CME

Effect of Octreotide on Colonic Motility in Pediatric Patients With Chronic Recalcitrant Constipation

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ABSTRACT

Objective: The aim of the present study was to study the effect of octreotide on colonic motility in pediatric patients with recalcitrant chronic constipation/encopresis and other suspected colonic motility disorders.

Methods: This was a nonrandomized, single-center, open-label, prospective study evaluating the effect of a single subcutaneous dose of octreotide on colonic motility.

Results: Thirteen patients (5 boys) were enrolled in the study. The age range was 4.6 to 16.2 years. Eleven patients (84%) had normal colonic manometry and 2 patients (16%) had colonic neuropathy. Motility Index (MI) (mmHg) for the 15 minutes before and after octreotide infusion was 6.03 ± 1.26 (95% confidence interval [CI] 5.35–6.72) and 5.32 ± 1.66 (95% CI 4.42–6.23), respectively, with *P* value of 0.08. MI for the 30 minutes before and after octreotide infusion was 6.89 ± 1.37 (95% CI 6.14–7.64) and 6.71 ± 1.47 (95% CI 5.91–7.52), respectively, with *P* value of 0.55. MI for the 45 minutes before and after octreotide infusion was 7.73 ± 1.32 (95% CI 7.01–8.45) and 7.53 ± 1.38 (95% CI 6.78–8.28), respectively, with *P* value of 0.8.

Conclusion: Our study showed that the administration of octreotide resulted in no significant changes in colonic MI in pediatric patients with chronic recalcitrant constipation.

Key Words: colonic dysmotility, colonic manometry, constipation, Motility Index, octreotide

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What Is Known

- Treatments options for patients with intractable constipation and colonic dysmotility are very limited.
- Octreotide induces phase III of the migrating motor complex in the small intestine.

What Is New

- Octreotide causes no significant changes in colonic motility index in pediatric patients with chronic recalcitrant constipation and a normal colonic manometry.

Constipation is a common problem worldwide with an estimated prevalence of 3% (1). In the Western world 10% to 20% of adults have constipation (2). Constipation is commonly encountered in pediatrics too, contributing to 3% of the general pediatrician office visits, and 25% of pediatric gastroenterology visits (3). Bongers and Benninga (4) studied the long-term prognosis of pediatric patients with constipation; nearly 30% of patients continued to be symptomatic despite aggressive medical and behavioral therapy, with a mean follow-up of 11 years. These subsets of patients with intractable constipation often need a colonic motility study to determine whether their symptoms are because of a colonic dysmotility (5). Based on the results of the study, appropriate therapeutic interventions may be recommended. Patients with intractable constipation and normal colonic motility are often offered surgical treatment (MACE [Malone antegrade continence enema]/cecostomy) if all medical therapy has failed (6). Patients with true dysmotility may need MACE/cecostomy or total or segmental colonic resection depending on severity of the colonic dysmotility. There is a need to identify newer medical therapies to treat patients with intractable constipation and colonic dysmotility because treatments options are very limited (5).

Octreotide is a synthetic octapeptide analog of somatostatin (7). It has several gastrointestinal actions (8–11). Octreotide induces phase III of the migrating motor complex in the small intestine (12). Von der Ohe et al (13) conducted a randomized blind study assessing the regional effects of octreotide on the gastrointestinal tract; the study showed improvement in the colonic Motility Index (MI) and statistically significant phasic pressure activity in the octreotide group compared with placebo. Soudah et al (14) showed that octreotide stimulated rectosigmoid motility via cholinergic pathways resulting in improved colonic transit. Scarpignato and Pelosini (15) used octreotide in small pulse doses in patients with irritable bowel syndrome and noticed that it accelerated intestinal transit. Cullen et al (16) used octreotide in postoperative ileus and showed that octreotide has a dose-dependent action on colonic motility; used in low doses, it acted as a prokinetic agent and resulted in patients having a bowel movement earlier.

We have used octreotide during colonic motility studies in 7 patients who had no response to a standard dose of bisacodyl. All of the 7 patients had colonic high-amplitude propagated contractions (HAPC) within 5 to 10 minutes of administration of octreotide and tolerated the medication well (17). There might have been a confounding factor, however, given that all of the patients received bisacodyl before octreotide.

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The aim of this pilot study was to investigate the effect of octreotide on colonic motility in pediatric patients with recalcitrant chronic constipation/encopresis and other suspected colonic motility disorders.

METHODS

This was a nonrandomized single-center open-label prospective study. The study was approved by the institutional review board of Indiana University after obtaining an Investigational New Drug application from the Food and Drug Administration. This study was registered at *www.clinicaltrials.gov* and the trial identification number is NCT01917773.

For inclusion criteria, any child between 1 and 18 years of age who was undergoing a colonic motility study at Riley Hospital for Children (Indianapolis, IN) was eligible to participate in the study. The exclusion criteria were subjects with known or suspected allergy to octreotide; subjects with known prolonged corrected QT (QTc) syndrome or highest-risk QTc-prolonging agents (including mifepristone); subjects with known history of ventricular arrhythmia; subjects with a history of organ transplant taking cyclosporine at the time of the motility study; subjects with a history of small bowel transplant; subjects <1 or >18 years of age; subjects with severe renal impairment; subjects with severe hepatic impairment; subjects taking bromocriptine, insulin, oral hypoglycemic agents, β-blockers, calcium channel blockers, quinidine, terfenadine, pimozide, sildenafil, tadalafil, and any agents to control fluid and electrolyte imbalance.

All of the eligible patients referred for colonic manometry to the gastrointestinal motility laboratory at Riley Hospital for Children between September 2013 and June 2014 were invited to participate in the study. Informed consent was obtained from parents/legal guardians of each enrolled child, and assent was obtained from all patients >7 years.

Protocol of Colonic Manometry

Laxatives were discontinued 48 hours before colonic manometry. A standard bowel preparation (oral or nasogastric infusion of polyethylene glycol/electrolyte) was prescribed the day before colonoscopy for motility catheter placement. On the day of the motility, catheter placement colonoscopy was performed, and a motility catheter was placed under direct visualization. Colonoscopy was performed under standardized general anesthesia protocol consisting of premedication with midazolam and induction and maintenance of anesthesia using sevoflurane. The motility catheter was grasped by a polypectomy snare and was advanced to the most proximal point in the colon that was accessible. A plain abdominal x-ray was ordered within 2 to 3 hours after completion of the procedure and again in the middle of the colonic motility study to document the approximate location of the pressure ports on the catheter.

The protocol for manometry was as follows:

1. Fasting motility was recorded for $\geq$60 minutes.
2. Octreotide 1 μg/kg, maximum of 50 μg, was administered subcutaneously (1 hour after application of eutectic mixture of local anesthetics topical cream). Motility was then recorded for 45 to 60 minutes.
3. Patients were then offered a high-fat, high-energy meal as described elsewhere, and motility was recorded for 60 minutes (18).
4. Patients then received 1 to 2 doses of bisacodyl (0.2 mg/kg, maximum of 10 mg) through the motility catheter, and motility was recorded (19).

Data and Statistical Analysis

Colonic motility was measured using a solid-state catheter. The catheter had 36 sensors spaced 5-cm apart for the first 15 sensors and 1-cm apart for the remaining sensors. Pressures were transmitted to a transducer and recorded on a personal computer system (Medical Measurement Systems USA, Dover, NH). Manometry tracings were visually analyzed for the presence of HAPCs, defined as contractions of $\geq$60 mmHg in amplitude, 10 seconds in duration, and propagating for $\geq$30 cm of the colon. Normal manometry was defined as the presence of $\geq$1 HAPC originating in the proximal colon and propagating to the sigmoid colon (20). We did not define normal manometry by the presence of a gastrocolic reflex because we have not found this information to be a reliable predictor of normal colonic motility in our clinical experience. Neuropathy was defined as the persistent presence of a pattern of low- or high-amplitude contractions that were nonpropagating (retrograde or simultaneous). Myopathy was defined as complete absence of contractions or persistence of a pattern of contractions with normal propagation but abnormally low amplitude in a nondilated colon. MI was calculated using the Medical Measurement Systems computer program. The MI represents the area under the curve of the pressure tracing for a certain period (21). The MI was calculated for each channel. The MIs from all of the channels were then averaged to give each patient 1 average MI for the particular period under study. In this study, MI was calculated for the periods of 15, 30, and 45 minutes before and after infusion of octreotide. MI is reported as millimeters of mercury (mmHg) per 15, 30, or 45 minutes.

There are no commonly accepted norms for colonic MI in children using the solid-state colonic motility catheter technique. Reported MIs and standard deviations in healthy volunteers from an adult study were used to calculate sample size (22). A sample size of 13 patients was deemed adequate to detect a 25% change in MI with 80% power. The Wilcoxon signed-rank test was used to analyze change in MI. Values were considered to be significant if $P < 0.05$.

RESULTS

Demographics

Twenty-four patients were assessed for eligibility to participate in the study. Eight patients were excluded because they did not meet the inclusion criteria. Three patients/parents refused to be a part of the study. Thirteen patients were enrolled in the study. The age range was 4.6 to 16.2 years with a mean age of 9.3 ± 3.3 years. Seven patients were boys and 6 patients were girls. Twelve patients were white and 1 patient was black. Indications for colonic manometry included refractory constipation with encopresis (11), constipation without encopresis (1), and constipation after pull-through procedure for Hirschsprung disease (HD) (1). Seventy-seven percent of patients had significant comorbidities (Table 1). Eleven patients had undergone anorectal manometry, and results showed the presence of rectoanal inhibitory reflex (RAIR) and normal defecation dynamics (5), presence of RAIR with paradoxical contraction during simulated defecation (3), absent RAIR and normal rectal biopsy (2), and absent RAIR after HD surgery (1) (Table 1). All 3 patients with positive RAIR with paradoxical contraction during simulated defecation had failed the biofeedback therapy. Six patients had undergone rectal biopsy, and ganglion cells were present in 5 patients (1 was diagnosed with Hirschsprung disease).

A motility catheter was placed via colonoscopy in all of the 13 patients. The catheter was advanced to the cecum in 7 patients, ascending colon in 3, and hepatic flexure in 3. Six patients complained of mild discomfort with the administration of subcutaneous

TABLE 1. Patient demographics

Patient	Age, y	Sex	Ethnicity	Indication for study	Comorbidities	ARM	Colonic Motility Study Diagnosis
1	8.3	Female	White	C with FI	A, DD	+RAIR	Normal
2	10.75	Male	White	C with FI	None	+RAIR and PC	Normal
3	12.2	Male	White	C with FI	None	+RAIR and PC	Neuropathy
4	8.7	Female	White	C with FI	ME, CP, FD, SD, NB	−RAIR	Normal
5	16.25	Male	White	C with FI	ADHD	ND	Normal
6	6.75	Female	White	C with FI	ADHD, VUR	+RAIR and PC	Neuropathy
7	4.6	Male	White	C after HD surgery	HD, A, DD	−RAIR after HD surgery	Normal
8	10.25	Female	White	C with FI	A, DD, PDD, E	+RAIR	Normal
9	4.9	Male	White	C with FI	AI, TC	−RAIR	Normal
10	5.25	Female	White	C with FI	DD, ADHD, SZ, VUR	+ RAIR	Normal
11	11.3	Female	Black	C	None	ND	Normal
12	11.6	Male	White	C with FI	ADHD	+ RAIR	Normal
13	9.7	Male	White	C with FI	None	+ RAIR	Normal

A = autism, ADHD = attention-deficit/hyperactivity disorder, AI = Arnold-Chiari status/post decompression, ARM = anorectal manometry, C = Constipation, FI = fecal incontinence, CP = cerebral palsy, DD = developmental delay, E = enuresis, FD = feeding dysfunction, HD = Hirschsprung disease status/post proctocolectomy and endorectal pull through, ME = mitochondrial encephalomyopathy, NB = neurogenic bladder, ND = not done, PC = paradoxical contraction, PDD = pervasive developmental disorder, RAIR = rectoanal inhibitory reflex, SD = seizure disorder, TC = tethered cord status/post laminectomy, VUR = vesicoureteral reflux.

octreotide but did not require any analgesic because discomfort was short lived. Three patients complained of mild abdominal cramping. None of the patients developed hypoglycemia.

Qualitative Analysis of the Effect of Octreotide

Eleven patients had normal manometry. Two patients had colonic neuropathy. Of the 11 healthy patients, none had fasting HAPCs, 1 had postoctreotide HAPCs, 2 had postprandial HAPCs, and all of them had postbisacodyl HAPCs. Octreotide failed to produce any noticeable visual changes in the manometry pattern compared with the fasting period in all but 2 patients.

Quantitative Analysis of the Effect of Octreotide

Average MI for all of the patients was calculated over 15, 30, and 45 minutes before and after the administration of octreotide. The MI for the 15 minutes before and after octreotide infusion was 6.03 ± 1.26 mmHg/15 min (95% confidence interval [CI] 5.35–6.72), and 5.32 ± 1.66 mmHg/15 min (95% CI 4.42–6.23), and $P = 0.087$. The MI for the 30 minutes before and after octreotide infusion was 6.89 ± 1.37 mmHg/30 min (95% CI 6.14–7.64) and 6.71 ± 1.47 mmHg/30 min (95% CI 5.91–7.52), and $P = 0.552$. MI for the 45 minutes before and after octreotide infusion was 7.73 ± 1.32 mmHg/45 min (95% CI 7.01–8.45) and 7.53 ± 1.38 mmHg/45 min (95% CI 6.78–8.28), and $P = 0.807$. MI increased in 3, 6, and 7 patients at 15, 30, and 45 minutes, respectively, after the administration of octreotide (Fig. 1). Overall MI decreased, however, after octreotide administration during each time period. Only in 1 patient, MI increased >25% from baseline following administration of octreotide (patient 11).

A subanalysis of 11 patients with normal colonic manometry showed no significant changes in MI 15, 30, and 45 minutes after octreotide administration. The MI for the 15 minutes before and after octreotide administration was 5.99 and 5.27 mmHg/15 min ($P = 0.075$), respectively. The MI for the 30 minutes before and after octreotide was 6.84 and 6.64 mmHg/30 min ($P = 0.534$), respectively. The MI for the 45 minutes before and after octreotide was 7.66 and 7.5 mmHg/45 min ($P = 0.86$), respectively.

A secondary analysis on all of the 13 patients after bisacodyl infusion showed no significant changes. The average 15 minutes of MI after bisacodyl infusion was 6.7 mmHg compared with pre-bisacodyl MI of 6.03 mmHg ($P = 0.249$). Reanalysis of the 11 patients with normal colonic manometry alone showed significant changes after bisacodyl infusion as expected. The average 15 minutes MI after bisacodyl infusion was 7.2 mmHg compared with prebisacodyl MI of 5.992 mmHg ($P = 0.049$).

DISCUSSION

Octreotide is a synthetic octapeptide analogue of somatostatin. Octreotide is used to treat several pediatric disorders including secretory diarrhea, gastrointestinal hemorrhage, dumping syndrome, gastrointestinal fistula, and pseudoobstruction (11). Octreotide has been shown to have several actions on the colon including increased phasic pressure activity and increased transit time (13–16). We chose to use the dose of 1 μg/kg with a maximum of 50 μg based on reports in the literature (23). A similar 1-μg/kg dose has been used during antroduodenal motility studies in

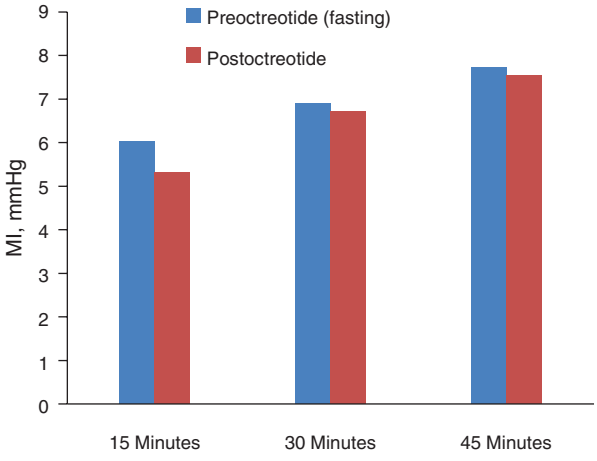

FIGURE 1. Comparison of changes in MI at 3 intervals after octreotide injection during colonic manometry. MI = motility index.

pediatric patients to induce phase III of the migrating motor complex. Di Lorenzo et al (12) reported using this dose in their prospective study of pediatric patients undergoing antroduodenal motility studies without any adverse effects. Also, octreotide is used for gastrointestinal bleeding in which 1 μg/kg is given as a bolus intravenous dose, followed by 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 48 hours (24). We used sevoflurane anesthesia protocol because we have shown previously that anesthesia protocol does not alter colonic motility study findings (25).

In our study octreotide was overall well tolerated. Six patients had mild discomfort with the administration of subcutaneous octreotide. Three patients had mild abdominal discomfort.

In this study, the effects of a single subcutaneous dose of octreotide on colonic motility were evaluated in pediatric patients with chronic recalcitrant constipation. The study shows that octreotide did not increase colonic MI. In fact, in the first 15 minutes after octreotide administration the MI decreased. Octreotide induced HAPCs in only 1 patient. Based on this observation, we conclude that octreotide is unlikely to benefit patients with chronic intractable or recalcitrant constipation.

We have used octreotide previously in patients who had no HAPCs after bisacodyl infusion during a colonic motility study. Octreotide induced HAPCs within 5 to 10 minutes in most of these patients (17). When we compare this study result to our previous experience, it appears that octreotide may augment bisacodyl's effects but is not able to induce HAPCs on its own.

Our study has a few limitations. We did not have a healthy control group; however, it will be difficult to enroll healthy controls and expose them to an invasive and expensive procedure. The study was an open-label design and not a randomized double blind control study; however, the risk of bias is minimal because we are studying an objective data, that is, colonic MI, which is computer generated. Because we had only 2 patients with colonic neuropathy, it is difficult to reach any meaningful conclusions on the effect of octreotide on colonic motility in patients with colonic neuropathy.

In conclusion, our study shows that the administration of octreotide resulted in no significant changes in colonic MI in pediatric patients with chronic recalcitrant constipation and a normal colonic manometry study. Additional studies are needed to assess the response to octreotide in patients with colonic neuropathy and myopathy. We previously have shown that octreotide induced HAPCs in patients who had no response to a standard dose of bisacodyl. This observation suggests that octreotide likely enhances the effect of bisacodyl; however, further research is needed to confirm this hypothesis.

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