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Foley catheter plus misoprostol versus misoprostol alone for labor induction

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SUMMARY

OBJECTIVE: This study aimed to analyze the effects of Foley catheter combined with misoprostol in the labor induction process.

METHODS: This is a nonblinded, block randomized, controlled trial that compared the association between transcervical Foley catheter/vaginal misoprostol 25 µg combination and vaginal misoprostol 25 µg alone in normal-risk and healthy pregnant women undergoing labor induction in the south of Brazil.

RESULTS: A total of 230 patients with indications for labor induction were evaluated and classified into the "combined" group (Foley catheter plus misoprostol), consisting of 107 patients, and the "misoprostol" group (misoprostol only), consisting of 123 patients. The "combined" group was observed to have a shorter labor induction time (p=0.008). In addition, there was a lower need for misoprostol use for overall cervical ripening (p<0.001) and a lower relative risk of needing a second, third, or fourth misoprostol tablet in the "combined" group (risk ratio [RR] 0.80, 95% confidence interval [CI] 0.71–0.91; RR 0.41; 95%CI 0.31–0.56; and RR 0.29, 95%CI 0.17–0.52, respectively) (p<0.001). No statistically significant difference was found in induction failure rate, cesarean section rate, or perinatal outcomes.

CONCLUSION: A combination of methods leads to shorter labor induction, lower need for misoprostol doses, and lower risk of cesarean section, with no increase in the rate of perinatal complications. REBEC number is RBR-7xcjz3z.

KEYWORDS: Labor. Induced labor. Misoprostol.

INTRODUCTION

Labor induction is the stimulation of uterine contractions in a pregnant woman before labor begins to achieve vaginal delivery, reducing the cesarean section rates[1,2]. It is indicated when the birth is beneficial for the mother and/or the fetus. The most frequent causes are as follows: late-term pregnancies, premature membrane rupture, gestational diabetes, intrauterine growth restriction, and elective reasons[1,3].

Several factors can interfere with the response to induction, but the most important is cervical ripening[4]. If induction is indicated and the state of the cervix is unfavorable, agents for cervical ripening must be used[5]. In this sense, the Bishop index aims at assessing cervical ripening, taking into account the following characteristics of the cervix: dilation, fading, consistency, position, and fetal presentation height. Many studies have shown that values ≤6 present a lower probability of vaginal delivery. The use of artificial methods to prepare the cervix increases the chances of a successful vaginal delivery[6].

Due to the long time and experience of their use, prostaglandins misoprostol (E1) and dinoprostone (E2) are considered the main pharmacological agents. Misoprostol is a low-cost synthetic analog of prostaglandin E1 and can be kept at room temperature, advantages that make it the preferred method in Brazil[7]. The transcervical Foley catheter is a mechanical method that has long been used for cervical ripening. Its insertion is performed through a specular examination, with the catheter passing through the cervix or under direct vision, and subsequently inflating the cuff with 30–60 mL of distilled water. A few studies have shown that the mean response time to the catheter is 12 h, but it can safely remain for up to 24 h[2,8].

A synergistic effect has been shown when pharmacological and mechanical methods are used in association, in addition to the safety and benefits for both the mother and neonate[1,3,9,10]. However, no evidence was found regarding the use of this technique in the Brazilian population. Also, considering the overcrowding of maternity hospitals and the increasing number of patients who need labor induction, the benefits of this association could affect patients undergoing the fastest and effective methods as well as the health system by reducing costs of hospitalization and procedures. In this sense, this

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study was designed to compare the association between the transcervical Foley catheter/vaginal misoprostol 25 µg combination and vaginal misoprostol 25 µg alone and to evaluate the effectiveness of both the methods associated and their safety, in normal-risk pregnant women undergoing labor induction at two public teaching-maternity hospitals in the south of Brazil.

METHODS

This is a multicenter, open-label, two-arm randomized clinical trial executed between August and December 2021 and was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee. All participants signed the informed consent form, and the data collected were anonymized.

The investigation included healthy pregnant women with normal-risk pregnancies, aged between 18 and 40 years, admitted for late-term labor induction, and with a Bishop index ≤6 at admission, assisted at two public teaching-maternity hospitals in the south of Brazil. Both hospitals have similar induction protocols.

The selection of the participants was carried out by convenience. The patients who agreed to participate in the study were drawn by block randomization. For sample size calculation, the OpenEpi software (version 3.01) was used for a hypothesis test to compare means and detect a possible difference in labor induction time.

Patients with contraindications to the use of misoprostol (e.g., previous cesarean section or placenta previa) or use of a Foley catheter (e.g., membrane rupture, vaginal infection, or chorioamnionitis) and with cervical dilation ≥3 cm were excluded from the study, as well as those with nonreassuring preinduction cardiotocographic evaluation and the patients who underwent cesarean sections due to induction failure before completing the hospital protocol. Patients with difficulties in positioning the transcervical Foley catheter were also excluded from the "combined" group.

The patients were classified as the "combined" and "misoprostol" groups. An 18F transcervical Foley catheter was inserted in the patients from the "combined" group, inflated with a volume of 60 mL at admission, and removed after 24 h if it was not spontaneously expelled. In addition, they received misoprostol 25 µg vaginally every 4 h until satisfactory cervical ripening was achieved (Bishop index >6) or a maximum of six doses. The patients in the "misoprostol" group received misoprostol alone, according to the protocol described above. Oxytocin was administered to all patients who did not achieve at least three regular contractions in a maximum of 10 min within 4 h of administering the last misoprostol dose. Amniotomy was performed during labor at the discretion of the assisting professional or earlier if the induction protocol was near completion.

The primary outcomes of this study included the frequency of induction failure, defined as failure to achieve labor after six doses of misoprostol 25 µg; administration of oxytocin with a maximum infusion rate of 32 mUI/min in an infusion pump; and rupture of the amniotic membranes.

The secondary outcomes were as follows: the interval from induction initiation to labor in hours, the interval from labor initiation to birth in hours, maximum tablets of misoprostol used, maximum oxytocin infusion rate, frequency of adverse maternal outcomes, adverse perinatal outcomes, and the interval from induction initiation to discharge in hours.

The information obtained was analyzed using the IBM SPSS Statistics version 24.0 software (2016). The non-normal distribution of variables was determined using the Kolmogorov-Smirnov test and analyzed using Fisher's exact test and Mann-Whitney U test. In all the statistical inference processes, p-value ≤0.05 was considered significant.

RESULTS

Between August and December 2021, 250 pregnant women participated in the study. Of the 20 subjects excluded, 11 had a Bishop index of >6 or cervical dilation of >3 cm, 8 refused to participate, and 1 had a latex allergy. After randomization, six pregnant women could not progress the Foley catheter through the cervix, five withdrew from participating, and seven underwent cesarean sections before the induction protocol was completed in the "combined" group. There were only two losses in the "misoprostol" group due to cesarean section before the induction protocol was achieved.

Thus, 230 pregnant women at usual risk who required labor induction due to late-term pregnancy were evaluated. A total of 123 were allocated to the "misoprostol" group, representing 53.5% of the sample, and 107 to the "combined" group, representing 46.5% of the cases studied.

The study population consisted of pregnant women with a mean age of 27 years, 0.76 previous vaginal deliveries, 40.92 weeks of gestational age at admission, and a Bishop index of 2.2. There was no statistical difference between both groups, characterizing the homogeneity of the samples (Table 1).

When analyzing the mode of delivery, it was observed that 17% of the inductions progressed to cesarean sections. Regarding evolution to vaginal delivery, the corresponding rate in the "combined" group was 82.2% versus 83.7% in the "misoprostol" group, with no statistical difference between the groups (p=0.869). There was no difference in the induction failure rate between the groups (Table 2). In most of the cases, the indications for cesarean section were related to nonreassuring fetal status (60.0%), arrest of labor progression (24%), and

induction failure (10%), with no relevant statistical differences between the groups.

When evaluating the number of misoprostol doses used, the "combined" group required one fewer misoprostol tablet (median of two misoprostol tablets vs. the need for three tablets in the control group, p<0.001). There was no significant difference in the maximum oxytocin dose used in the two groups (Table 3).

Table 1. Demographic and obstetric characteristics of normal-risk pregnant women undergoing labor induction with misoprostol/Foley catheter combination or misoprostol alone at two public teaching-maternity hospitals in the south of Brazil, 2021 (n=230).

	Intervention				p-value
	Combined (n=107)		Misoprostol alone (n=123)		
	Mean	SD	Mean	SD	
Maternal age	27.75	6.82	26.9	6.11	0.120
Parity*	1.75	1.111	2	1	0.538
Gestation (weeks)	41	0.22	40.89	0.32	0.155
Bishop index	2.14	1.25	2.32	1.66	0.242
Birthweight (g)	3419.02	393.05	3413.54	425.73	0.619

SD: standard deviation. *Nulliparity was found in 65% on the "misoprostol" group and 68% on the "combined" group (p=0.610).

Table 2. Maternal, labor, and neonatal outcomes of normal-risk pregnant women undergoing labor induction with misoprostol/Foley catheter combination or misoprostol alone at two public teaching-maternity hospitals in the south of Brazil, 2021 (n=230).

	Intervention				RR (95%CI)	p-value
	Combined (n=107)		Misoprostol alone (n=123)			
	n	%	n	%		
Induction failure						
No	104	97.2	120	97.6	1.0 (Reference)	
Yes	3	2.8	3	2.4	1.08 (0.48–2.43)	0.869
Misoprostol (doses)						
1	107	100	123	100	1.0 (Reference)	
2	79	73.8	113	91.9	0.80 (0.71–0.91)	<0.001
3	33	30.8	92	74.8	0.41 (0.31–0.56)	<0.001
4	12	11.2	47	38.2	0.29 (0.17–0.52)	<0.001
>4	2	1.9	10	8.1	0.23 (0.52–1.03)	0.054
Mode of delivery						
Vaginal	88	82.2	103	83.7	1.0 (Reference)	
Cesarean section	19	17.8	20	16.3	1.09 (0.62–1.93)	0.762
Complications						
None	90	84.1	101	82.1	1.0 (Reference)	
Yes	17	15.9	22	17.9	0.92 (0.63–1.36)	0.821
PPH	5	4.8	7*	5.7	–	–
Uterine hyperstimulation	0	0	1	0.8	–	–
Abruptio placentae	0	0	1	0.8	–	–
Apgar score <7	12	11.2	14*	11.4	–	–
NICU admission	0	0	4	3.2	–	–

PPH: postpartum hemorrhage; NICU: neonatal intensive care unit; RR: relative risk; CI: confidence interval. *On one occasion, there was a concomitant PPH and Apgar score <7.

Table 3. Number of misoprostol tablets administered, labor induction and active labor time, length of stay, and oxytocin dose used in normal-risk pregnant women undergoing labor induction with misoprostol/Foley catheter combination or misoprostol alone at two public teaching-maternity hospitals in the south of Brazil, 2021 (n=230).

	Intervention				p-value
	Combined (n=107)		Misoprostol alone (n=123)		
	Median	Range	Median	Range	
Misoprostol (doses)	2	6	3	7	<0.001
Maximum oxytocin dose (mUI/min)	5	32	4	32	0.456
Induction time (h)	10	33	12	22	0.008
Labor time (h)	5	8	16	35	0.051
Length of stay (h)	56	42	60	132	<0.001

Regarding the need for additional misoprostol doses, the patients in the "combined" group were less likely to receive a second (73.8% vs. 91.9%, p<0.001), third (30.8% vs. 74.8%, p<0.001), or fourth misoprostol tablet (11.2% vs. 38.2%, p<0.001) when compared to the "misoprostol" group. This reduced the need for a second, third, or fourth misoprostol dose by 20% (relative risk [RR] 0.80; 95% confidence interval [CI] 0.71–0.91], p<0.001), 59% (RR 0.41; 95%CI 0.31–0.56; p<0.001), and 71% (RR 0.29; 95%CI 0.17–0.52; p<0.001), respectively. There were no differences in the need to administer the fifth or sixth misoprostol dose (Table 2).

When comparing the induction, labor, and hospitalization times, the pregnant women in the "combined" group had a 2-h reduction in the induction time (median of 10 h in the "combined" group vs. 12 h in the "misoprostol" group, p=0.008) and a 4-h reduction in the hospitalization time (median of 56 h in the "combined" group vs. 60 h in the "misoprostol" group, p<0.001). There was no significant difference in labor time (Table 3).

In most cases, no complication was observed during the hospitalization (83.0%). However, we noticed one patient with uterine hyperstimulation, abruptio placentae, 28 cases of Apgar score below 7, 4 cases where the newborns were admitted to the NICU, and 12 cases of postpartum hemorrhage. On one occasion, there was concomitant postpartum hemorrhage, and an Apgar score below 7. No relevant statistical differences were identified between the two groups (Table 2).

DISCUSSION

To the best of our knowledge, this is the first randomized study in the Brazilian population evaluating the Foley catheter/vaginal misoprostol combination or vaginal misoprostol alone for cervical ripening and labor induction.

This study did not identify any significant difference between the groups when evaluating the vaginal delivery and cesarean section rates, as was the case in the research by Osoti et al.[9] and Hill et al.[10] who observed that the cesarean section rates presented no statistical significance. However, Levine et al. evaluated 492 pregnant women paired in 4 groups with 123 participants each (i.e., misoprostol only, Foley catheter only, misoprostol plus Foley catheter, and oxytocin plus Foley catheter) and observed that the women who received the combined methods were twice as likely to have vaginal deliveries when compared to those who received misoprostol alone[7]. The induction failure rates found in this study also had no statistically significant difference, similar to the studies by Osoti et al.[9] and Kehl et al.[11].

We observed a significant difference when comparing the number of misoprostol tablets used in induction, in the same way that the propensity to need more misoprostol doses was reduced in the "combined" group up to the fourth dose. A similar result was observed by Osoti et al. with the "combined" group, presenting a reduced need to receive the second misoprostol tablet at 25% induction and the third tablet at 68%[9].

When assessing the time from induction to active labor, there was a significant difference of 2 h less in labor induction in the "combined" group. Aduloju et al. found a similar result with the transcervical catheter group, with a mean of 22.84 h (SD 4.69), misoprostol: 18.74 h (SD 4.43), and combined: 17.79 h (SD 2.85), with p=0.001[12].

We did not find any statistically significant difference between the two groups regarding labor time. In contrast, in a meta-analysis involving only the use of a balloon catheter associated with misoprostol versus misoprostol alone, Ornat et al. observed 15 randomized clinical trials that showed a statistically significant reduction in the time from induction initiation to delivery[8]. However, this difference may be related to the lack of distinction between the induction and labor times, which in this study were evaluated separately. Aduloju et al. also found a similar result, with a significant reduction in the

induction, labor, and delivery times[12]. Hill et al. also found a significantly shorter time to vaginal delivery (mean: 14.6±6.9 vs. 20.8±13.8 h, p<0.0001)[10]. Levine et al. also identified that the association of methods reduces labor time with statistical significance (p<0.001)[7].

Interestingly, most patients evaluated in this study did not present any complications during hospitalization. The most prevalent were nonreassuring fetal status and postpartum hemorrhage, with no significant difference between the groups. Osoti et al. found similar results, with most of the inductions progressing uneventfully, with the two main complications being postpartum and uterine hyperstimulation, without statistical significance between the groups[9].

We did not find any significant difference between the study groups when assessing fetal vitality. Osoti et al. found a similar result regarding the NICU admission rates in both the control (18.9%) and the combined (16.7%, p=0.697) groups[9]. In contrast, Ornat et al. found a lower NICU admission rate in the "combined" group (p=0.03)[8].

Despite this strong evidence, our research had some limitations mainly related to the nonblinding of the assistants due to the nature of the study, which may have influenced patient management. The higher occurrence of losses due to early interruption of the induction protocol can reflect this situation.

CONCLUSION

Combining the vaginal misoprostol and transcervical Foley catheter methods did not significantly reduce the induction failure rates. However, it did reduce the labor induction and hospitalization times, in addition to reducing the number of misoprostol tablets used for induction and the need for more than one misoprostol dose, without interfering with the risk of adverse maternal and perinatal outcomes, proving to be an interesting method to be added to the protocols of the services involved in the study.

Additional studies are suggested to evaluate other variables involved in the induction process, such as costs of the procedures and maternal satisfaction.

AUTHORS' CONTRIBUTIONS

JAE, BAA: Data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, and writing – review & editing. **LKV:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, and writing – review & editing.

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