ORIGINAL RESEARCH

The difference of Bishop score change and labor event between oral and vaginal misoprostol in pregnancy beyond 41 weeks

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Article Info
Received Dec 1, 2022
Revised Feb 7, 2023
Accepted Mar 10, 2023
Published Aug 1, 2023

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Keywords:
Oral misoprostol
Bishop score
Cervical ripening
Maternal health

ABSTRACT

Objective: To compare Bishop score changes and labor event between oral and vaginal misoprostol in pregnancy beyond 41 weeks.
Materials and Methods: A total of 52 pregnant women with more than 41 weeks of gestation, had a Bishop score less than 5, and were undergoing induction labor were randomly divided into two groups: oral and vaginal misoprostol. In the oral misoprostol group, participants were given 25 mg of misoprostol in a solution with a concentration of 1 ug/ml every 2 hours. In the vaginal misoprostol group, a 25 mg misoprostol tablet was inserted into the posterior fornix every 6 hours. The two groups were compared in terms of Bishop score during the first 6 hours, changes in Bishop score, labor at term events, neonatal outcomes, complications, and side effects after the administration of misoprostol.
Results: The oral group showed significantly higher changes in Bishop score compared to the vaginal group (5.5 vs 3.6; p=0.0001). The median interval times for induction of labor at term, induction at stage II, and induction at birth were found to be shorter in the oral misoprostol group compared to the vaginal group (7.3 hours vs 10.6 hours, 14.0 hours vs 16.8 hours, and 14.6 hours vs 17.6 hours; p=0.002, 0.003, 0.002). Labor at term occurred much more frequently in the oral group (53.8% vs 15.4%). Additionally, the oral misoprostol group had a 3.5 times higher likelihood of experiencing labor at term within the first 6 hours after the initial administration compared to the vaginal group (OR 3.5, 95% CI 1.33-9.23).
Conclusion: Oral administration of misoprostol for cervical ripening has been demonstrated to be more effective than vaginal administration, greater bishop score changes while maintaining an equivalent level of safety.

How to cite: Maskasoni, Dewantiningrum J. The difference of Bishop score change and labor event between oral and vaginal misoprostol in pregnancy beyond 41 weeks. Majalah Obstetri & Ginekologi. 2023;31(2):61-67.
doi: 10.20473/mog.V31I22023.61-67.

Highlights:

1. Oral misoprostol is more effective than vaginal misoprostol in cervical ripening as a part of induction of labor.
2. Oral misoprostol is as safe as vaginal misoprostol.

INTRODUCTION

Perinatal mortality and morbidity rates tend to increase in pregnancies that go beyond 41 weeks.[1] Morbidity in such cases can be attributed to issues like placental dysfunction, decreased amniotic fluid volume, and macrosomia.[2-5] Effective management of induction labor and regular antenatal care are crucial strategies for reducing perinatal mortality and morbidity.[6] The use of misoprostol for cervical ripening in the induction of labor for pregnancies beyond 41 weeks with an unfavorable cervix is a well-established approach.[7] Both oral and vaginal administration of misoprostol have been shown to be effective in inducing labor, with oral administration offering the advantages of lower risks of surgical complications and reduced uterine hyper-

stimulation.[5,8] Additionally, the use of oral misoprostol is more convenient for both healthcare providers and patients.[9]

The Bishop score is a widely used scoring system in obstetrics to assess the readiness of the cervix for labor induction. It evaluates specific cervical parameters, including cervical dilation, effacement, consistency, position, and fetal station.[10] Each parameter is assigned a score ranging from 0 to 3 or 4, depending on the scoring system used.

The Bishop score provides valuable information about the cervical status and helps healthcare providers determine the appropriate method and timing of labor induction. Higher Bishop scores indicate a more favorable cervix, which is associated with increased chances of successful induction and shorter labor duration.[10] On the other hand, lower Bishop scores suggest an unfavorable cervix that may require additional cervical ripening methods before proceeding with labor induction.

The changes in the Bishop score over time during labor induction reflect the progress of cervical ripening and readiness for childbirth. As the cervix ripens, it becomes softer, effaced, and dilated, resulting in an increase in the Bishop score. Monitoring the changes in the Bishop score allows healthcare providers to assess the effectiveness of cervical ripening methods and make informed decisions regarding the management of labor induction.[10] The aim of this study was to compare changes in the Bishop score and labor events between patients receiving oral and vaginal misoprostol for labor induction in pregnancies that have gone beyond 41 weeks.

MATERIALS AND METHODS

This experimental study was conducted in maternity room of the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Diponegoro, Kariadi Hospital, Semarang, Indonesia, and its satellite hospital (Dr. Soeselo Hospital in Slawi, Dr. R Soetrasno Hospital in Rembang, Margono Hospital in Purwokerto, and Semarang Regional Hospital, all in Indonesia), from January 2019 until the desired sample size was fulfilled. The study included pregnant patients with a gestational age of ≥41 weeks, singleton pregnancies, and a Bishop score <5 who were admitted to Dr. Kariadi Hospital and its satellite hospitals for labor induction. Patients with conditions such as premature rupture of membranes, fetal abnormalities, placentomegaly, urinary tract infections, asthma, diabetes, dyslipidemia, obesity, hypotension, anemia, and autoimmune diseases were excluded from the study. Patients were considered drop-outs if they experienced uterine rupture, uterine hyperstimulation, fetal distress, or refused to continue with the induction process.

We employed the consecutive sampling method and divided the participants into two groups using a simple randomization method, with each group consisting of a minimum of 20 patients. The first group received oral misoprostol by dissolving 200 µg misoprostol tablets into 200 cc of mineral water, and then 25 cc of the solution was given to the patient every 2 hours, up to a maximum of six doses. Intravaginal placebo tablets were also administered to this group. The second group received oral placebo tablets following a similar method as the first group, along with intravaginal misoprostol tablets. If a patient entered the labor phase, misoprostol administration was discontinued. The Bishop score examination was performed before and after the treatment, and changes in the scores were calculated by subtracting the pre-treatment score from the post-treatment score. The examinations were conducted by a senior resident. To minimize measurement bias we employed Interrater Reliability analysis using the Intraclass Correlation method. A coefficient value above 0.8 was considered indicative of good correlation. The WHO modified Bishop score, as shown in Table 1, was utilized for the assessment.

Table 1. Modified Bishop score

Score	Dilatation	Cervical length (cm)	Station	Consistency	Position
0	0	>4	-3	Firm	Posterior
1	1-2	3-4	-2	Intermediate	Medial
2	3-4	1-2	-1	Soft	Anterior
3	≥5	<1	1/2		

Prior to the study, informed consent was obtained from all participants, ensuring their understanding and voluntary participation. In cases where uterine tachysystole was observed, the patient received 250 µg of the medication intravenously to either manage acute tocolysis or proceed with a cesarean section if necessary. The administration of terbutaline/salbutamol was discontinued if the patient's heart rate exceeded 140 beats per minute. Statistical analysis was performed using the independent t-test for ratio variables and the Chi-square test for nominal variables. Multivariate analysis was conducted using logistic regression analysis to assess the relationships between variables. Results were considered statistically significant if $p<0.05$. This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro (Approval No: 15/EC/FK-RSDK/1/2019).

RESULTS AND DISCUSSION

A total of 52 people was included in our study, 26 people in the oral misoprostol group and 26 in the vaginal misoprostol group, with the characteristics as seen in Table 2, where there are no significant differences in subjects' age, parity, abortion, gestational age and BMI between the two treatment groups.

Table 2. Subject characteristics.

	Groups						
	Oral			Vaginal			
	Mean ± SD	Median (min-max)	N (%)	Mean ± SD	Median (min-max)	N (%)	P
Age (years)	26 ± 3.0	26 (22.0-32.0)		25 ± 4.0	24 (19-34)		0.14*
Parity		0 (0.0-2.0)			0 (0.0-2.0)		0.71*
Abortion		0 (0.0-1.0)			0 (0.0-1.0)		1.00*
Gestation age (weeks)	41.2 ± 0.37	41 (41.0-42.0)		41.2 ± 0.37	41 (41.0-42.0)		1.00*
BMI	26.3 ± 2.3	26.2 (22.0-32.4)		25.6 ± 1.9	25.8 (20.2-28.3)		0.22#
Normoweight			2 (7.7)			1 (3.8)	
Overweight			7 (26.9)			9 (34.6)	
Obese			17 (65.4)			16 (61.5)	

*Mann Whitney test; # T-Independent test

Table 3. Bishop score differences.

	Group				p
	Oral		Vaginal		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Preripening	1.2 ± 0.99	1.0 (0.0-3.0)	1.0 ± 1.11	1.0 (0.0-3.0)	0.411
After 6 hours	5.5 ± 1.36	5.5 (3.0-7.0)	3.6 ± 1.60	3.0 (2.0-7.0)	0.0001
Bishop score differences	4.3 ± 1.19	4.0 (2.0-6.0)	2.5 ± 0.81	2.0 (1.0-4.0)	0.0001
Induction - first stage labor interval (hours)	7.3 ± 2.80	6.0 (3.5-12.25)	10.6 ± 2.92	11.25 (4.0-14.5)	0.0001
Induction - second stage labor interval (hours)	14.0 ± 2.97	14.4 (8.5-20.0)	16.75 ± 3.95	17.5 (7.5-21.5)	0.003
Induction - delivery (hours)	14.6 ± 3.1	14.75 (8.75-21.0)	17.6 ± 4.03	18.6 (8.0-22.5)	0.002

Mann-whitney test

Table 4. Labor events differences

		Labor		Total	p	OR	IK 95%
		Yes	No				
Treatments	Oral	14 (53.8)	12 (46.2)	26 (100.0)	0.004	3.5	1.33-9.23
	Vaginal	4 (15.4)	22 (84.2)	26 (100.0)			

Chi-square test

Table 5. Neonatal outcomes, complications and side effects of misoprostol

		Groups				p
		Oral		Vaginal		
		n	%	n	%	
Apgar Score	≥7	25	96.2	26	100.0	1.00
First five minutes	<7	1	3.8	0	0.0	
Threated uterine rupture	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	
Hyperstimulation	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	
Meconeum	Yes	0	0.0	2	7.7	0.54
	No	26	100.0	24	92.3	
Nausea and Vomiting	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	
Fever	Yes	2	7.7	0	0.0	0.54
	No	24	92.3	26	100.0	
Diarrhea	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	

Chi-Square test

Table 3 shows significant differences in mean Bishop scores within six hours after misoprostol administration in both groups (p=0.0001). Bishop scores changes in oral group were greater than vaginal misoprostol group (5.5 vs 3.6). The mean interval between induction to first stage labor, induction to second stage labor and induction to delivery was also shorter in oral than vaginal misoprostol group (7.3 hours vs. 10.6 hours, 14.0 hours vs 16.8 hours, and 14.6 hours vs. 17.6 hours; p=0.002; 0.003; 0.002, respectively). Table 3 shows that within six hours of misoprostol administration, labor incidence was greater in the oral compared to the vaginal group (53.8% vs 15.4%). The oral misoprostol group was 3.5 times more likely to be in labor after six hours after the first administration than the vaginal group (OR 3.5 ’95% CI 1.33-9.23).

First five-minute APGAR score <7 was only found in the oral misoprostol group (3.8%; p=1.00). Meconeum stain in amniotic fluid occurred in 2 patients in vaginal misoprostol group (7.7%; p=0.54) and 2 cases of fever in the oral misoprostol group (7.7%; p=0.54). The administration of oral misoprostol was as safe as vaginal misoprostol in terms of fetal outcome, complications and side effects of the drug.

Several maternal characteristics were associated with successful cervical ripening and labor induction, including: parity and gestational age. Age and pre-pregnancy body mass index (BMI) also related to successful cervical ripening and labor induction.[11-13] In our study, age, parity, BMI, and pre-ripening Bishop scores variables did not show any significant differences between two groups. Therefore, it can be excluded as confounding factor.

The clinical parameters commonly used to predict successful labor induction are Bishop scores. The relationship between Bishop scores and successful labor induction varies.[14] In our study we found that Bishop scores mean difference in the oral group were greater than in the vaginal group (5.5 vs 3.6). The mean interval between induction to first stage labor, induction to second stage labor and induction to delivery also shorter in the oral misoprostol than in the vaginal group (7.3 hours vs. 10.6 hours, 14.0 hours vs 16.8 hours, and 14.6 hours vs. 17.6 hours, respectively).

Cochrane Systematic Review by Alfirevic's et al, from nine RCT studies found that oral misoprostol was more effective than placebo.[15] RCTs showed that oral misoprostol is as effective as vaginal misoprostol.[4,15] WHO recommendation in labor induction was to use 25 µg misoprostol oral, and compared to placebo, oral misoprostol reduced the risk of 24 hours vaginal delivery failure six times greater than placebo.[4] Compared to vaginal misoprostol, oral misoprostol has similar efficacy.[15]
Abbassi’s study that compared safety and effectivity of oral and vaginal misoprostol for labor induction at term pregnancy showed that Bishop scores changes after six hours were greater in the oral group than in the vaginal group (3.6 ± 3.09 vs. 3.3 ± 3.45). Induction to delivery interval was shorter in the oral compared to vaginal group (7.5 ± 4.4 hours vs. 7.5 ± 4.4 hours).[16] Successful vaginal delivery in the oral group was greater than in the vaginal group (95 % vs 80%).[13] Paungmora et al. found that the induction to delivery interval in the oral misoprostol group was shorter than the vaginal group (14.3 hours vs. 15.8 hours).[17]

Oral misoprostol efficacy is due to the fast-oral absorption. It reaches peak concentration after 12 minutes, half-life of 20-30 minutes). Misoprostol vaginal takes longer to work, has a lower peak value with peak concentration after 60 minutes, but the effect

is more persistent. Vaginal misoprostol had greater reproductive tract effects than gastrointestinal tract will decrease. If a misoprostol tablet is placed in the posterior fornix of the vagina. The plasma concentration of misoprostol reaches a peak after two hours and will slowly decreases. Vaginal administration of misoprostol causes slow increase of plasma concentration and its peak value was also lower compared to oral administration, but the overall effect of the drug is higher.[18]

Misoprostol as a cervical ripening agent, stimulate fibroblasts to synthesize hyaluronan through EP4 receptors. Hyaluronan (HA) is a glycosaminoglycan that will draw water into the cervical stroma and soften the cervix.[18-22] Degradation of hyaluronan by hyaluronidase enzyme into small molecules will trigger an inflammatory response in the cervix, followed by leukocytes influx. Degranulation of neutrophils will release collagenase enzyme (MMP-8) and trigger IL-6 and IL-8 cytokines production, followed by disorganization of extra cellular collagen matrix. Inflammatory cells influx is also triggered by misoprostol via EP-2 receptors by increasing capillary permeability in order to facilitate leukocyte diapedesis.[21]

In our study, we found first five-minute APGAR score <7 in 3.8% of oral misoprostol group and meconium amniotic fluid stain in 7.7% of the vaginal misoprostol group, but both of them were not statistically significant. Similar to our findings, a meta-analysis by Alfirevic et al. also showed first five-minutes APGAR scores <7 as neonatal outcomes after labor induction with oral misoprostol was lower compared to vaginal misoprostol (RR 0.6 CI 95% 0.44-0.82).15 Meconium excretion risk was also higher in the oral misoprostol group (RR 1.22 CI 95% 1.03-1.44). Compared to placebo, the complications of uterine hyperstimulation in labor induction with oral misoprostol did not differ significantly (RR 4.78 CI 95 % 0.73-31.32) from that in vaginal misoprostol group (RR 2.67 CI 95% 0.73-9.76).[15] In our study, the uterine hyperstimulation complications did not occur in either group of study subjects.

Side effects of misoprostol administration in our study were fever in 7.7% oral misoprostol group, while gastrointestinal side effects did not occur. From this result, in terms of fetal outcome, drug complications and side effects, the safety of oral misoprostol administration was similar to vaginal misoprostol. Our results also confirmed a study by Alfirevic et al which found that nausea, vomiting, diarrhea and shivering in oral misoprostol induction was similar in oral and vaginal misoprostol administration.[15]

Prostaglandin E increased thermostat set point, resulted in body shivering and increased body temperature. This side effects is related to dosage and route of administration.[23] Per rectal misoprostol administration appears to be associated with lower serum concentrations and milder side effects compared to oral administration.[24] Clinical trials in the United Kingdom report that the side effects of shivering are more common in 600ug oral compared to vaginal misoprostol. These side effects were independent with per rectal route dose.[18] Shivering is self-limiting side effect and does not need further treatment, and the outcome as good as other cases without fever.[23] Some pathogenesis of the fever was unknown. Genetic and environmental factors may influence the occurrence of these side effects which requires further research.[23]

Misoprostol may cause diarrhea because it has an effect to increase cyclic AMP in gastrointestinal tract. This increment will cause secretion of CL- and HCO3-, also passive expenditure of Na+, K+, and water, and inhibits Na+ and CL- into the erythrocyte.[25]

Our study was a second phase clinical trial in phase III humans to compare the efficacy of standard treatment method of vaginal misoprostol and oral misoprostol for labor induction. Screening for several confounding factors and maternal characteristics, which may have affected our study results, were done through inclusion and exclusion criteria as well as through the comparison study between maternal characteristics in both treatment group and control group. Randomization and blinding were also performed to reduce the selection bias in our study. The power in our study was set to 80% with type I error 5%. Bias found in the study was caused by Bishop Score measurement and treatment was delivered by one appointed research assistant, a yellow pin, operator level, obstetric resident. Several limitations in our study were Bishop Score parameter and labor measurement still used traditional methods by cervical examination and uterine contraction palpation. These methods were very subjective. However, they were still the standard method in obstetric department. The more objective alternative for Bishop score measurement is ultrasonography and chemical biomarker, which are still under research. The administration of vaginal misoprostol tablet of 25 mg was divided into 8 parts (200 mg) by research assistant. Thus, the allocation may not be equal and it was one of the limitations in our study. Then, oral administration of 25 ug was given every 2 hours. Thus, the cumulative dosage in oral misoprostol group was higher than in vaginal misoprostol group, even though the clearance effect in oral misoprostol group is about ± 2 hours. This may be a factor that needs further investigation.

CONCLUSION

Oral misoprostol administration as a cervical ripening agent may be more effective compared to vaginal administration. Furthermore, in oral misoprostol treatment group there was greater change in Bishop score and shorter interval time of induction to first stage of labor as well as shorter induction to second stage of labor and induction to delivery. The output for neonates, maternal complications, and adverse events of medication suggested that oral misoprostol administration is as safe as misoprostol administered vaginally.

DISCLOSURE

Acknowledgment

We would like to thank dr. Agus Sunanto, SpOG as the Head of the Department Obstetrics and Gynecology of Soetrasno General Hospital; Dr. Jaenudin, SpOG as the Head of the Department Obstetrics and Gynecology, Doeselo General Hospital; and dr. Adi Setiawan, SpOG as the Head of the Department Obstetrics and Gynecology, Margono General Hospital for their cooperation.

Conflict of interest

All author has no conflict of interest.

Funding

No funding or sponsorship was received for this study or publication of this article

Author contribution

All authors have contributed to all process in this research.

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