

MISOPROSTOL VERSUS LAMINARIA FOR CERVICAL RIPENING IN PREGNANCIES WITH FETAL DEATH

MISOPROSTOL VERSUS LAMINÁRIA PARA PREPARO CERVICAL EM GESTAÇÕES COM MORTE FETAL

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ABSTRACT

Introduction

Among the several agents for cervical ripening studied worldwide, prostaglandins and laminaria tents have been shown to be safe and effective. Prostaglandins are more routinely used in the majority of the countries. However, in Brazil only PgE₁ methyl-analog (misoprostol) is commercially available, and its use in obstetrics has increased significantly because of its low cost compared to other prostaglandins, showing no loss in efficacy.

Methods

To evaluate the degree of cervical ripening using two different methods, a randomized and blind controlled clinical trial was carried out on 60 women who had fetal death, gestational age over 15 weeks and Bishop Index under 6, and were not in labor. They were allocated into two groups: one using a 200µg misoprostol tablet and the other a laminaria tent, which were inserted through the external cervical os, 24 hours before starting labor induction with oxytocin.

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Results

There were no significant differences in control variables nor in maternal side effects, but there were different effects on the cervix between the two groups. In the misoprostol group 78.9% of women delivered vaginally within the first 24 hours reserved for cervical ripening. Furthermore, the total amount of oxytocin used, time of hospitalization and total hospital costs were significantly lower in this group.

Conclusion

Both methods were effective and safe for cervical ripening. However misoprostol, in the amount and route used, showed efficacy not only as a method for cervical ripening, but also as an effective agent for labor induction in pregnancies with fetal death.

Index terms: misoprostol, laminaria, cervical ripening, fetal death, randomized controlled trials.

RESUMO

Introdução

Entre os vários agentes mundialmente estudados para o preparo cervical, as prostaglandinas e laminárias têm se mostrado seguras e eficazes. As prostaglandinas têm sido mais utilizadas na maioria dos países; entretanto, no Brasil apenas a PGE₁ metil-análoga (misoprostol) está disponível comercialmente, e seu uso em obstetrícia tem aumentado significativamente em virtude de seu custo mais baixo em relação às outras prostaglandinas, com eficácia comparável.

Métodos

Para avaliar o grau de modificação cervical obtido utilizando dois métodos distintos, foi realizado um ensaio clínico randomizado e cego com 60 gestantes que apresentaram morte fetal em gestação com mais de 15 semanas e índice de Bishop inferior a 6 e estavam fora de trabalho de parto. As gestantes foram alocadas em dois grupos: um utilizando um comprimido de 200µg de misoprostol e outro uma laminaria, inseridos por via intracervical 24 horas antes de iniciar a indução ocitócica.

Resultados

Não houve diferença entre as variáveis de controle, nem com relação às complicações maternas. No entanto, houve diferença de efeitos entre os dois grupos, e 78,9% das mulheres que utilizaram misoprostol evoluíram para parto durante as 24 horas reservadas para o preparo cervical. Além disso, neste grupo foram significativamente menores a dose de ocitocina utilizada, o tempo de internação e o custo hospitalar.

Conclusão

Ambos os métodos foram seguros e eficazes para o preparo cervical. Contudo, o misoprostol, na dose e via em que foi utilizado, demonstrou ser um método eficaz não só no preparo cervical, mas também na indução de parto na população estudada.

Termos de indexação: misoprostol, laminaria, preparo cervical, morte fetal, ensaios controlados aleatórios.

INTRODUCTION

Labor induction with an unripe cervix is a major challenge in modern Obstetrics. Bishop³ demonstrated that successful labor induction

depends on cervical conditions and developed the Bishop Index in order to evaluate cervical changes at the end of pregnancy, which are mainly due to the production of local prostaglandins^{7,9,11}.

The most suitable cervical ripening method should be non-invasive and cause changes similar to those that occur physiologically. Many biochemical and mechanical methods have already been applied in an attempt to reach this goal. Among the mechanical methods, the laminaria tent perhaps is the most important one (*Laminaria digitata* or *Laminaria japonica*). It is a dehydrated seaweed with hygroscopic properties, made into a cylinder-shape to be used as a cervical dilation device. The efficacy and safety of laminaria and other mechanical methods have already been proven recently⁵. Its mechanical action is a result of radial expansion and as it occurs slowly it causes no cervix muscle fiber damage. Laminaria has also a biological effect causing a foreign body reaction, which in turn releases prostaglandins.

However, the most currently used methods are those with a biochemical mode of action, especially the prostaglandin. One of these prostaglandins is misoprostol [Cytotec®], a PgE₁ methyl-analog, used not only in developing but also in developed countries. Apart from the fact that PgE₂ is not commercially available in Brazil, misoprostol is cheaper, thermally stable, and easily stored. This drug was first used, in Brazil, in high doses by oral administration and only for fetal death¹⁵. Its side effects were mainly in the gastrointestinal tract; however, nowadays, repeated low dosages are administered in the vagina or cervix or orally with a significant decrease in side effects. Recently it has been used on live fetuses, not only for cervical ripening but also for labor induction^{4,20,23}.

The aim of this study was to evaluate the safety and efficacy of two cervical ripening methods available for women from developing countries, by comparing the use of 200µg of intracervical misoprostol to the use of laminaria tents, in pregnant women with fetal death.

MATERIAL AND METHODS

A randomized and blind controlled clinical trial was performed to evaluate cervical ripening in

pregnant women with fetal death, using two different methods: misoprostol and laminaria.

Sample size was calculated based on the results of previous studies of misoprostol and laminaria with for the same objective^{17,10}. Using an α error of 0.01 and a β error of 0.05, the total size of the sample was estimated in 60 women. According to a computer generated random number list, 29 women were allocated to the misoprostol group and 31 to the laminaria group. Only the principal investigator knew to which group the women had been allocated. Bishop Indexes (initial and final) were analyzed by another clinician who did not know which method had been chosen in each case.

The inclusion criteria were: fetal death confirmed by ultrasound exam, gestational age over 15 weeks, hemoglobin serum level of 10g/dL or more, normal coagulogram, no uterine contractions and Bishop Index under 6. The exclusion criteria were: rupture of membranes, intrauterine infection, two or more cesarean sections, abruptio placentae, placenta praevia, fever, polyhydramnios and uncontrolled maternal disease.

The independent variable was the method used to evaluate cervical ripening: a single dose of 200mg of misoprostol or a number 16 laminaria tent was applied intracervically. Twenty-four hours after the application, the cervix was reevaluated and an oxytocin infusion was initiated if the onset of labor had not yet occurred.

The main outcomes analyzed were final Bishop Index (Bif), variation of Bishop Index (Δ BI), length of time in hours of induction with oxytocin infusion, amount of oxytocin used, genital bleeding through the hemoglobin level after delivery, time elapsed from cervical ripening until the onset of labor (latent period-T₁), time elapsed from cervical ripening until delivery (T₂), number of hospitalization days, cost of procedure, side effects during cervical ripening and puerperal complications.

The results were controlled according to maternal age, gestational age, parity, previous cesarean section, previous pregnancies and abortions, live children, initial Bishop Index (BI) and hemoglobin level before delivery.

After being admitted to the study and having one method randomly inserted, the patients remained in hospital and were reevaluated after 24 hours, when oxytocin induction was initiated, provided the onset of labor had not occurred. The first dose was 2mIU/min, doubled every 30 minutes until labor was established. Intramuscular meperidine (1mg/Kg) was used for women presenting either labor discomfort or pain. Induction failure was only established after 72 hours of oxytocin induction without labor.

Statistical analyses were performed by comparing the groups with Student *t* test for continuous numerical variables and with Mann-Whitney test for discrete variables. Survival analysis curve, with its significance evaluated by Kaplan-Meier method by means of Log-rank test, was also used.

This research received the approval of the Institutional Review Board and all the women signed an informed consent before being enrolled in the study and after being carefully informed about the procedures.

RESULTS

The data were collected at the Department of Obstetrics, University of Campinas, Brazil. Sixty women with fetal death were included, 29 using misoprostol and 31 using laminaria tents for cervical ripening. Each method to be used was known only by the main investigator and after the patient was enrolled in the study by opening an opaque envelope

containing the method according to a random list. No woman left the study and there were no losses of follow-up.

They show that the randomization procedure was successful, considering there were no statistical differences between the two groups. The presence of the main maternal pathological conditions was similar in both groups (data not shown). The presence of one previous cesarean section was also similar in both groups and did not change the evaluation of these cases (Table 1).

Of the total amount of women studied, 40% delivered in less than 24 hours, after the beginning of cervical ripening. However, in the misoprostol group this event occurred in 78.6% of women and in the laminaria group in only 6.5%. This represented a statistical difference between the groups. In these cases, the final Bishop Index was considered 13, the maximum score for this index.

All variables, which analyzed the efficacy of methods, showed a statistical difference between the groups and demonstrated better results for the misoprostol group. In this group, approximately 80% of the women did not need additional oxytocin induction and the doses used were five times lower than in the laminaria group (Table 2).

The variation of the hemoglobin serum level before and after delivery showed no statistical difference, proving that there was no greater vaginal bleeding with misoprostol than with laminaria in these cases.

Table 1. Some characteristics of women according to the method used for cervical ripening.

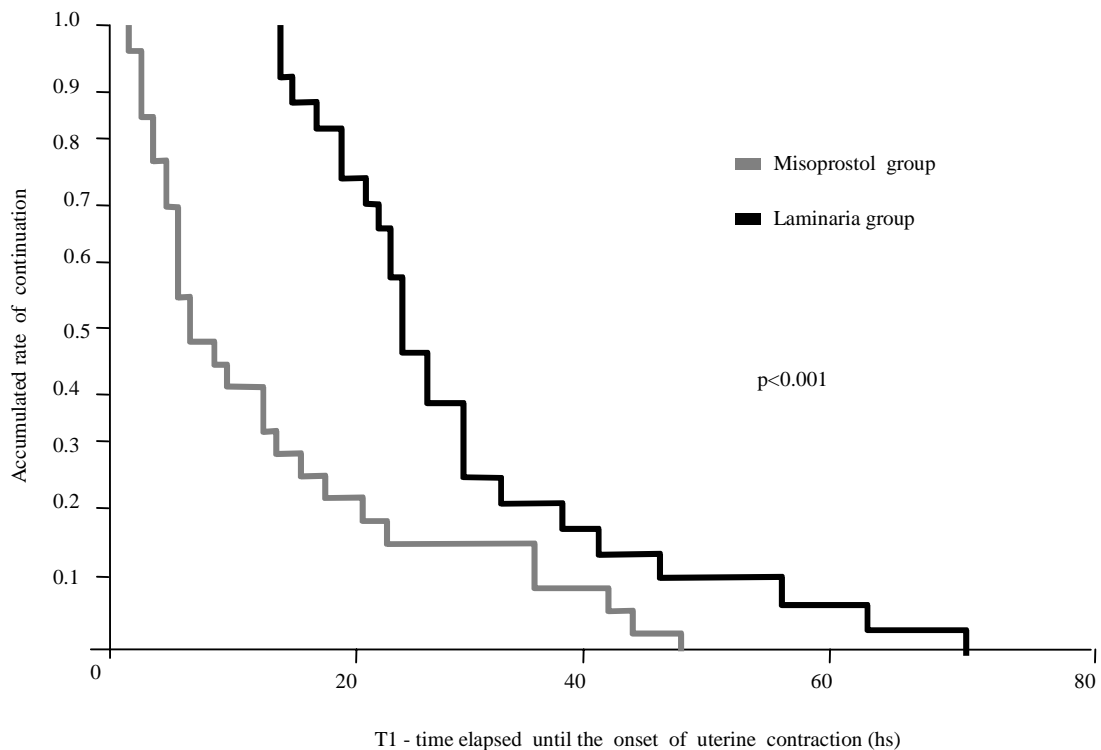
Variables	Misoprostol	Laminaria	<i>p</i> value
Maternal age•	27.5 ± 6.8	27.4 ± 5.2	NS
Gestational age*	28.0 ± 5.5	29.5 ± 6.5	NS
Previous pregnancies*	3.6 ± 4.1	3.0 ± 1.8	NS
Parity*	2.0 ± 2.4	1.6 ± 1.4	NS
Previous abortion*	0.6 ± 1.7	0.3 ± 0.7	NS
Live children*	1.6 ± 2.3	1.4 ± 1.3	NS
Hemoglobin level before delivery•	11.9 ± 1.8	11.9 ± 1.7	NS
Initial Bishop Index*	2.1 ± 1.4	2.7 ± 1.1	NS

NS = not significant; * Mann-Whitney test; • Student *t* test.

Table 2. Main outcomes according to the method used for cervical ripening.

Variables	Misoprostol	Laminaria	<i>p</i> value
Final Bishop Index*	11.0 ± 13.4	5.7 ± 9.5	<0.00001
Δ Bishop Index*	9.0 ± 11.7	3.0 ± 8.3	<0.00001
Time of oxytocin induction (hs)•	4.8 ± 11.9	26.7 ± 25.9	0.0001
Amount of oxytocin used (IU)*	6.8 ± 18.3	33.9 ± 33.9	<0.00001
Hemoglobin level after delivery(g/dl)•	11.4 ± 1.8	11.1 ± 2.4	NS
Number of hospitalization days*	3.2 ± 1.0	4.8 ± 1.5	0.0001
T ₁ latent period (hs)•	13.5 ± 13.5	30.6 ± 14.7	0.0001
T ₂ time cervical ripening-delivery (hs)•	19.6 ± 15.9	42.7 ± 15.9	0.0001
Cost of procedure (US\$)•	180.3 ± 85.0	202.8 ± 54.7	0.0001

NS = not significant; * Mann-Whitney test; • Student *t* test.

**Figure 1.** Accumulated rate of continuation until the onset of uterine contractions according to cervical ripening methods.

The time elapsed from cervical ripening until the onset of uterine contractions (T_1) is shown in Figure 1. This curve shows the accumulated rate in function of time for women who had not already presented regular uterine contractions. There was a statistical difference between the groups. While in the misoprostol group 82% of women had uterine contractions in the first 24 hours reserved for cervical ripening, only 40% were in this situation in the laminaria group.

The time elapsed from cervical ripening until delivery (T_2) is shown in Figure 2. This curve shows the accumulated rate in function of time for women who had not already delivered. There was also a statistical difference between the groups, showing dramatically favorable results for the misoprostol group.

Side effects during cervical ripening and puerperal complications were similar in both groups.

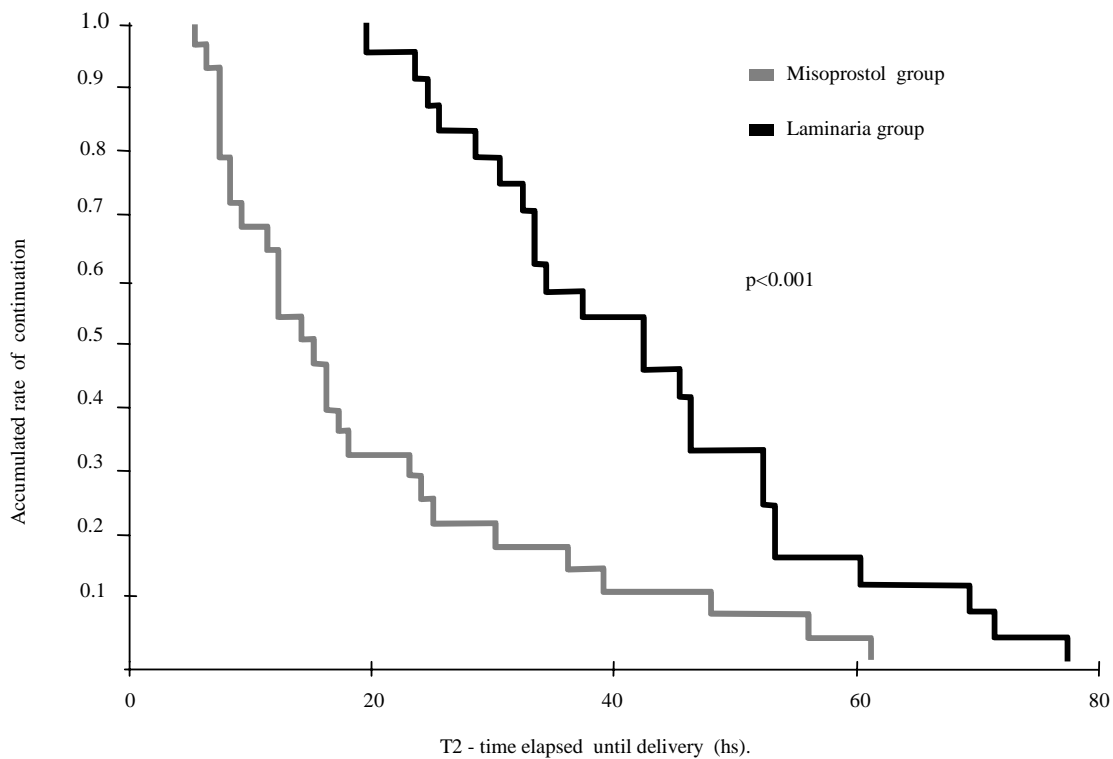


Figure 2. Accumulated rate of continuation until delivery according to cervical ripening methods.

There were one woman who presented tachysystole in the misoprostol group and one woman with vaginal bleeding during cervical ripening in the laminaria group. During the puerperal period there were one woman with fever and another with uncontrolled cardiac disease in the misoprostol group, while in the laminaria group there were two women with fever and another two with vaginal bleeding.

DISCUSSION

The results of this clinical trial showed an important difference between the methods used for cervical ripening in fetal death. The laminaria tent was effective for cervical changes; on the other hand, misoprostol, in the amount and the route used, was not only more effective than laminaria, but also showed to be a good labor induction method.

This conclusion becomes evident when observing that 82% of women started labor during

the first 24 hours reserved for cervical ripening and that 79% delivered without oxytocin when misoprostol was used. Consequently, the time of induction and the amount of oxytocin, when used, were far less for the misoprostol group.

It is a known fact that fetal death helps labor induction when compared to the response with a live fetus, at the same gestational ages⁸. However, in the misoprostol group, delivery occurred, on average, 20 hours after the beginning of cervical ripening in women who were not in labor and presented unripe cervixes. This was perhaps due to the dose and consequent increased contractility.

In fact, lower doses of misoprostol for inducing labor in pregnant women with live fetus is a worldwide trend^{4,6,10,13,20}. However, uterine contractility was not systematically evaluated in this study, although it would be important to know the pattern of uterine contractility with this dose (200µg) of misoprostol.

The purpose of this study was to find a safe, effective, cheap and commercially available method

for cervical ripening that could be used for cases of fetal death. Although misoprostol has been used in different doses and for many reasons in Obstetrics, there are still doubts about its safety for the mother and fetus.

Two studies which used misoprostol in fetal death for cervical ripening and inducing labor^{6,15} are in agreement about the safety and efficacy of this drug. They used up to 800µg, but the great majority of the women had delivery between 15 and 18 hours after the use of misoprostol with a mean dosage of 100µg. These data are similar to those found in this research, and the results of all three studies show no contraindications to the use of this drug for fetal death, demonstrating that high dosage and oral administration are unnecessary. This observation is important for the routine application of misoprostol in Brazil, where it is used empirically in high doses, including oral administration.

Misoprostol has been used in some countries for cervical ripening, abortion and labor induction in fetal death, and lastly for labor induction in live fetus^{2,4,10,18,20,22,23}. Its efficacy and low cost make it very attractive.

Laminaria tents, however, have been used for cervical ripening for a long time, showing efficacy and safety for women and for their fetuses^{12,14,16}. This method was evaluated through a randomized clinical trial comparing the use or not of laminaria in women with fetal death, and a statistical difference in cervical changes after its application was found, but there was no difference with regard to time elapsed until delivery¹⁷.

There is no statistical difference in complications during the puerperal period. Surprisingly, in the laminaria group two women had puerperal bleeding. Some papers describe the association of high dosage of Pg and puerperal bleeding, quite probably due to fiber fatigue and decrease in uterine contractility¹⁹. There was no statistical difference between both groups in terms of hemoglobin serum level before and after delivery.

The variable cost of procedure showed statistical difference between the two groups. This was due to the fact that misoprostol not only is cheaper, but also proved to be more effective than

laminaria, reducing the time of hospitalization for the women.

One of long term implications of this study would be to show the necessity of having misoprostol really available in Brazil. Misoprostol is safe, effective, easy to apply and cheap, but this drug was removed from circulation as it was used in abortions which are illegal in Brazil. After many studies showed the importance of its use in Obstetrics, it is now available for hospitals only and with some restrictions. Recently a new vaginal tablet of 25µg of misoprostol was approved for commercial use in Brazil, but it is mainly directed to induce labor with live fetuses.

These data showed that for pregnancies with fetal death there are only advantages in the use of misoprostol for cervical ripening. However, in pregnancies with live fetus the situation is not exactly the same, and the results of scientific studies carried out with adequate methods can be used to find the most appropriate dose for misoprostol in these cases.

Up to now there is no scientific support for the use of high doses of misoprostol. In addition, it was demonstrated that the misoprostol used vaginally had a stable serum level, at least for a four-hour period, when compared to the same dose used orally^{1,24}. However, recently, low doses by oral route have been described with good results²¹.

Summarizing, the intracervical misoprostol application (200µg) in intrauterine fetal death was shown to eliminate the use of oxytocin and to lower the time of hospitalization for women in these conditions, without any other hazard consequence proving to be safe and effective. On the other hand, the use of laminaria tent should not necessarily be abandoned, but be reserved for selected cases where only cervical ripening is desired and where misoprostol would be contraindicated.

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