Interruption of a study of cervical ripening with isosorbide mononitrate due to adverse effects

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Summary

Purpose of investigation: The objective of this study was to evaluate cervix length and the presence of cervical gland area (CGA) in ultrasounds performed before and after the administration of vaginal isosorbide mononitrate (IMN) for cervical ripening. *Methods:* We performed an observational, descriptive, and longitudinal study of pregnant patients indicated for labor induction and with a Modified Bishop Score (MBS) lower than six. For cervical ripening, 40 mg of vaginal IMN was administered at 0, 16, and 24 hours after the initiation of cervix preparation. *Results:* After enrolling 11 patients, the study had to be discontinued due to adverse effects. Three patients requested that they be withdrawn. Headaches were reported by all patients. Nausea, dizziness, dyspnea, and vomiting were also reported. The average cervical lengths at 0, 16, 24 and 36 hours were 27.6, 27.7, 25.9, and 23.0 mm, respectively. CGA disappeared in one of seven patients. *Conclusions:* The use of IMN appears to increase the MBS, slightly reducing cervical length without altering the appearance of CGA. Considering the importance of maternal wellbeing during labor, the routine use of IMN cannot be recommended for cervical ripening in the third trimester due to the frequency and intensity of side-effects.

Key words: Cervical ripening; Isosorbide; Adverse effects; Cervical length measurement; Induced labor.

Introduction

According to the World Health Organization, cesarean sections (C-sections) should ideally account for no more than 15% of all deliveries. However, rates of surgical deliveries are often much higher than this standard, especially in Brazil [1]. Studies analyzing patients submitted to a C-section have found that the failure to induce labor is one of the main indications for surgical birth, occurring particularly among patients with a Modified Bishop score (MBS) lower than six [2-7]. It is estimated that 20% of pregnant women need to have their labor induced due to maternal or fetal reasons [8].

Several cervical ripening treatments have been tested, but the existing literature does not always agree about the efficacy of such treatments, indications, side-effects, risks, and the criteria indicating their selection. The ideal method should be fast and effective in terms of inducing cervical ripening, with minimal maternal and fetal side-effects, and it should be compatible with use at home. Currently, the principal method of inducing labor in patients with unfavorable cervixes involves the use of prostaglandins and their derivates. This method has the characteristic of causing cervical ripening, increasing the chances of success in birth induction; however, the method also causes uterine contractions that may lead to hypersystole and hypertonia, requiring inpatient fetal vitality monitoring.

Isosorbide mononitrate (IMN) was originally used for the prevention and treatment of precordial pain [9], but over the past years, IMN has been administered as a pre-induction cervical preparation method. IMN is a precursor of nitric oxide (NO), which acts on the cervix by stimulating enzyme pathways that release prostaglandins and guanosine monophosphate, thus generating morphological alterations in the cervix similar to the alterations associated with spontaneous cervical ripening [10, 11]. The recent literature reports that this method has better results as compared with a placebo [12, 13], as well as having lower tachisystole levels [8, 9] when compared with prostaglandins. Nevertheless, the literature has not yet reached a consensus about optimal dosage, nor has it satisfactorily determined the incidence and intensity of side-effects. Twenty-four hours after the administration of 40 mg of vaginal IMN, Bullarbo *et al*. [12] found 22% of patients to have begun labor, while Osman *et al*. [8], after 24 hours and two 40 mg doses, found 55% of the patients either in labor or having a MBS less than or equal to six. Headache is the most commonly reported side effect, although there is great disagreement regarding its frequency, which may vary from 11 to 88% of cases according to different publications [8, 12-14]. The intensity of the headache is also contradictory: while some authors classify it as mild [8], other authors refer to it as moderate [12].

The evaluation of the method's efficacy is based on the increase of MBS, a method that likely introduces significant intra-examiner variation due to the subjective nature of the criteria that compose the score (position, consistency, effacement, dilation, and fetal station) [15]. Cervical length, as evaluated by endovaginal ultrasound, is effective in predicting the success of full-term labor induction, and it may constitute a more objective method of evaluation. According to the literature, a cervical

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length of less than 27 mm is associated with successful labor induction in 76% of patients [16-24].

The high rate of C-sections performed in Brazil, as well as the lack of consensus regarding both the best cervix preparation method and the criteria that should guide cervix preparation, motivated this study on the use of vaginally-administered IMN in cervical ripening. The study's objectives were to compare the ultrasound (US) characteristics of the uterine cervix before and after the use of vaginal IMN in cervical ripening and to assess the efficacy and safety of the treatment.

Materials and Methods

The study, approved by the Ethics Research Committee of São Paulo Federal University (UNIFESP), used both observational and descriptive methods. Data were collected in 2009 at the University's Obstetric Center. Patients with clinical indications for labor induction were invited to participate in the research when the following inclusion criteria were met: modified Bishop score of less than six; gestational age greater than 32 weeks; fetal vitality preserved for a live fetus (evaluated by normal cardiotocography, obstetric US and umbilical artery Doppler velocimetry); and an ability to understand the nature of the study. Patients were excluded when there were contraindications for vaginal delivery; two or more previous C-sections; breech presentation; chronic headache; if there were contraindications for the use of isosorbide mononitrate; or when the fetal or maternal condition required delivery in less than 72 hours. Patients who satisfied the inclusion and exclusion criteria were invited to voluntarily participate in the study and were carefully informed of the study objectives and procedures, as well as the medication's mechanism of action, safety, and potential side-effects. After signature of the informed consents, the patients' data were recorded in a spreadsheet.

Prior to the administration of the medication, an endovaginal US was performed to evaluate the longitudinal length of the uterine cervix and the presence or absence of endocervical glands. This procedure was performed using a SonoAce 8000 Live (Medison, Seoul, Korea) machine with a 7.5 MHz endovaginal transducer. A subsequent vaginal US evaluation was performed following the vaginal administration of 40 mg IMN. Sixteen hours after the first treatment, the cervical evaluation and US were repeated, and another dose of IMN was administered if the patient's MBS was below six. Twenty-four hours after the first dose of the test medication, a final evaluation was performed, and a new dose of the medication was administered if the MBS was below six. After 36 hours, misoprostol was administered vaginally in cases in which the patient's MBS was below six and no contraindications were present. In cases of MBS greater than six, patients were given oxytocin instead.

During each evaluation, patients were questioned about possible adverse events such as headaches, dizziness, palpitations, nausea, vomiting, abdominal pain, and vaginal bleeding. To evaluate the headaches' intensity, we used a numeric pain scale (1 to 10).

Results

A pilot study was performed to determine the sample size that would be required for a full-scale study. However, due to the intensity of the side effects, the research had to be discontinued after enrolling only 11 patients. Due to the small number of cases, we report the results in a descriptive manner.

The average patient age was 25 years, varying from 19 to 33 years old. The average gestational age was 40 weeks and two days, varying from 32 weeks and six days to 41 weeks and five days. This study included eight nulliparae, two primiparae and one multipara. In ten cases (90.9%) the indication for cervical preparation was post-term gestation and in one case the indication was fetal death.

The initial analysis of each patient's MBS through vaginal examination, longitudinal cervix length, and endocervical glands (CGA) was performed by the same examiner via endovaginal US. The average initial MBS was 2.6 (ranging from 1-4), with a standard deviation of 0.9. We observed that CGA was present in seven out of the 11 patients, and no correlation was observed between the presence of CGA and the patient's MBS. The average functional cervical length was 27.6 mm. Sixteen hours after the first dose of IMN, average MBS increased from 2.6 to 3.9. Patient 3 presented an MBS increase from 4 to 6, indicating the need for intravenous oxytocin. Patient 8 was in labor. The remaining nine patients all had an MBS score lower than 6. Out of the 11 patients, nine (82%) experienced headaches, and three (27%) asked to withdraw from the study because of this side-effect (patients 2, 3, and 5). To evaluate pain intensity, patients were asked to rate their pain on an analogical scale (0-10). On average, they reported pain of 5.7 during the first reevaluation. The patients who withdrew from the study reported the following intensities in their headaches, respectively: 5, 6, and 10. In addition to headaches, the following side-effects were each cited once: nausea, vomiting, dizziness, and hyperthermia. Out of the remaining patients with cervixes resistant to induction, two asked to leave the study (patients 2 and 5), opting for vaginal administration of misoprostol instead. One woman with favorable cervix conditions also asked to withdraw from the study (patient 3) and opted to induce labor with oxytocin. One patient was in labor during the first reevaluation, and seven patients remained for the continuation of cervical evaluation. Following confirmation of fetal vitality, a new IMN dose was administered to these seven women. The US evaluation did not demonstrate alterations in average cervical length, which stayed at 27.6 mm. To measure the uterine cervix length, three measurements were taken during each evaluation and then averaged. This method was supported by the intraclass correlation coefficient (ICC). At 0, 16, and 24 hours after the initiation of treatment, the following measurements were obtained, respectively: 0.978, CI (95%) [0.941; 0.994]; 0.993, CI (95%) [0.980; 0.998]; and 0.993, CI (95%) [0.971; 0.999]. The CGA remained visible in six of the seven patients in whom CGA was revealed during the US at the beginning of the cervical preparation. Assessing patients' blood pressure, we observed that mean arterial pressure (MAP) tended to decrease. In the initial evaluation, the average MAP was 87.64 mm Hg. The average MAP was 81.84 mm Hg two

Table 1. — *Characterization of physical and ultrasound exams at 0, 16, 24, and 36 hours.*

Patient	Bishop				CGA				Cervical length			
	0	16	24	36	0	16	24	36	0	16	24	36
1	3	5	5	L	Absent	Absent	Absent	L	36	37.7	38	L
2	2	2	I	I	Absent	Absent	W	W	36	33.3	W	W
3	4	6	I	I	Present	Absent	W	W	28.3	27.3	W	W
4	3	3	4	L	Present	Present	Present	L	26	26	23.7	L
5	2	2	I	I	Present	Present	W	W	25	25	W	W
6	4	4	5	VD	Absent	Absent	Absent	VD	19.3	21	20	VD
7	1	8	-	CD	Absent	L	–	CD	22	L	-	CD
8	2	4	8	CD	Present	Present	Present	CD	24.3	19.7	19.7	CD
9	3	4	AFD	CD	Present	Present	AFD	CD	30	29.7	AFD	CD
10	2	2	3	3	Present	Present	Present	Present	29	29	28	23
11	3	3	4	L	Present	Present	Present	L	28	28	27.6	L
Average	2.6	3.9	4.8	3					27.6	27.6	26.2	23

L = labor; VD = vaginal delivery; CD = cesarean delivery, AFD = acute fetal distress; I = patient requested study withdrawal.

hours later, 77.33 mm Hg four hours later, and 78.87 mm Hg six hours later. The average maternal heart rate increased after drug administration. At the successive readings, women's average heart rates were, respectively, 85, 92, 97, and 99 beats per minute. Twenty-four hours into the study, the average MBS was 4.8, indicating a 0.9 increase from the 16-hour reevaluation and a 1.2 increase since the initial physical exam. One patient (8) was in labor, and the unit shift staff recommended that she be given intravenous oxytocin. During the vitality evaluation, one of the study patients (patient 9) presented an altered cardiotocography, indicating the need for a C-section. In that case, the presence of meconium had been detected in the amniotic fluid. Among the remaining patients, average cervical length decreased from 27.6 to 26.2 mm, and there was no reduction in the prominence of the CGA. Two patients (patients 1 and 6), initially asymptomatic, reported headaches with a 5/10 intensity after 24 hours. During this same period, another patient described worsening headache symptoms with no improvement despite having received oral analgesics. However, this patient reported the same intensity on the pain scale (8/10). Drowsiness and dyspnea were reported by one of the patients. A new dose of IMN was administered to the five patients with MBS score lower than 6. After 36 hours, one patient (patient 6) had delivered her baby prior to the final cervical evaluation. Three patients were in labor (patients 1, 4 and 11) and receiving oxytocin, as recommended by the hospital shift staff. One of the patients (patient 10) maintained an MBS lower than 6. Her score did not increase from the second reevaluation, remaining at 3. Her cervix showed a reduction of 5 mm in average length, and the CGA remained present. The administration of vaginal misoprostol was indicated after the evaluation of fetal vitality (Table 1).

This method's efficacy was evaluated by looking at alterations in MBS and cervical length, which was the central objective of this study. Considering that patients 2, 3 and 5 were excluded from the study due to side-effects, only the remaining eight patients were considered for the analysis.

Three vaginal deliveries and five cesarean deliveries were performed. The average time from the beginning of cervical preparation with IMN to delivery was 50 hours and 30 minutes. Considering only vaginal deliveries, the average time was 60 hours and 33 minutes. The average weight of the babies was 3,405 g and the average Apgar score was 8.75 at the first minute and 9.5 at the fifth minute (Table 2).

Discussion

Recently published data regarding cervix preparation with IMN [8, 25] was the motivation for this study. Those preliminary results indicated that the drug is low risk and does not increase fetal distress, suggesting that IMN could be a good alternative for the outpatient setting.

This research was initiated with a pilot study that, in agreement with the literature [8,25], demonstrated that IMN is an efficacious method for preparing the cervix. However, in this sample the side-effects were intense and lasting, making continuation of the research unfeasible. The principal side-effects of the drug were headaches, which were mentioned by all patients and cited by three as their reason for withdrawing from the study. These complications forced us to interrupt the protocol and report these adverse events to the Research Ethics Committee.

Regarding cervical changes with IMN, our results demonstrated an MBS increase of 1.3 ± 1.9 after 16 hours and 2.2 ± 1.7 after 24 hours. These data accord with the findings of the study with the largest sample size in the current literature [8], which reported increases of 1.36 ± 1.26 and 1.35 ± 1.15, respectively. Through the exclusive use of the medication, two patients, or 18% of the study sample, reached MBS values greater than or equal to six. Five patients, or 45% of the sample, were in labor before all of the reevaluations could be performed (at 16, 24, or 36 hours). Four of the patients used oxytocin, which precluded a reliable MBS assessment. Therefore, out of a total of 11 patients, seven patients experienced successful cervical preparation or labor induction (63.6%). Based on

Table 2. — *Perinatal outcome of the cervical preparation with isosorbide mononitrate.*

Patient	Type of delivery	ΔT	Weight (g)	Apgar
1	CD	49 h 45 m	3550	9/10
2	CD	27 h	3780*	9/9
3	VD	32 h 40 m	2050*	OF
4	VD	80 h 20 m	3295	8/9
5	CD	47 h 30	2940*	9/ 10
6	VD	37 h 30 m	3570	9/10
7	CD	51 h 45 m	3450	9/10
8	CD	48 h 30	3195	8/9
9	CD	26 h 14 m	3130	9/9
10	VD	70 h 30 m	3225	9/10
11	CD	46 h 20 m	3830	9/9
Average	–	50 h 30 m**	3405**	8.75/9.5**

*Patients excluded from the study within 16 hours. These patients were submitted to induction with misoprostol.
**To calculate the average, the excluded patients were not considered.
CD = cesarean delivery; VD = vaginal delivery.

Table 3. — *Incidence of side-effects after administering isosorbide mononitrate.*

Symptom	N	T (h)	Trimester	Headache	Nausea	Dizziness
Thomsone *et al*. [14]	66	3	1st	23%	5%	5%
Chanrachakul *et al*. [32]	35	24	3rd	7.3%	5.5%	2.6%
Li *et al*. [33]	21	3	1st	33%	17%	7%
Ekerhovd *et al*. [34]	30	4	3rd	80%	3.3%	20%
David *et al*. [35]	15	3	1st	0	0	0
Osman *et al*. [8]	200	36	3rd	88%	19%	8.7%
Bullarbo *et al*. [12]	100	24	3rd	88%	19%	0
Rameez *et al*. [36]	78	72	3rd	60%	0	0
Habib *et al*. [9]	51	36	3rd	11.7%	0	0
Bollapragada *et al*. [25]	130	48	3rd	66%	17%	16%

N = sample size; T = time of evaluation after administering the test drug.

evidence that reduced cervical length is associated with premature labor and that prior to labor induction reduced cervical length is associated with a higher success rate in inducing labor, a decrease in the cervical length was expected after IMN-induced cervical ripening. However, upon evaluating the study results, we observed no significant alteration in cervical measurements, which did not meet our initial expectations.

In 1988, Sekya *et al*. suggested that there is a correlation between CGA disappearance and the beginning of labor [26]. In agreement with this analysis, Asakura et al. demonstrated in 2009 that CGA absence should be considered as an independent factor in predicting labor in pregnant women suspected of premature labor [27, 28]. We hypothesized that IMN-induced cervical inflammatory alterations could lead to diminished CGA visibility. However, this hypothesis was not confirmed in our study. It is important to note that the small sample size of this study limited the evaluation.

Analysis of the interval between the beginning of treatment and the delivery was hindered by the high frequency of side-effects. These adverse effects caused patients to become dissatisfied and ask to be withdrawn from the study, which then resulted in a high rate of surgical labor outcomes (7/11). Until the 21th century, psychopathological explanations of primary headaches assumed that they stemmed from brain vasodilatation. However, the most currently accepted theory is that headaches originate from an inflammatory alteration and that vasodilatation is a secondary effect of this process [29]. Previous studies have demonstrated that roughly 42% of cardiac patients initially reported experiencing headaches after taking IMN orally [30]. Nevertheless, tolerance of the drug improved during the treatment, and the headaches tended to disappear [31]. This tolerance did not affect the drug's vascular dilation effect. In addition to being a strong vasodilator, IMN is an inflammatory precursor, which explains the high rate of side-effects found in the majority of publications on its workings. Data from the literature are in conflict regarding the side-effects of IMN when it is used for labor induction. While Thomson *et al*. [14] found a headache incidence of 23%, Osman *et al*. [8] reported an incidence of 88%.

Variations in administration route and pregnancy status could explain the different incidences of this side-effect. The vaginal route of administration results in faster absorption than the oral route, therefore potentially leading to a greater frequency of side-effects. When analyzing headache incidence distribution compared to gestational age, we observed that headaches were more frequent in studies performed during the third trimester compared to those performed during the first three months (Table 3) [32-36].

Past the halfway point in the pregnancy, especially during the third trimester, a fourfold increase in vasopressinase occurs. This is an aminopeptidase produced by the placenta that degrades vasopressin, a molecule that stimulates vascular contraction and elevates blood pressure [37]. The use of IMN during the third trimester probably accentuates the vasodilatation state caused by reduced vasopressin levels. This phenomenon could explain the greater incidence of headaches in that period when compared to the first trimester of pregnancy. Similarly, such vasodilatation is probably also responsible for the decreased blood pressure and increased heart rates observed after the medication's administration. In addition to recording headaches in 100% of the cases, this study found that 18% of patients suffered from nausea and 9% from dizziness, similar to findings reported in the literature (Table 3).

Regarding fetal vitality evaluations, one patient had an alteration in her cardiotocographic readings showing the presence of meconium during labor. Reviewing the side-effects described in the literature, we found no reports of fetal distress associated with IMN. Since the case in this study was an isolated event, it did not seem to be related to the use of medication. Labor represents a decisive, transitional period for the patient and the fetus. It is an emotional time characterized by intense maternal and familial involvement. In the context of human labor care, labor induction, even when necessary, must be a peaceful, efficient, and satisfactory procedure for the patient.

In our study, the use of IMN generated significant and intense side-effects. These side-effects, most notably

strong headaches during labor, caused both patients and their families intense discomfort and fear that other factors could be influencing the labor process and increasing the risks to mothers and babies. We also perceived that the medical team exhibited anxiety and insecurity in the presence of side-effects. This whole context certainly influenced the high rate of cesarean delivery reported in the study: seven out of 11 pregnancies (63.6%). It is important to note that the side-effect was so serious that we felt the study should be discontinued. While we made the decision to discontinue the research on ethical grounds, communicating these negative data is also an essential step.

In Brazil, patients are used to a high rate of cesarean deliveries. This lack of incentive to undergo vaginal delivery leads patients to tolerate less pain, including headaches. It is very important that obstetricians know about these findings, which, small sample size notwithstanding, concisely demonstrate the presence of side-effects. It is also important to highlight that IMN is a method intended for preparing the cervix, not inducing labor. Accordingly, it should not be utilized in patients who need to deliver in a short period of time, which also limits the conditions under which the use of this medication is indicated.

In conclusion, due to the intensity and frequency of side-effects, we cannot recommend the routine use of IMN to induce cervical ripening in vaginal delivery in patients who have already reached the third trimester of pregnancy.

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