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The Effect of Buccal versus Vaginal Misoprostol on Time to Favorable Simplified Bishop Score

ABSTRACT

OBJECTIVE: To evaluate whether buccal or vaginal Misoprostol provides a statistically significant shorter time interval to a favorable simplified Bishop score, and to determine if there is a significant difference in time to delivery between these two modes of administration.

DESIGN: Retrospective cohort study via chart review

SETTING: Augusta University, Augusta, Georgia

PATIENTS: Mothers who delivered full term singleton gestations after being admitted for induction of labor at Augusta University from January 1, 2015 to July 31, 2018 with an initially unfavorable simplified Bishop score on cervical exam. Exclusion criteria: (1) Favorable initial simplified Bishop score (>5) at the time of onset of induction of labor, (2) multiple gestation, (3), pre-term gestation and (4) use of multiple different modalities for cervical ripening.

INTERVENTION: Medical records were reviewed to determine if mothers meeting the criteria above had a statistically significant difference in time to favorable simplified Bishop score using vaginal versus buccal Misoprostol and/or a statistically significant difference in time to delivery.

MAIN OUTCOME MEASURE: The primary outcome was time to favorable simplified Bishop score (>5). The secondary outcome was time to delivery.

RESULTS:

- Primary outcome- no significant difference between the buccal and vaginal groups in median time from initial Misoprostol dose to time of favorable simplified Bishop score (p=0.371).
- Secondary outcome- no significant difference between the buccal and vaginal groups in median time from initial Misoprostol dose to time of delivery (p=0.371).
- No significant difference in complication rate between the buccal and vaginal groups (p=0.199).

INTRODUCTION

Labor induction is a common procedure in Obstetrics. Misoprostol is one of many medications commonly used during the labor induction process. It is a prostaglandin (PGE-1) analog, which can be administered buccally, vaginally, or orally to cause cervical ripening. Typically, either vaginal or buccal administration are favored over oral, as they both bypass first-pass metabolism. Currently, choosing between vaginal and buccal administration continues to be provider specific. A 2017 survey demonstrated provider preferences as follows: 73% preferred vaginal, and 20% preferred buccal. Interestingly, in their study population, only the resident physician and certified nurse midwife providers endorsed preferring the buccal route (Townes et al, 2017).

A simplified Bishop score uses only three components, dilation, effacement and station, to quantify the Bishop score. A 2011 study demonstrated that using a simplified Bishop score of

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>5 is functionally equivalent to what is considered a favorable full Bishop score (>8) in both labor inductions and spontaneous labor at term and preterm (Loughton et al, 2011). There is a lack of evidence supporting any specific route of administration of Misoprostol in terms of a shorter time to favorable Bishop score. Therefore, the primary aim of this study was to determine whether there is a statistically significant difference in time to a favorable simplified Bishop score (>5) using buccal versus vaginal Misoprostol for cervical ripening. The secondary aim of this study was to determine if a significant difference exists in terms of time to delivery between these two routes of administration. Through the results of this study, if a significant difference were to exist, Misoprostol could be used more effectively and efficiently during the cervical ripening and labor induction process.

METHODS

The project design is a retrospective cohort study that examined medical records of deliveries at Augusta University from January 1, 2015 to July 31, 2018. Eligible mothers included patients with full term singleton gestations undergoing induction of labor with an initially unfavorable simplified Bishop score on cervical exam.

A power analysis was performed in advance of data collection in order to determine how many charts to review. It was determined that sample sizes of approximately 117 patients in the buccal and vaginal Misoprostol groups would yield 85% power to detect an effect size of 0.41 or larger using a significance level of 0.05. This effect size was comparable to that found in the study by Marsdal et al. (2018) that compared Misoprostol vaginal insert vs. Misoprostol vaginal tablets in terms of time to delivery. Allowing for missing charts, missing information on simplified bishop score, etc., decision was made to pull a total of 350 charts for review in order to obtain complete data for 117 mothers in each group. A census was then created and 350 maternal charts during our designated time frame that used Misoprostol were pulled from the electronic medical record using the i2b2 database.

Medical records were then further reviewed to obtain demographic information about the mother and subsequently were further narrowed down based on the exclusion criteria. Patients were excluded from the study if they met any of the following criteria: (1) favorable simplified Bishop score (>5) at the time of onset of induction of labor, (2) multiple gestation, (3) pre-term gestation, and (4) use of multiple different modalities for cervical ripening (i.e. Foley bulb placement coinciding with Misoprostol administration, or Dinoprostone administration prior to Misoprostol administration).

Once the qualifying subjects were identified, the following data was recorded from each patient's chart: maternal age at delivery, maternal race, maternal BMI, inpatient/outpatient medication regimen, dosing, and administration information, number of gestations, number of pregnancies, pregnancy or delivery complications, gestational age at delivery, mode and time of delivery, cervical examination information, antepartum complications, and length of hospital stay. For each cervical examination, a simplified Bishop score was calculated. Subsequently, for each patient, the amount of time in minutes from each patient's initial dose of Misoprostol to their first favorable simplified Bishop score (>5) was calculated and recorded. Additionally, the amount of time in minutes from each patient's initial dose of Misoprostol to their time of delivery was also calculated and recorded.

After collection, categorical data were summarized using frequencies and percentages. Data measured at the ordinal level were summarized using the median and range (minimum, maximum). Data measured at the interval or ratio level were summarized using the mean ± standard deviation (S.D.). Fisher's exact test was used to compare the buccal and vaginal Misoprostol groups at baseline in terms of categorical variables (e.g., race). The median test was used to compare the buccal and vaginal groups at baseline in terms of ordinal variables (e.g., parity). Due to the high degree of skewness found in the variables measured at the interval or ratio level (e.g., BMI) the median test was also used to compare the buccal and vaginal groups in terms of these variables at baseline. Spearman correlation was used to examine the association between ordinal or higher level variables. Due to the high degree of skewness in the time from initial dose of Misoprostol to time of favorable simplified Bishop score and time from initial dose of Misoprostol to time of delivery, the median test was used to compare the buccal and vaginal groups in terms of these variables. To identify potential confounders, each of the patient characteristics was examined for significant associations with time from initial dose of Misoprostol to time of favorable simplified Bishop score and time of delivery using the methods described above.

The Kaplan-Meier method was then used to construct "survival" curves separately in the buccal and vaginal groups. Here "survival" is used generically to refer to the time from initial dose of Misoprostol to time of favorable simplified Bishop score. The log-rank test was used to compare the "survival" curves in the buccal and vaginal groups. Similar analyses was used to examine the effect of buccal vs. vaginal Misoprostol on time from initial dose of Misoprostol to delivery. All analyses was performed using SAS software (Version 9.4; SAS Institute, Inc., Cary, N.C.; 2016); all tests were two-tailed and were performed using a significance level of 0.05.

RESULTS

After exclusion criteria was applied, ultimately data was obtained for a total of 23 study patients: 17 received Misoprostol via the buccal route (74%) and 6 via the vaginal route (26%). The two groups were very similar at baseline, and there were no significant differences between groups in terms of any patient characteristics (Table 1). Almost all of the patients were either black (48%) or white (39%); mean age at time of delivery was 28.9 ± 5.9 (median 29, range 19-40). Median gravity was 2 (range 1-7) and median parity was 1 (range 0-6). Mean BMI was 35.4 ± 9.4. The median initial simplified Bishop score was 2 (range 0-4). Following administration of Misoprostol via either the buccal route or the vaginal route, all patients achieved a favorable simplified Bishop score (> 5). The median initial favorable simplified Bishop score was 6 (range 6-8).

Overall, 57% of the patients experienced no complications. In the buccal group, 65% experienced no complications, whereas 67% of the vaginal group experienced at least one. However, this difference did not achieve statistical significance ($p = 0.199$). Almost ¾ of the patients (74%) were delivered via SVD. Median length of hospital stay was 3 days (range 2-6).

Median time from initial Misoprostol dose to time of favorable simplified Bishop score did not differ significantly between the buccal and vaginal groups ($p = 0.371$). See Table 2 for details. The only patient characteristic significantly associated with time from initial Misoprostol dose to time of favorable simplified Bishop score was BMI (Spearman $r_s = 0.594$, $p = 0.003$). Adjusting

for BMI had no substantial effect on the comparison of the buccal and vaginal group in terms of time from initial Misoprostol dose to time of favorable simplified Bishop score.

"Survival" curves comparing the buccal and vaginal groups in terms of time from initial dose of Misoprostol to time of favorable simplified Bishop score are given in Figure 1. "Survival", as explained earlier, in this context refers to the time from initial dose of Misoprostol to the time of favorable simplified Bishop score. The survival curves did not differ significantly between the two groups by the log-rank test ($p = 0.659$). Median "survival time" estimated using the life table results interval was 714 for the buccal group and 885 for the vaginal group.

Median time from initial Misoprostol dose to delivery did not differ significantly between the buccal and vaginal groups ($p = 0.371$). See Table 3 for details. The only patient characteristics significantly associated with time from initial Misoprostol dose to delivery were BMI (Spearman $r_s = 0.638$, $p = 0.001$) and length of hospital stay (Spearman $r_s = 0.479$, $p = 0.021$). Adjusting for BMI or LOS had no substantial effect on the comparison of the buccal and vaginal group in terms of time from initial Misoprostol dose to time of delivery.

"Survival" curves comparing the buccal and vaginal groups in terms of time from initial dose of Misoprostol to time of delivery are given in Figure 5. "Survival" in this context refers to the time from initial dose of Misoprostol to time of delivery. The survival curves did not differ significantly between the two groups by the log-rank test ($p = 0.962$). Median "survival time" estimated using the life table results interval was 1074 for the buccal group and 1320 for the vaginal group.

DISCUSSION

Currently, Misoprostol is widely used as a cervical ripening agent, however, its route of administration, as mentioned earlier, continues to be provider specific. Our study sought to determine whether a specific route of administration, between the vaginal and buccal routes, provided a significantly shorter time to a favorable simplified Bishop score, and ultimately, a shorter time to delivery. Shortening the time frame to both of these endpoints would benefit our patients by providing shorter induction times, and would also be more cost effective.

Overall, our study demonstrated that the times from initial Misoprostol dose to the time of favorable simplified Bishop score did not differ significantly between the buccal and vaginal groups ($p=0.659$). In regards to our secondary aim, the time from initial dose of Misoprostol to the time of delivery did also not differ significantly between the two groups ($p=0.962$). Therefore, at this time, our study does not support any specific mode of administration of Misoprostol over another for cervical ripening during the labor induction process. Our study does seem to suggest that BMI has an effect both on time to initial favorable simplified Bishop score, and time to delivery, however, it is unclear if this result would be reproducible if we had larger sample sizes.

There were many limitations of our study. The main limitation was its severely limited sample size, resulting in our study being unable to reach its desired power. Our desired sample size was originally 117 patients in each group in order to yield 85% power to detect an effect size of 0.41 or larger using a significance level of 0.05. Upon review of 350 charts, the vast majority of the

charts did not qualify for the study based on our inclusion and exclusion criteria. One oversight of our chart collection process was the fact that the majority of the charts excluded from our study used Misoprostol as an agent to control postpartum hemorrhage, and not as a medication for labor induction. Ultimately, only 23 of 350 charts that were reviewed were able to be included in the study, not meeting the calculated goal from our power analysis. Another limitation of our study includes the fact that data collectors were not blinded to the study design or hypothesis. Additionally, there was no distinction made between any differences in doses of Misoprostol during our study. Finally, cervical examination is still considered to be somewhat variable amongst providers, and it is impossible to know the exact accuracy in charting of the cervical check timing and details of each patient, and how that has affected our data. Ultimately, if the results of our study were reproducible with larger sample sizes, it would greatly benefit our patients to know if the route of administration does not in fact have an effect on time to delivery or time to favorable Bishop score.

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TABLES

Table 1. Comparison of Misoprostol Route Groups- Patient Characteristics

Characteristic	Buccal (n = 17)	Vaginal (n = 6)	Total (n = 23)
Ethnicity (%)			
Asian	1 (6%)	0 (0%)	1 (4%)
Black	8 (47%)	3 (50%)	11 (48%)
Hispanic	1 (6%)	0 (0%)	1 (4%)
Multi	1 (6%)	0 (0%)	1 (4%)
White	6 (35%)	3 (50%)	9 (39%)
Maternal Age*	28.0 ± 5.1	31.3 ± 7.7	28.9 ± 5.9
Misoprostol Dose			
25 mcg	14 (82%)	5 (83%)	19 (83%)
50 mcg	3 (18%)	1 (17%)	4 (17%)
Gravity[#]	3 (1-7)	2 (1-5)	2 (1-7)
Parity[#]	1 (0-6)	1 (0-3)	1 (0-6)
BMI*	34.7 ± 8.2	37.4 ± 12.9	35.4 ± 9.4
Initial Simplified Bishop Score[#]	1 (0-4)	3 (0-3)	2 (0-4)
Initial Favorable Bishop Score (> 5)[#]	6 (6-8)	6 (6-8)	6 (6-8)

*Mean ± S.D.

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[#]Median (range)

Table 1, cont.

Characteristic	Buccal (n = 17)	Vaginal (n = 6)	Total (n = 23)
Complications			
Arrest of Dilation	1 (6%)	0 (0%)	1 (4%)
Mediolateral Episiotomy	2 (12%)	0 (0%)	2 (9%)
Postpartum Hemorrhage	3 (18%)	3 (50%)	6 (26%)
Uterine Atony	0 (0%)	1 (17%)	1 (4%)
None	11 (65%)	2 (33%)	13 (57%)
Mode of Delivery			
pLTCS	4 (24%)	0 (0%)	4 (17%)
SVD	12 (71%)	5 (83%)	17 (74%)
VAVD	1 (6%)	1 (17%)	2 (9%)
Length of Hospital Stay (Days)[#]	3 (2-6)	3 (2-4)	3 (2-6)

[#]Median (range)

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Table 2. Comparison of Misoprostol Route Groups – Time from Initial Misoprostol Dose to Favorable Bishop Score

Route	n	Mean	Std. Dev.	Median	Min	Max
Buccal	17	763.1	283.2	714.0	435	1425
Vaginal	6	828.8	378.7	889.5	373	1366
All Subjects	23	780.2	303.0	729.0	373	1425

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Table 3. Comparison of Misoprostol Route Groups – Time from Initial Misoprostol Dose to Time of Delivery

Route	n	Mean	Std. Dev.	Median	Min	Max
Buccal	17	1303.5	827.8	1074.0	452	4216
Vaginal	6	1124.3	465.3	1337.5	516	1627
All Subjects	23	1256.8	743.9	1160.0	452	4216

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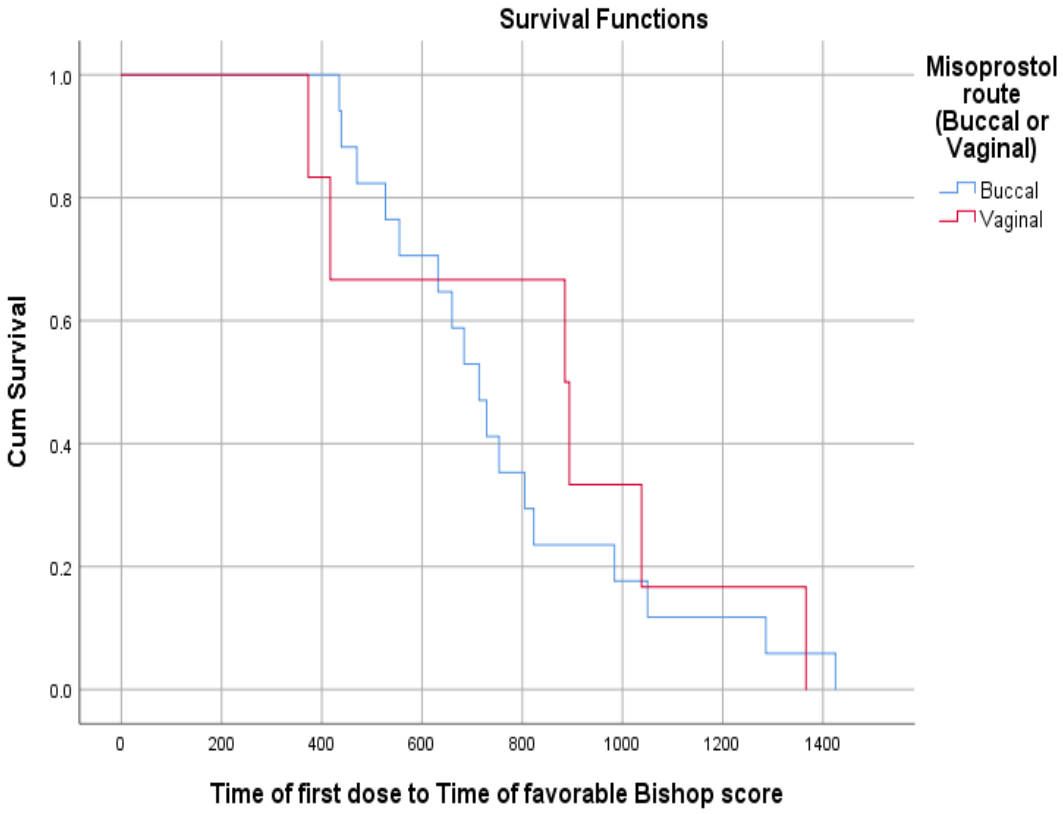

Figure 1. "Survival" curves comparing the buccal and vaginal groups in terms of time from initial dose of Misoprostol to time of favorable Bishop score. "Survival" in this context refers to the time from initial dose of Misoprostol to time of favorable Bishop score. The survival curves are not significantly different (log-rank test, p = 0.659).

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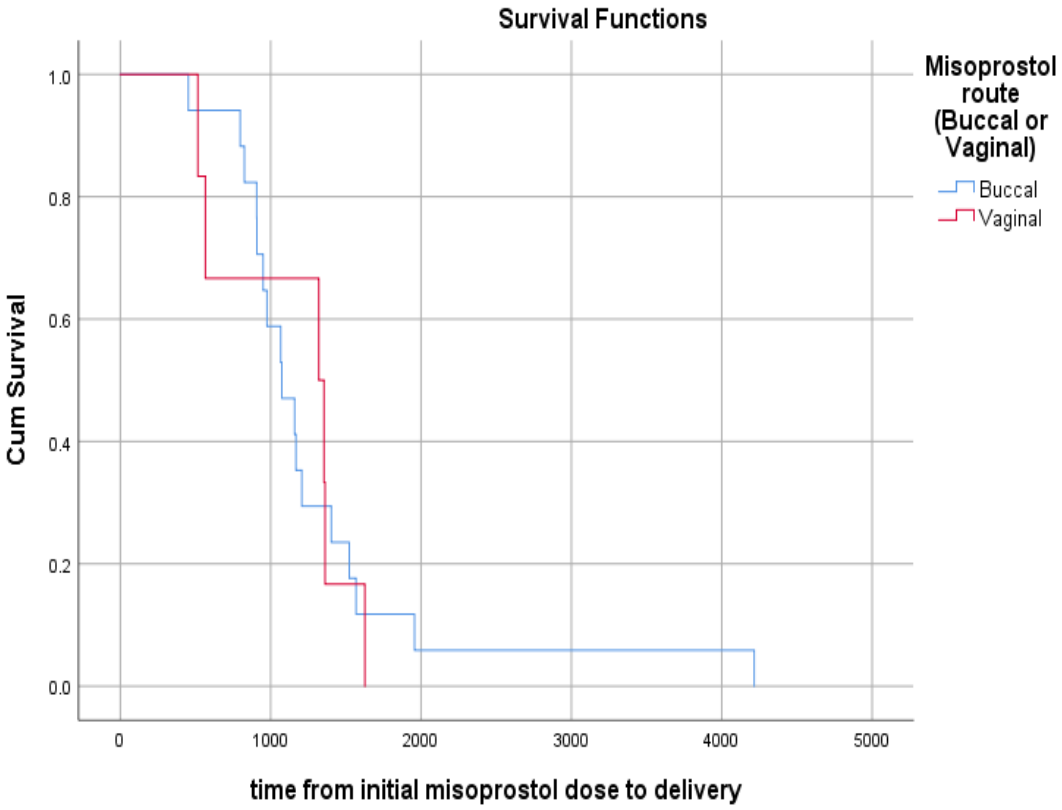

Figure 5. "Survival" curves comparing the buccal and vaginal groups in terms of time from initial dose of Misoprostol to time of delivery. "Survival" in this context refers to the time from initial dose of Misoprostol to time of delivery. The survival curves are not significantly different (log-rank test, p = 0.962).

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