

# The effects of bit chewing on borborygmi, duodenal motility, and gastrointestinal transit time in clinically normal horses

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## Abstract

**Objective:** To determine the influence of bit chewing on gastrointestinal transit in clinically normal horses.

**Study design:** Prospective crossover designed study.

**Animals:** Six healthy adult horses.

**Methods:** Horses were assigned randomly to treatment (apple flavored bit) and control (no-bit) groups and studied for 2 × 1-week trial periods with a 2-week washout period between trials. Horses were fasted for 24 h and slowly refed over 3 days. The bit was placed for 20 min every 6 h. Duodenal contractions and borborygmi auscultations were evaluated every 12 h, approximately 5 min following bit placement. Gastrointestinal total transit time (GI TTT) was measured by administering 200 colored beads via stomach tube and then collected in the manure until 50% and 80% were recovered. Measured variables were compared using an ANOVA or Wilcoxon signed-rank test and the *P* value was noted.

**Results:** The GI TTT was shortened in the bit chewing group (median: 106.37 h, range: 70–171 h) compared to the no-bit group (median: 170.1 h, range: 149–186 h) (*P* = .0156) at 80% bead passage (only 4/6 horses passed 80%). Borborygmi (*P* = .8193), duodenal contractions (*P* = .2605), and 50% bead passage (*P* = .0781) showed no differences.

**Conclusion:** Bit chewing was safe, inexpensive, and well tolerated. Bit chewing shortened GI TTT and might be an adjunct therapy to augment GI TTT. Further clinical studies are warranted.

**Clinical significance:** Ileus is a common complication following equine abdominal surgery with no current consistently successful treatment. Bit chewing may be a simple and inexpensive way to augment progressive GI motility.

## 1 | INTRODUCTION

Postoperative ileus (POI), or a disruption of normal gastrointestinal motor activity, is a recognized complication following abdominal surgery in horses. Causes of POI include general anesthesia, opioids, inflammation due to intestinal manipulation and distention, and endotoxemia.<sup>1,2</sup> The reported prevalence of POI following exploratory celiotomy varies from 6%–61.7%,<sup>2</sup> with the percentage increasing substantially if a small intestinal lesion is present.<sup>2–5</sup> Persistent POI has been demonstrated to lead to an increased likelihood of repeat laparotomy, development of laminitis, and increased cost, due to medications and increased hospital stay.<sup>2,6,7,8</sup> The mortality rate of horses that develop POI has been reported to be as high as 86%.<sup>6</sup>

Many therapies have been proposed to prevent and decrease the duration of POI in horses but no specific treatment has been considered completely effective.<sup>2,9</sup> For this reason, a multimodal treatment approach, including surgical intervention, appropriate nonsteroidal anti-inflammatory, pro-kinetic and anti-endotoxin therapy, gastric decompression as needed and appropriate fluid administration, is currently employed in attempts to prevent and treat POI with varying success.<sup>2</sup>

In human medicine, several nonpharmacological treatments have been evaluated to decrease POI, including early feeding and gum chewing.<sup>10</sup> Multiple studies in people have evaluated chewing gum as a form of sham feeding, which can be initiated before the gastrointestinal tract is able to tolerate bulk food.<sup>11–14</sup> Previous reports have speculated that gum chewing is a safe and well tolerated method to reduce the time from surgery to first fecal passage successfully following open and laparoscopic GI surgery in humans.<sup>11–14</sup>

Early feeding in equine patients that are actively refluxing is discouraged but the idea of sham feeding warrants evaluation in horses with POI. Giusto et al. evaluated the effects of bit chewing by placing a snaffle bit with toggles in the mouth of 10 adult horses and evaluating borborygmi in the right upper flank with the use of a digital phonendoscope. This study found that bit placement for 20 min produced consistent mastication and swallowing in all horses.<sup>15</sup> In addition, the study showed a substantial increase in short (<3 s) gut sounds in the first 5 min of bit application. These short contractions have been correlated with cecal segmental contractions, resulting in ingesta mixing.<sup>15</sup> The bit chewing was well tolerated by all horses in the study and no negative side effects were reported.<sup>15</sup> This information, and the promising information regarding effects of gum chewing on ileus in people, warrants further evaluation of the effects of bit chewing on the gastrointestinal tract of horses.

The purpose of this study was to evaluate bit chewing as a form of sham feeding, on total gastrointestinal transit time (GI TTT), duodenal motility, and borborygmi in clinically normal horses. We hypothesized that bit chewing would shorten overall GI TTT, increase borborygmi, and increase the frequency of duodenal contractions as seen on transcutaneous abdominal ultrasound when horses are bit chewing compared with when they are not.

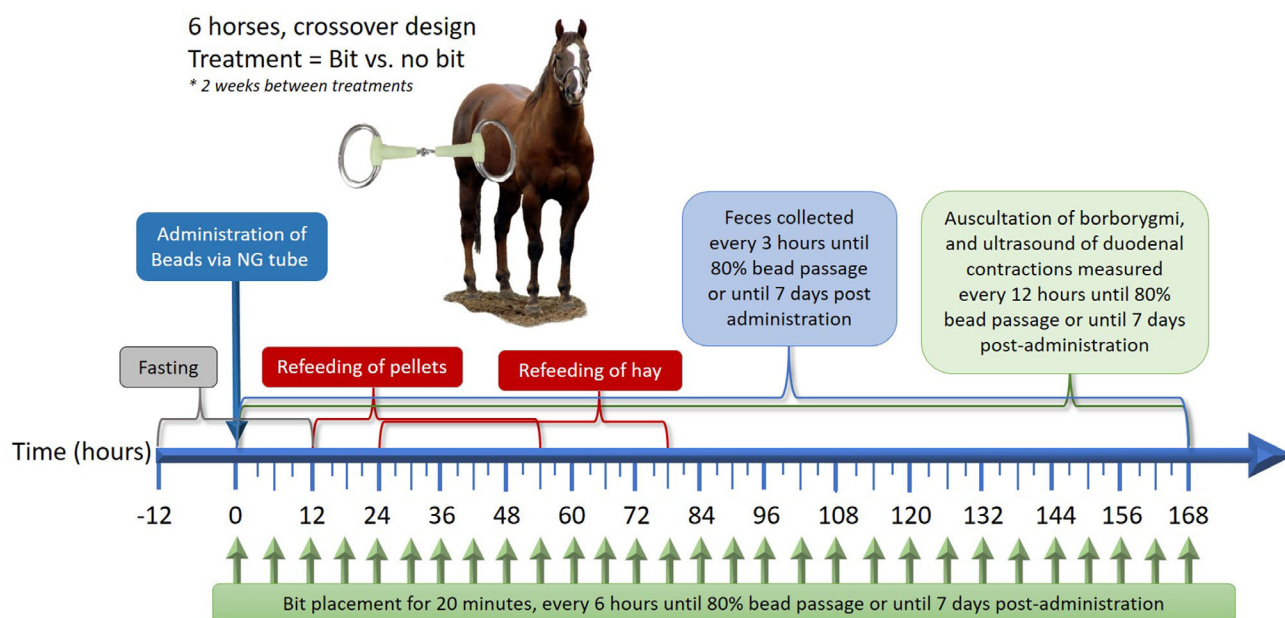
## 2 | MATERIALS AND METHODS

### 2.1 | Animals

All procedures performed on the horses were approved by the institutional animal care and use committee (Approval #: 18:094). Six healthy horses (quarter horses,  $N = 4$ ; thoroughbreds,  $N = 2$ ) of both sexes (geldings,  $N = 3$ ; and mares,  $N = 3$ ), with ages ranging from 5–14 years with a median body weight of  $500 \pm 42$  kg were included in the study. With a standard deviation difference of 0.5<sup>15</sup> with an  $\alpha$  of .05 and power of 80%, it was estimated that 12 horses would be required to measure differences between groups with sufficient sensitivity (Graph pad StatMate version 2.0, San Diego, CA). To utilize a smaller number of horses we elected to perform a crossover design allowing each subject to serve as its own control. All horses used in the study were part of the university's research herd. Inclusion criteria included having no history of gastrointestinal disease, a normal physical examination, and being on similar diets/pasture.

### 2.2 | Study design

The study was conducted as a prospective 2-period crossover whereby horses were studied for 2 weeks and had a 2-week washout period between treatments (bit or no bit; Figure 1). To reduce the influence of changing weather patterns, 3 horses were studied in the winter months and 3 horses were studied in the summer months. For each group, horses on identical feed were brought in from the same pasture and placed in individual  $3 \times 3$  m stalls in a nonenvironmentally controlled barn where horses could see other horses in stalls and pastures and were given a 24 h acclimation period. Horses were randomly placed in either the “bit” group or the “no-bit” group via a coin toss. After part 1 of the study was performed, all horses were returned back to the same pasture for 2 weeks as a washout period. The horses were then brought back into individual stalls and the study was repeated, with the



**FIGURE 1** Timeline of the experimental design. Duration of time horses were fasted (–12 h to 12 h); timing of the gradual refeeding pelleted food (from 12 h to 54 h); timing of the gradual refeeding of hay (from 24 h to 78 h); timing of bead administration (0 h); timing of bit placement (starting at 0 h for 20 min and continuing every 6 h until the 80% of beads were passed or 7 days postbead administration); initiation (0 h) and duration of fecal collection (every 3 h until the 80% of beads were passed or 7 days postbead administration), and initiation (0 h) and duration of auscultation for borborygmi and ultrasound of duodenal contractions (every 12 h until the 80% of beads were passed or 7 days postbead administration) are shown. Note that the horses were back to the full amount of pelleted feed at 54 h and the full amount of hay at 78 h postbead administration. NG, nasogastric

horses previously in the “bit” group now in the “no-bit” group and vice versa.

## 2.3 | Feeding schedule

In attempts to standardize the feeding schedule and simulate conditions similar to those of a horse presenting for colic, horses were fasted for 12 h prior to administering nondigestible beads. After an additional 12 h fast following bead application, a gradual and consistent refeeding schedule (see Table S1) was implemented in each horse to standardize total feed intake throughout the entire project. This feeding plan was based on a typical refeeding schedule in our hospital for a horse recovering from abdominal exploratory surgery. A gradual increase in pelleted food was provided from hour 12 until hour 54 of the study (500–600 g pellets every 4 h from hour 12 until hour 54, then 750–850 g pellets every 6 h until study completion). Grass hay was reintroduced at hour 24 and gradually increased until hour 78 (200–250 g hay every 4 h from hour 24–30, then 500–600 g hay every 4 h from hour 30–54, then 700–750 g hay every 6 h from hour 54–78, then 900–1000 g hay every 6 h until study completion). Horses were fed every 3 h until hour 54 of the study, followed by every 6 h until the end of the study.

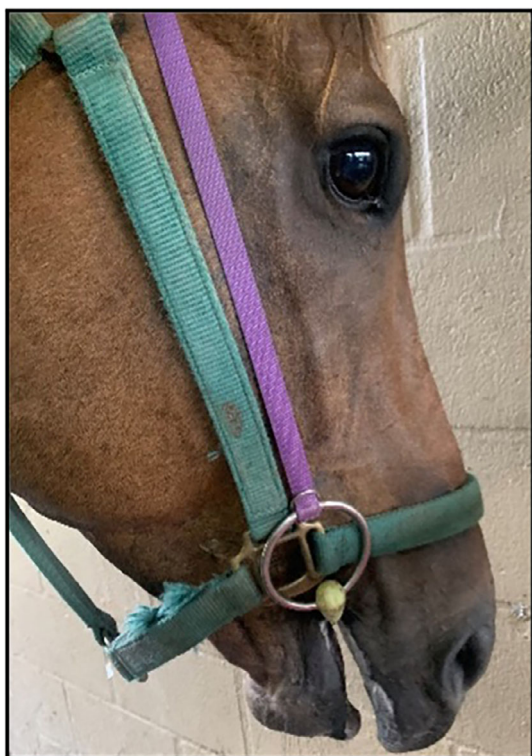
## 2.4 | Administration of beads: Transit markers

To measure GI TTT, nondigestible beads (200, 6 mm × 8 mm colored pony beads; Hobby Lobby Stores, Inc., Oklahoma City, OK) were administered without sedation using a nasogastric tube as previously reported.<sup>16</sup> In one horse, NG intubation was not possible without administering xylazine (0.2 mg/kg, IV) due to temperament. These beads were administered at time 0 of the study, after the initial 12 h fasting period (Figure 1). After the beads were administered, the nasogastric tube was removed, and each horse was fasted for an additional 12 h.

## 2.5 | Treatment: Bit chewing

Bit placement was initiated at time 0 after the initial 12 h fasting period, immediately following bead administration via nasogastric intubation (Figure 1). Each horse in the “bit” group had an apple flavored snaffle bit (Horze Equestrian, Watertown, Connecticut) placed in their mouth for 20 min every 6 h until they passed 80% of the nondigestible beads or for 7 days (whichever came first).

Application of the bit, which was kept in place using a modified headpiece that was placed slightly tighter than



**FIGURE 2** A horse chewing on an apple-flavored bit. Note that the bit is placed slightly tighter than a normal riding bit and chewing is evident by the presence of saliva around the bit and lips

one would place when riding (located within the interdental space with the presence of 2-3 wrinkles noted in the skin at the commissure the lips), led to consistent mastication, saliva production (Figure 2), and swallowing for the entire 20 min of bit placement. A researcher observed the horse for the entire bit-chewing period to ensure adequate mastication. The bit was gently agitated if the horse did not constantly masticate during these 20 min, resulting in consistent chewing behavior. Bit chewing was not performed at the same time as feeding, to prevent cephalic-vagal stimulation with food administration<sup>17</sup> from potentially confounding the results.

## 2.6 | Borborygmi: Gut sounds

Abdominal sounds in each of the four abdominal quadrants were auscultated with a stethoscope (3M Littman Classic III, 3M Company, St. Paul, MN) and short (<3 s) borborygmi were counted for 2 min in each of the four abdominal quadrants every 12 h (Figure 1). This was performed by the same investigator for each evaluation, to decrease interobserver variability. Each 12 h borborygmi measurement was obtained 5 min following initial placement of the bit and while the horse was still bit chewing, or at an equivalent time for horses in the “no-bit” group

similar to what was reported by Giusto et al.<sup>15</sup> The average number of borborygmi at each of the four abdominal quadrants were added together to determine the overall total number of borborygmi for each 12 h time throughout the study period.

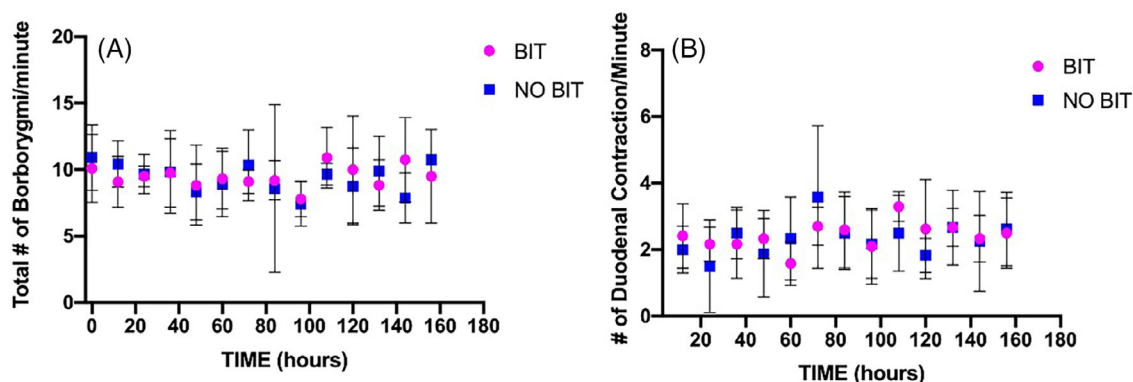
## 2.7 | Abdominal ultrasound: Duodenal motility

In this study, duodenal motility<sup>18</sup> was observed via transcutaneous abdominal ultrasound by the same investigator at every data collection point for 2 min. Prior to ultrasound, the hair was clipped at the level of the 14th-15th intercostal space in the dorsal aspect of the middle third of the abdomen at the level of the descending duodenum. The duodenum was visualized via ultrasound (Universal Ultrasound S9, Point Pleasant, New Jersey) using a 3 MHz macroconvex probe. A contraction was recorded when there was complete opening followed by complete closing of the duodenal lumen. The overall number of duodenal contractions were counted over a 2 min period and averaged per minute for each time point assessed. Duodenal contraction measurements were taken immediately following borborygmi auscultation and were recorded every 12 h until the end of each trial.<sup>18</sup>

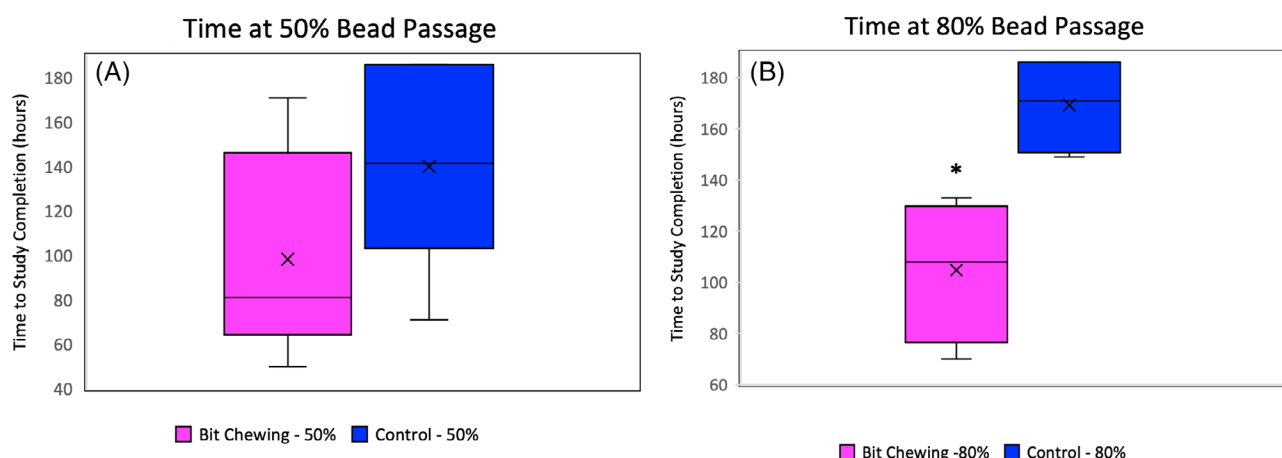
## 2.8 | Total gastrointestinal transit time: Bead collection

All fecal material was collected from the horse's individual stall every 3 h following colored pony bead administration. Beads within the fecal material were collected and counted every 3 h until 80% (160) of the beads were passed or 7 days had elapsed, whichever came first. Small, nondigestible beads are inert, passed easily through the lumen of a nasogastric tube, and were similar in weight to pelleted feed.<sup>16</sup> When administered for the determination of GI TTT, the bead passage was used to compare transit times between treatment groups, as previously reported.<sup>16</sup> Different colored beads were used in the second study period to ensure no confusion if all beads did not fully pass through the horses' gastrointestinal tract (GIT) in the initial study period. Initially, 80% bead passage was elected as the cutoff point to allow for bead loss due to errors, such as being missed within a manure pile, being lost either once outside of the horse or within the horse (presumably settled within the apex of the cecum or the ventral colon) or being stepped on by the horse and broken. Unfortunately, not all horses passed 80% of beads during the study period; however, all





**FIGURE 3** Scatter plot of borborygmi/minute and duodenal contractions/minute. (A) Mean total number of borborygmi per minute  $\pm$  SD (bars) over time in the bit (pink circles) and no-bit (blue squares) groups. There was only a very small difference ( $P > .05$ ) between treatments at any time over the study period. (B) Mean number of duodenal contractions observed ultrasonographically per minute  $\pm$  SD (bars) over time in the bit (pink circles) and no-bit groups (blue squares). There was only a small difference ( $P > .05$ ) between groups at any time over the study period



**FIGURE 4** Box-and-whisker plots of gastrointestinal transit time. (A) Time at which 50% beads passed in the bit (pink box) versus the no-bit (blue box) groups. There was only a small difference ( $P = .0781$ ) between 50% groups. (B) Time at which 80% beads passed in the bit (pink box) and no-bit (blue box) groups. There was a difference ( $P = .0156$ ) between the 80% groups, symbolized by an asterisk (\*)

horses did pass 50% of beads. For this reason, 50% bead passage was also evaluated in data analysis. The time for fecal passage of 50% and 80% of beads administered orally was recorded for each horse undergoing each treatment.

## 2.9 | Data analysis

The average numbers of duodenal contractions and borborygmi were compared over time between treatment groups using a mixed ANOVA with Tukey for post hoc comparisons. Treatment, time points and their interactions were entered as the fixed effects and each horse was entered as the random effect. Data was presented as mean  $\pm$  SD. Assumptions of these models (linearity, normality of residuals, and homoscedasticity of residuals)

and influential data points were assessed by examining standardized residual and quantile plots. The GI TTT was analyzed using the Wilcoxon signed-rank test and were presented as median (minimum-maximum). If the event was not observed during the experiment, the highest rank was assigned (186 h, the end of the study). Data analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

## 3 | RESULTS

Bit wearing was well tolerated by all horses in the study. There was an average of  $9.5 \pm 2.3$  total borborygmi auscultated per minute in the four abdominal quadrants in the bit group and  $9.4 \pm 2.9$  total borborygmi auscultated

per minute in the no-bit group. There was no difference in the number of borborygmi auscultated in any of the individual quadrants (right upper,  $P = .7433$ ; right lower,  $P = .4225$ ; left upper,  $P = .8049$ ; left lower,  $P = .4426$ ) or for the total number of borborygmi ( $P = .8193$ ) auscultated (Figure 3A) between treatment groups. There was an average of  $2.35 \pm 0.84$  duodenal contractions observed per minute in the bit group compared to an average of  $2.29 \pm 1.15$  in the no-bit group. There was no difference between treatments or between treatments over time for number of duodenal contractions per minute ( $P = .2605$ ) observed ultrasonographically (Figure 3B).

Although there were no differences in the number of borborygmi auscultated or duodenal contractions observed, GI TTT at 80% bead passage when horses were bit chewing was shorter when compared with the controls ( $P = .0156$ ) in 4 out of 6 horses that passed 80% of beads. The median time for 80% of the nondigestible beads to pass in the bit chewing groups was 106.375 h (range: 70–133 h) compared with the no-bit group at 170.125 h (range: 149–186) (Figure 4). The same 2 of 6 horses in both groups did not pass 80% of the beads in either group, but did pass 50% by the end of the study period, which was then evaluated retrospectively as a time point for all 6 horses. However, there was no difference in time to pass 50% of the nondigestible bead markers between the treatment groups ( $P = .0781$ ; Figure 4).

## 4 | DISCUSSION

The goal of this study was to determine the effects of bit chewing on gastrointestinal motility of normal horses to assess whether bit chewing would have any effect on the number of borborygmi auscultated, duodenal contractions observed, or GI TTT via passage of nondigestible beads. Results from this study refuted our hypotheses that bit chewing increased borborygmi auscultation and duodenal contractions via transcutaneous ultrasound. Our hypothesis of shortened GI TTT when horses were bit chewing in comparison with the control, however, was supported by the results.

The idea of bit chewing in the horse was inspired from reports of using gum chewing postoperatively in people as a common means to stimulate the cephalic-vagal response in attempts to stimulate the GIT without overwhelming the intestine with feed.<sup>9,19</sup> Some studies show no significant change in gum-chewing populations<sup>20</sup> in comparison with the control but a recent meta-analysis reported a reduced risk of POI in people who chewed gum postoperatively compared with those who did not.<sup>21</sup> That same report also demonstrated decreased time to passing of flatus and time to defecation in people who utilized gum

chewing postsurgery.<sup>21</sup> Sham feeding, whether in the form of chewing gum in humans or an apple flavored bit in horses, could be beneficial in patients that are not able to tolerate enteral feeding due to gastrointestinal stasis, which in horses can result in the production of gastric reflux. Multiple ways to decrease the risk of developing POI in the horse have been reported,<sup>2</sup> but POI remains a common complication associated with colic surgery in the horse.<sup>22</sup> Furthermore, the use of additional therapeutics in the postoperative period, including various prokinetic drugs such as lidocaine, metoclopramide, erythromycin lactobionate, and neostigmine,<sup>2,23,24</sup> increase monitoring, cost, and the potential for unwanted side effects for the hospitalized patient. Other therapies that can be used synergistically with various prokinetic medications, such as early ambulation and early feeding have become mainstay treatment additions in both human and equine medicine.<sup>18,25</sup> Sham feeding, however, has yet to gain popularity in equine patients, although there are no side effects and the additional expense is minimal.<sup>21</sup>

In this study three relatively noninvasive methods to evaluate gastrointestinal motility were utilized including: borborygmi auscultation, duodenal contractions via transcutaneous ultrasonography, and GI TTT measured through the passage of ingested inert beads.<sup>26–29</sup>

In contrast with findings by Giusto et al.,<sup>15</sup> this study did not demonstrate an effect of bit chewing on number of borborygmi auscultated (neither total or any single individual abdominal quadrant) at any time throughout the study. While auscultation remains a useful tool in the clinical patient, variable results, such as those found in our study, appear common in research settings, especially when not compared with a separate cohort receiving medications known to decrease borborygmi, such as  $\alpha$ -agonists.<sup>27,30</sup> Borborygmi auscultation has also been reported previously to have low interobserver agreement compared with intraobserver agreement.<sup>9</sup> For this reason only one observer auscultated each horse at all times. It is possible that this subjective measurement of gastrointestinal motility was not sensitive enough to find a difference in this study in normal horses. Interestingly, other therapies used for their prokinetic effects clinically, such as lidocaine, have also been shown to have no effect on number of borborygmi in normal horses when compared with a placebo.<sup>17</sup>

Abdominal ultrasound has become a mainstay diagnostic tool to evaluate the horse's gastrointestinal function in clinical patients,<sup>31,32</sup> and has also been reportedly used experimentally to evaluate intestinal motility.<sup>26,33,34</sup> In this study, bit chewing did not have an effect on duodenal contraction rates when compared with the no-bit horses. In retrospect, duodenal ultrasound may have detected differences between groups if each horse had

been evaluated more frequently or for a longer period. Perhaps comparing pretreatment assessment (ie, before bit placement) with assessments of each horse during treatment and/or post-treatment would have demonstrated an alteration in motility. The chewing of food without swallowing, or chewing gum,<sup>19,35</sup> creates a cephalic-vagal response in people within 15 min of initiation but it is possible that the parasympathetic response to chewing the bit in the horse takes longer than 7 to 10 min to cause changes in the duodenal contraction rate. It is also possible that the use of transabdominal ultrasound to evaluate gastrointestinal motility is too insensitive for this experimental model. Although ultrasound evaluation of duodenal contraction has been used successfully to demonstrate the effects of neostigmine and to a lesser extent metoclopramide on intestinal contractility in normal horses,<sup>36</sup> its use in a research setting has variable efficacy in multiple other reports.<sup>26,27,32</sup>

Although there was no effect of bit chewing on borborygmi or duodenal contraction, bit chewing did have an effect on overall GI TTT as determined by the passage of nondigestible beads. When horses had a bit placed, the time to 80% bead passage was hastened compared with the no-bit controls. Unfortunately, not all horses passed 80% of the beads by the end of the study period. It was anticipated that not all 200 beads would be recovered but it was expected that horses would pass at least 80% of beads within 186 h postadministration. In a previously reported study, normal horses passed 75% of beads in  $42 \pm 11$  h.<sup>17</sup> A reduction in the number of gastrointestinal sounds due to fasting has been reported in horses<sup>37</sup> and although we did not see a difference in number of borborygmi between treatment groups, it is possible that the fasting and slow refeeding schedule used in this study delayed transit more than expected in regards to bead passage. Retrospectively, as all horses did pass at least 50% of administered beads, it was decided to evaluate 50% bead passage to determine if there was an unidentified early effect of bit chewing on gastrointestinal transit time in the normal horse; however, there was no difference at this point between groups. Overall, despite the small sample size and the possible confounding factor of decreased food intake early in the study period, bit chewing did hasten bead passage, suggesting that the application of a bit could have an effect on some aspect of gastrointestinal motility under certain conditions.

This study has several limitations, including the methods available to assess gastrointestinal motility in the horse accurately. Methods used to assess gastrointestinal motility in the horse are limited. We selected three techniques, which are relatively noninvasive, to determine if bit chewing would have an effect gastrointestinal motility. Limitations involving the evaluation of borborygmi and

duodenal contractions include the timing and duration of assessment. Evaluating for longer periods of time or at different times points in relation to bit chewing may have demonstrated differences not appreciated in the current study. This current study design of evaluating duodenal contraction and borborygmi auscultation every 12 h was altered after the initial study period, where each motility assessment was performed every 6 h instead of every 12. Preliminary statistical analysis of these initial data did not reveal a difference between study groups, and for this reason the assessment frequency was decreased to every 12 h, which is why 12 h interval data was only reported in this paper. With hindsight this could have affected the outcome of the study, although the initial results did not reveal any indication of the sort.

As previously stated, nondigestible beads used in this study served as biomarkers to objectively evaluate GI TTT.<sup>16</sup> Ideally, the use of a recordable camera or tracker within the GIT would have been implemented in each horse to determine GI TTT more accurately. Unfortunately, wireless ambulatory capsules, recordable cameras or trackers have been used with limited success to measure GI transit time in our equine patients, due to limitations arising from the body mass of horses, limited battery life, and cost.<sup>38,39</sup> The invention of a more efficient system would be fundamental to equine intestinal research and would likely be more accurate than the use of beads as biomarkers. Until that time, however, beads, such as those used in this study or radiopaque beads,<sup>40</sup> are used as biomarkers to determine GI TTT.

Another limitation of this study is the collection of data from a small sample size. The number of horses used in this study was based on a previous study where a total of 10 horses ( $n = 5$  per group) demonstrated a difference in number of borborygmi in the right dorsal quadrant after bit placement.<sup>15</sup> Unfortunately, our crossover study with 6 horses ( $n = 6$  per group) did not yield similar results. We were not able to find a difference in duodenal contractions, number of borborygmi or GI TTT at 50% bead passage. We did, however, demonstrate a hastening of nondigestible bead passage at 80% when horses had the bit placed compared to when they did not. This finding alone does not prove that bit chewing will increase gastrointestinal motility in all normal horses or prevent or treat POI in clinical cases but it does suggest that further studies are warranted. A large multicenter study, randomly assigning postoperative horses to the bit versus control group should be performed to determine the effect of bit chewing on POI. Ideally the inclusion criteria for this future study would include horses at a higher risk of developing postoperative reflux, such as those with small intestinal lesions or with those undergoing small intestinal resection and anastomosis. Finally,

one horse in the study had to receive sedation (xylazine), a drug known to cause ileus, albeit transiently, for nasogastric intubation, which could have altered results. The exact same dose was given to the horse for both study periods, however, and due to personnel safety, it was a necessary risk.

In conclusion, the results of this preliminary study demonstrate that bit chewing was safe and well tolerated in horses and resulted in reduction of GI TTT. Benefits of bit chewing as a potential tool to augment gastrointestinal motility include being very well tolerated, having negligible side effects, and being inexpensive, especially compared with currently available prokinetic medications or the administration of replacement fluids. It can also be used in conjunction with other treatment protocols already established in hospital settings with little to no added work or difficulty for personnel. Although the clinical significance of bit chewing (for 20 min every 6 h) to hasten the time of 80% bead passage in normal horses is unknown, the results of this study support further investigation into the use of the bit, particularly in cases with compromised gastrointestinal motility.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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