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Effect of Caffeine on Colonic Manometry in Children

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ABSTRACT

Objectives: Coffee and caffeinated products have been widely consumed for many centuries. Previous adult studies have suggested that both coffee and decaffeinated beverages induce colonic motility. However, no study has been conducted in pediatrics, and the role of caffeine alone in pediatric colonic motility needs to be explored.

Methods: A prospective study of pediatric patients undergoing standard colonic motility testing that were able to consume caffeinated coffee, decaffeinated coffee, and caffeine tablet during colonic manometry. Patients who had a gastrocolonic reflex and high amplitude propagated contractions (HAPCs) in response to intraluminal administration of bisacodyl in the colon were included in the final analyses.

Results: Thirty-eight patients were recruited, 22 of which were excluded, 11 due to abnormal studies (no HAPC seen in response to intraluminal response to bisacodyl), and 11 due to inability to consume all study agents or complete the study. Sixteen patients met criteria for final analyses. Intracolonic bisacodyl produced a larger area under the curve (AUC) compared to all other agents. Caffeinated coffee resulted in a higher AUC, motility index (MI), and time to HAPC compared with decaffeinated coffee ($P < 0.05$). There was no significant difference between caffeinated coffee and caffeine tablet, or caffeine tablet and decaffeinated coffee.

Conclusions: Caffeine is indeed a colonic stimulant; however, other components of caffeinated and non-caffeinated beverages likely induce colonic response and require further evaluation for possible use as a colonic stimulant.

Key Words: caffeine, coffee, colonic motility, decaffeinated coffee, gastrocolonic reflex, HAPC

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What Is Known

- Coffee is a colonic stimulant.
- Decaffeinated coffee acts as a colonic stimulant.
- Adult studies have shown beneficial effect of coffee to reduce postoperative ileus.

What Is New

- Caffeine acts as a colonic stimulant in pediatric patients.
- Both decaffeinated coffee and caffeinated coffee showed colonic stimulant effects suggesting there may be components other than caffeine aiding in this response.
- Caffeinated coffee produces a faster colonic response than decaffeinated coffee.

Coffee has been consumed for many centuries, and thought to have stimulant effects on the gastrointestinal system (1). In 2 adult studies, caffeinated coffee (CC) along with decaffeinated coffee (DC) produced colonic stimulation (2,3). Interestingly, in the study by Rao et al (2) there was a significant increase in the area under the curve (AUC) when comparing DC with water, specifically in the transverse and descending colon. In the study by Brown et al (3) motility index (MI) was similarly increased following ingestion of CC and DC compared to baseline. Therefore, it is suggested that colonic response maybe independent of caffeine.

Evaluation of colon function using colonic manometry especially in pediatrics, includes identification of high amplitude propagated contractions (HAPC), as this is most notably associated with mass movement, defecation, and is the most recognizable motility pattern (4). The onset of HAPC in response to intraluminal bisacodyl challenge is the most clinically significant part of the test (5). Some have suggested that the study could be abbreviated to include only the bisacodyl challenge (6). The gastrocolonic response to meal helps to identify normal, myopathic, and neuropathic colons (5,7). Interpretation of the gastrocolonic response is typically visual and relies upon age-based changes in motility patterns. There is consensus that the colonic manometry can be considered normal when there is an increase in contractility after a meal and the occurrence of spontaneous, meal-induced, or bisacodyl-induced HAPC propagating to the recto-sigmoid junction (5).

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While the effects of both CC and DC have been evaluated in adults, no study has investigated the effects of coffee in pediatric patients. In addition, it is unknown if the impact on colonic motility is due to caffeine versus other components of coffee stimulating the colon. Our primary research question was to assess whether caffeine is a colonic stimulant in pediatrics. In addition, we looked to evaluate the colonic response to intraluminal administration of bisacodyl (IB) into the colon, compared to drinking CC, DC, and taking a caffeine tablet (CT). Response was measured as occurrence of HAPCs to different study agents and differences in the time to occurrence of HAPCs. Aside from this quantitative assessment of HAPCs, we report patient symptoms and clinical presentation before and after colonic motility testing.

METHODS

This is a prospective study in pediatric patients undergoing colonic motility testing for refractory constipation with or without encopresis at Arnold Palmer Hospital for Children. Patients enrolled in the study consented to consuming study agents—CC, DC, and CT during standard colonic manometry testing. Patients between 4 and 18 years of age who consumed all study agents and completed colonic manometry testing were included in the study. Intravenous propofol anesthesia without paralytics was used for colon catheter placement. There were no specific home medications discontinued prior to or during the study except for medications that may impact motility, such as magnesium and senna-based medications. Any medications used as part of a bowel regiment had been discontinued prior to clean out and were not used during the time of the study. None of our patients used narcotics during the study.

Patients who were unable to consume all the study agents—CC, DC, CT—had significant catheter migration, unable to complete the study, or did not have HAPC in response to IB were excluded from analysis.

The study was approved by the Institutional Review Board of Arnold Palmer Hospital for Children.

Survey

All patients were given a pre-procedure questionnaire that inquired about stool habits, caffeine intake, and defecation response to agents used 1 month prior to the procedure. A similar post-procedure questionnaire was given at the end of the study to determine patient response to agents including urge to defecate, having a bowel movement, any discomfort in response to each agent.

Colonic Motility Testing Protocol

All colonic manometry testing at our institution included continuous recording for up to 24 hours. Initially, the water-perfused motility catheters were placed with 6–8 sensors spaced 10–15 cm apart in retrograde fashion with the aid of the colonoscope. Catheter placement typically occurred in the early afternoon. Fluoroscopy and X-ray were routinely utilized to confirm placement. After placement of manometry catheter and patient recovered from anesthesia, standard protocol involved drinking water, consumption of meal, bisacodyl administered orally (PO), bisacodyl administered per rectum (PR) in the form of a suppository, and IB into the proximal colon using the motility catheter port. Dose of bisacodyl used was 0.2 mg/kg, rounded to 5 or 10 mg doses administered PO, PR, and IB (7). For inclusion in the study, additional study agents CC, DC, and CT were required to be consumed by patients during colonic manometry recording. Each step in the standard protocol and study agent administration was separated by at least 90–120 minutes intervals and given in the following order: day 0—warm water, meal with PO bisacodyl, DC (9 mg caffeine), and PR bisacodyl. Study was recorded overnight and patients typically slept at end of day 0 into day 1. After the patient was fully awake, day 1—CC (116 mg caffeine), IB, and CT (100 mg caffeine) were given (Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/C945*). Temperature of each liquid including water, CC, and DC was measured prior to consumption. Patients were asked to consume 6 oz of each liquid over a 10-minute time frame and told not to consume any other agent for that hour. Creamer and noncaloric sugar were allowed and documented. At least 2 hours were given between the evening meal and DC.

Data Collection

Time of consumption of food, drink, medications, study agents, urge to defecate, passing bowel movement, and any symptoms of pain were noted in a diary to correlate with readings obtained during the study. HAPC was defined as a colonic contraction at least 60 mmHg in amplitude, lasting 10 seconds and propagating through at least 3 channels (4). Initial calculations were done based on AUC from $T = 1$ to $T = 60$ minutes for the hour following agent consumption or administration of medication. Separate calculations were then conducted for HAPC during the hour after agent consumption or administration. HAPC were individually marked providing automated AUC, while MI of the HAPC were manually calculated. Briefly, AUC is the summation of pressure amplitudes over a period of time (8). MI = ln[(number of peaks × total amplitude) + 1] (9). Time to HAPC from agent consumption was recorded in minutes, along with presence of HAPC as Yes or No. Pre-test questionnaire statements "Never" and "Rarely" were deemed as No, while "Sometimes," "Often," and "Always" were deemed as Yes.

Data Analysis

Patients with increase in motility after a meal and the occurrence of spontaneous, meal-induced, or IB-induced HAPC propagating to the recto-sigmoid junction were included in the study and deemed to have functional colonic motility. Patients were excluded from analysis if they had abnormal motility testing with no colonic response to IB, and evidence of colonic inertia or colonic dysmotility.

Statistical Analyses

Data are reported as mean with standard deviation, and frequency with percentages. We initially conducted pairwise comparisons between each agent for AUC with Wilcoxon rank test. We further looked at pairwise comparisons of AUC and MI for HAPC present in the 60-minute period after each agent. More specifically, we were interested in differences of AUC and MI between IB, CC, DC, and CT. These comparisons were conducted with the Wilcoxon rank test. To assess time to occurrence of HAPCs based by agent type, we conducted a time to event analysis without censoring. Finally, results on the patient survey are reported descriptively. All statistical testing was conducted in (IBM Corp., Armonk, NY, USA) SPSS 26 and a $P < 0.05$ was used for statistical significance.

RESULTS

Our study recruited 38 individuals, of which 16 (42%) were used for analysis. Eleven individuals had abnormal studies with no HAPC recorded for the duration of the study, while the other 11 either did not consume the study agents (n = 3), had significant catheter migration (beyond transverse colon) (n = 4), or had an incomplete study (n = 4) which was due to the study being terminated before patients were able to consume all study agents in a 24-hour period.

Average age was 11±3 years, and 9 (56%) female. All patients had documented symptoms of chronic constipation, and 63% (n = 10) had encopresis. Of the 16 patients, 1 had Methylenetetrahydrofolate reductase (MTFHR) mutation with a 16p11.2 microduplication, 1 with small fiber neuropathy, 1 with vesicoureteral reflux and renal duplication, and 3 with attention deficit hyperactivity disorder.

A total of 88% (n = 14) had previously consumed caffeinated beverages of which 29% (n = 4) had recalled urge to defecate. Posttest survey response showed either urge to defecate, or actual bowel movement in 100% (n = 16) of patients after IB, compared to 81% (n = 13) after CC, 56% (n= 9) after CT, and 50% (n = 8) after DC (Table 1).

In addition, patient diary during study reported abdominal pain in 75% (n = 12) of patients that received bisacodyl medication, compared to 69% (n = 11) after CC, 69% (n = 11) after CT, and 38% (n = 6) after DC. In the hour after meal and PO bisacodyl, 13% (n = 2) had HAPC, 38% (n = 6) had urge to defecate, and 38% (n = 6) had abdominal pain, time to HAPC was 10.5 minutes (8–13 minutes). Among the 11 patients excluded due to abnormal study, 7 had documented urge to defecate with IB, 7 had urge to defecate after 1 or more of study agent CC, DC, or CT, and 2 had urge with study agent and not IB. Despite urge to defecate, none of these patients had any HAPC seen during study period and were excluded from the final analysis.

Comparison of Study Agents and IB

Based on AUC between $T = 1$ and $T = 60$ minutes after each agent, the response of the colon to IB was more robust, relative to other agents ($P < 0.05$). Both CC and DC had resulted in a higher AUC compared to CT ($P < 0.05$), but no significant difference between CC and DC (Fig. 1).

We additionally looked at the AUC and MI of HAPCs that were recorded an hour after each agent consumption. HAPCs in response to IB was 100% (n = 16), HAPCs were present in 88% (n = 14) with CC consumption, compared to 75% (n = 12) with administration of CT and 50% (n = 8) with DC consumption.

TABLE 1. Demographics along with responses to pretest and posttest surveys

Age, y	11±3
Female	9
Constipation	16 (100%)
Encopresis	10 (63%)
Urge to defecate pretest (n = 16)	
Morning	5 (31%)
Meals	9 (56%)
Laxative medications	11 (69%)
Caffeinated beverage (n = 14)*	4 (29%)
Urge to defecate posttest (n = 16)	
Morning	9 (56%
Meals	13 (81%)
Intracolonic Dulcolax	16 (100%)
Caffeinated coffee	13 (81%)
Decaffeinated coffee	8 (50%)
Caffeine tablet	9 (56%)

*Fourteen individuals had previously reported use of caffeinated beverages including soft drinks, tea, and/or coffee.

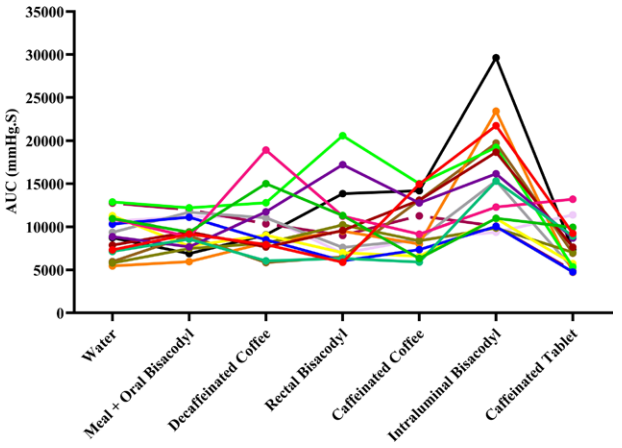

FIGURE 1. Colonic response of all individuals based on AUC (mmHg s) after consumption of each agent. Each line represents an individual and each dot is the response to the respective agent from $T = 1$ to $T = 60$ minutes following agent administration/consumption. AUC = area under the curve.

Both AUC and MI were higher for IB compared to other agents ($P < 0.05$). CC had a significantly higher AUC and MI compared to DC ($P < 0.05$), but not compared to CT. CT was not significantly different compared to DC in either metric (Fig. 2). Example of HAPC in response to the DC, CC, IB, and CT are shown in Figure 2, Supplemental Digital Content, *http://links.lww.com/MPG/C946*.

Across agents that produced HAPC, IB produced a response among all participants, and within 10 minutes, which was quicker than all other agents ($P < 0.05$). CC was quicker to produce a HAPC compared to DC ($P < 0.05$), but not CT. However, there was no difference in time to HAPC between DC and CT (Fig. 3).

DISCUSSION

This is the first study to evaluate the effect of CC, DC, and caffeine alone on colonic motility in pediatric patients with refractory constipation. While accounting for caffeine dose, the result of our study supports that caffeine is a colonic stimulant. However, we do not necessarily feel this is purely a dose-dependent phenomenon since DC (9 mg of caffeine) also showed stimulant properties in half of the patients suggesting a component other than caffeine in coffee may have contributed to a motor response.

The majority of patients with functional colonic motility, with HAPC in response to bisacodyl, had response to caffeinated agents. Interestingly, among patients excluded due to abnormal studies there was a sensory response to caffeinated agents, that is, urge to defecate without measurable HAPC. This highlights the complex sensory and motor pathways at play in colonic motility suggesting some element of the neural pathways maybe interrupted. The AUC comparison in the hour after each agent administration shows the most robust response to IB (Fig. 1). This pattern was also seen in favor of IB when evaluating the AUC and MI based on HAPC noted after each agent, and time to HAPC among all patients (Figs. 2 and 3).

Although not as robust as IB, there was HAPC present with CC, DC, and CT. There was, however, a difference in stimulatory response between CC, DC, and CT suggesting that there may be additional variables in coffee to aid in its colonic response. Indeed, the little difference between DC and CT highlights this well. Outside

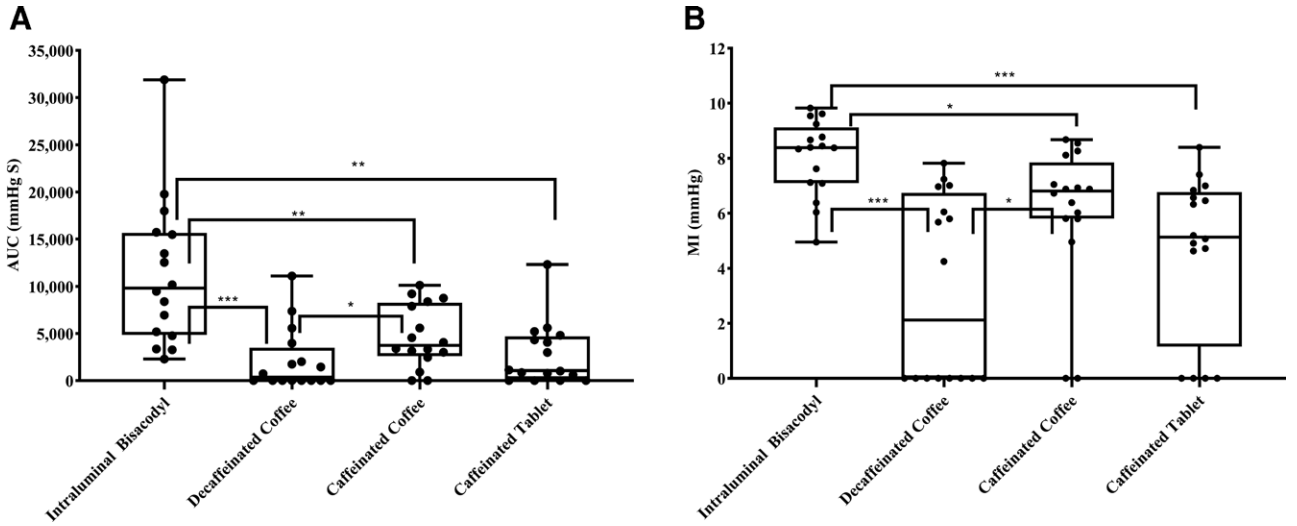

FIGURE 2. Colonic response to 4 stimulant agents based on HAPC. (A) AUC based on HAPC for each agent. (B) MI based on HAPC for each agent. Bars connecting various agents represent statistical significance as follows: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. AUC = area under the curve; HAPC = high amplitude propagated contraction; MI = motility index.

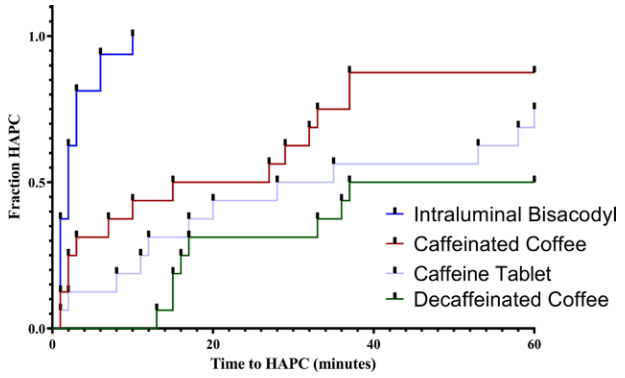

FIGURE 3. Time to event analysis of 4 stimulant agents that produced HAPC. Time to HAPC for intracolonic bisacodyl was significant versus all other agents ($P < 0.001$). Time to HAPC for CC versus DC was significant ($P < 0.05$). CC = caffeinated coffee; DC = decaffeinated coffee; HAPC = high amplitude propagated contraction.

of caffeine, coffee includes small amounts of protein, lipids, sugars, minerals as well as neurotransmitters and hormones such as serotonin. These components would not be present in a CT; thus, it is therefore possible that other components such as polyphenols or serotonin molecules have an impact (1,10).

Interestingly, in a study in which postoperative patients were given 100 mL DC, CC, and water 3 times a day, DC reduced time to first bowel movement compared to water and coffee (11). This suggests other components of coffee have a stronger influence on motility than caffeine alone, and maybe more concentrated in decaffeinated beverages. In our cohort, 2 individuals produced a HAPC faster with consumption of DC versus CC. A study by Brown et al (3) proposed that some individuals may be inherently more responsive to DC based on the finding of higher MI in DC compared to CC. On the other hand, in the study by Rao et al (2), the AUC for CC was higher than DC.

Gastrocolonic reflex is an important variable in colonic motility testing. Previous studies looking specifically at gastric and small intestinal transit found orocecal transit time to be a minimum of 60 minutes with no difference between coffee compared to water (2,12). As the time recorded for response to each agent in our study was 60 minutes, it seems more likely any affects related to CC, DC, and CT are not due to direct stimulation of the colon, but rather due to gastrocolonic reflex and neural or neurohumoral responses. While caffeine is rapidly absorbed, other molecules such as chlorogenic acid and melanoidins are not quickly absorbed in the stomach or first part of the duodenum, and so may continue to have an effect (13).

Another interesting aspect of the study was the response to warm water relative to meal. While a gastrocolonic response is typically associated with a high calorie meal, we did note the AUC over an hour was similar between water and a meal. One study in postoperative patients did note increased passage of flatus with warm water compared to control (14). To our knowledge this has not been evaluated with motility tracings in pediatrics and may require further investigation as to effect of temperature, Nil per os (NPO) status, and volume during ingestion of water.

In this study, use of artificial sweetener (AS) or small amount of creamer to change flavor were permitted. Thirteen out of the 16 patients had used some form of AS with equal amounts between caffeinated and decaffeinated beverages. Studies with cell lines and animal models suggested increase in glucagon like peptide 1 and serotonin release may impact gastric motility. Randomized studies in humans did not show an effect (15–17). However, there have not been any formal studies looking at AS effect on colonic motility. Di Stefano et al (18) found that caloric intake of 200 kcal was used to stimulate rectosigmoid activity. In our study, creamer use did not go above 100 kcal. In addition, AS and creamer use were the same within each subject (n = 13) for caffeinated and decaffeinated beverages, yet 15% (n = 2/13) of CC consumption versus 54% (n = 7/13) of DC consumption did not produce a HAPC suggesting addition of sweeteners and creamers did not have an effect.

As previously noted, use of caffeinated and decaffeinated products has been shown to decrease postoperative time to bowel movement and postoperative ileus (11,19). Our study supports this by showing objective colonic stimulatory results with coffee (DC and CC). A previous review by Nawrot et al discussed multiple small studies on caffeine in the pediatric population ranging

from 5 to 21 years of age. Max caffeine doses were 10 mg/kg/day or 400 mg/day (20). These studies were heterogeneous, but seemed to suggest positive cognitive outcomes, with variation in negative outcomes such as anxiety. Based on adult studies, negative effects were seen most in those with history of panic disorder and doses >400 mg/day (21). International data suggest average consumption in pediatric patients in the United States is 1 mg/kg/day, while in other countries it can go up to 3 mg/kg/day. The paper suggests that <2.5 mg/kg/day should be consumed in pediatrics (22). At these doses it appears to be safe and could allow for limited use in settings such as postoperative ileus. Additionally, physiological response to drinking coffee (urge to defecate/defecation) may serve as a predictive model to colonic function as only patients with normal colonic studies consistently displayed this response.

The primary limitation of our study is that it was conducted on patients who required motility testing for refractory chronic constipation with or without encopresis. Therefore, they do not represent a normal population. Another potential limitation involves the suggested effect of anesthesia. While some investigators suggest time is required for the colon to fully wake up following sedation, 1 pediatric study showed no difference in the presence of HAPC between 4 hours and 24 hours post placement (23).

One could certainly argue that any difference noted between CC (116 mg caffeine) and CT (100 mg caffeine) is due to the caffeine dose. However, as previously noted, DC has 9 mg of caffeine and motility indices were not statistically significant relative to CT, suggesting it is not a dose-dependent response.

In this study, PO bisacodyl was given a median of 2 hours 10 minutes (2.05–2.50) prior to DC, and more than 12 hours before CC, IB, and CT. Therefore, one cannot exclude the possibility of bisacodyl effect on DC or other agents. However, a literature review suggests onset of action of bisacodyl is between 6 and 12 hours, and one study that used scintigraphy in normal adults showed median time to ascending colon emptying of 6.5 hours (5–8 hours) (24). Based on this, PO bisacodyl is less likely to have impacted HAPC for those respective agents.

CONCLUSIONS

In conclusion, our study supports caffeine as a colonic stimulant in pediatric patients. The difference noted in vehicle of caffeine delivery (coffee liquid vs tablet) should be further investigated as there may be additional variables in coffee preparation that have colonic stimulant effects and may be of use in bowel management strategies, aiding in return of bowel function in postoperative pediatric patients.

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