	Coefficient with 95% CI	p-score
Constant	13.59 (6.41, 20.8)	<0.001
Drug*	2.50 (0.11, 4.89)	**0.041**
Age	0.06 (-0.16, 0.28)	0.59
Parity*	–3.15 (-5.68, -0.61)	**0.015**

*Categorical variables were coded as follows: drug (misoprostol=0, dinoprostone=1); parity (nullipara=0, multipara=1); 95% CI = 95% confidence interval

From the above analysis, it is clear that despite the statistically significant difference between the groups in the input variable of parity, the use of misoprostol statistically significantly reduced the duration of labor compared to dinoprostone (p=0.041), and multiparous women had a statistically significantly shorter labor than primiparous women (p=0.015). The age of the woman did not affect the duration of labor (Table 6).

Logistic regression analysis for mode of delivery

Table 7 shows the values of odds ratio in the logistic regression model with the associated 95% CI. The stated odds ratio is the ratio of the odds of cesarean section compared to vaginal delivery.

Table 7. Logistic regression analysis for mode of delivery

Variable	Odds ratio with 95% CI	p-score
Constant	0.06 (0.01, 0.49)	0.01
Age	1.04 (0.98, 1.11)	0.21
Drug*	3.29 (1.60, 6.76)	**0.001**
Parity*	0.52 (0.24, 1.14)	0.10
Bishop score	0.57 (0.23, 1.43)	0.23

*Categorical variables were coded as follows: drug (misoprostol=0, dinoprostone=1); parity (nullipara=0, multipara=1); 95% CI = 95% confidence interval

The type of drug used had a statistically significant effect on the outcome of labor. Specifically, patients who received dinoprostone had a 3.29 times greater risk of completing delivery by cesarean section than those who received misoprostol (Table 7). Other input variables did not have a statistically significant effect on the mode of delivery.

Logistic regression analysis for the presence of meconium stained amniotic fluid

Table 8 shows the values of odds ratio in the logistic regression model with the associated 95% CI. The given odds ratio is the ratio of the presence *versus* absence of intrapartum meconium stained amniotic fluid.

Table 8. Logistic regression analysis for meconium stained amniotic fluid

Variable	Odds ratio with 95% CI	p-score
Constant	0.05 (0.00, 0.58)	0.02
Age	1.05 (0.97, 1.13)	0.22
Drug*	0.89 (0.40, 2.01)	0.79
Parity*	0.61 (0.24, 1.54)	0.29
Bishop score	0.80 (0.28, 2.28)	0.68

*Categorical variables were coded as follows: drug (misoprostol=0, dinoprostone=1); parity (nullipara=0, multipara=1); 95% CI = 95% confidence interval

The type of drug used for induction, gestational age, parity and Bishop score did not have a statistically significant role in the frequency of meconium stained amniotic fluid occurrence during labor (Table 8).

Discussion

Childbirth is both a physical and an emotional challenge for a woman. Induction of labor, as one of the most common obstetric procedures, affects the time of delivery for the sake of the wellbeing of the mother and/or the child. Therefore, it is indicated when the risk of waiting for a spontaneous labor outweighs the risk of the induction procedure itself, and its goal is to achieve a successful vaginal labor that has numerous benefits for both the mother and the child.

Misoprostol and dinoprostone, along with amniotomy and mechanical dilation with a balloon catheter,

play an important role in labor induction as one of the most common obstetric procedures.

A Cochrane study from 2014, which analyzed 75 randomized controlled trials conducted on 13,793 women, indicates that orally administered misoprostol (PGE1) has a comparable effect to other pharmacological and non-pharmacological labor inducers[13] and has been used as a potent pharmacological inducer of labor for decades in European countries[14]. Despite this, in Croatia, only dinoprostone (PGE2) in the form of intravaginal and intracervical gel was (and still is) used as a pharmacological means of induction. Misoprostol was approved in Croatia by HALMED for induction of labor in 2018 (Angusta, Azanta Denmark A/S, Denmark), but was not available on the market until 2021. Even when Angusta appeared on the market, it was withdrawn very quickly due to defective product[15]. Currently, it is on the Croatian market again since April 2023.

This research presents the first results of oral administration of the magistral misoprostol preparation for induction of labor in Croatia, which was conducted at the Department of Obstetrics and Gynecology, Sveti Duh University Hospital. The study showed that orally administered misoprostol was an effective drug for labor induction. Orally administered misoprostol resulted in a shorter duration of labor compared to the administration of dinoprostone. Compared to women whose labor was induced with dinoprostone, women whose labor was induced with orally administered misoprostol had a lower risk of completing the delivery by cesarean section, which is particularly significant because of the increasing rate of cesarean section in Croatia. With a cesarean section rate of 271.8/1000 in 2020, Croatia is comparable to other European countries. The cesarean section percentage of 27.6% in 2021 in Croatia revealed an increase compared to 2019, when the cesarean section percentage was 26.6%[16]. We associate a lower cesarean section rate with the use of misoprostol with less fear and pain and, as a result, better cooperation of the mother during labor. The repeated administration of misoprostol in a dose of 25 μg leads to a more gradual achievement of contractions, which enables the woman in labor to gradually adapt to the pain caused by labor. Such a way of acting is important because fear and pain in labor are one of the most important causes of failed vaginal deliveries and completion of labor by cesarean section[17]. Also, women in labor whose labor was induced with misoprostol seemed to be more satisfied with the method of administration of the drug and its gradual effect, which is why they required less analgesia (*per os*, i.v., i.m., inhalation and epidural analgesia) and were more relaxed with the possibility of walking, going to the toilet, etc., during induction (subjective assessment of us students as observers and other medical staff). The use of misoprostol *per os* resulted in greater satisfaction of the women compared to the use of intracervical or intravaginal dinoprostone gel, which is also in accordance with literature data[18].

Finally, the research showed the advantage of using misoprostol in the induction of labor compared to the use of dinoprostone, which along with its stability at room temperature, affordability and wide availability make it a good and safe means for labor induction. All of the above is consistent with literature data[19].

The main limitations in this research were the retrospective nature of the research, parity difference between the groups, and insufficient extended data on the possible fetal and maternal complications (standard data were used, not extended data recorded in prospective studies).

The scientific contribution of this research is the fact that this is the first retrospective study of the effect of peroral administration of misoprostol in the Croatian population of women in labor, which confirmed its benefit in labor induction, and that it was used as a magistral preparation in the smallest doses that achieved full pharmacological effect with the least incidence of side effects.

Conclusions

Our results showed orally administered misoprostol to be an effective method of labor induction. Compared with dinoprostone, orally administered misoprostol has a lower cesarean completion rate and results in a shorter duration of labor. All study results were consistent with literature data. The frequency of the meconium stained amniotic fluid during childbirth did not significantly differ between the groups of mothers.

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Sažetak

INDUKCIJA POROĐAJA PROSTAGLANDINIMA: USPOREDBA UČINKOVITOSTI MIZOPROSTOLA I DINOPROSTONA

M. Šego, M. Došen, P. Glad Štritof, P. Zekan, M. Gotić Pavasović, V. Blagaić i *A. Boban Blagaić*

U razvijenim se zemljama gotovo kod svake četvrte rodilje inducira porođaj s ciljem stimulacije kontrakcija maternice prije spontanog početka porođaja. Cilj ovog retrospektivnog istraživanja provedenog na Klinici za ginekologiju i porodništvo Kliničke bolnice „Sveti Duh“ bila je usporediti učinkovitost primjene dvaju prostaglandinskih pripravaka, mizoprostola i dinoprostona, u indukciji porođaja. Ukupno je 200 ispitanica bilo podijeljeno u 2 skupine: skupina inducirana mizoprostolom (N=100) i skupina inducirana dinoprostonom (N=100). Kriterij uključivanja u istraživanje su bile žene sa živim fetusom primljene zbog programirane ili indicirane indukcije. Isključni kriteriji su bili stanje nakon carskog reza i plod u stavu zatkom. Rezultati studije su pokazali da je primjena mizoprostola značajno skratila trajanje porođaja te smanjila rizik od dovršenja porođaja carskim rezom u usporedbi s dinoprostonom. Rad je pokazao prednost primjene mizoprostola u indukciji porođaja u usporedbi s primjenom dinoprostona, što ga uz njegovu stabilnost na sobnoj temperaturi, pristupačnost i širokoj dostupnosti čine dobrim i sigurnim sredstvom za indukciju porođaja.

Ključne riječi: *Indukcija porođaja; Mizoprostol; Dinoproston; Trajanje porođaja; Carski rez*