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Flow through a mechanical distraction enterogenesis device: a pilot test

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Abstract

Background—We tested the coupling portion of a prototype intraluminal distraction enterogenesis device to allow flow-through of simulated enteric contents (SEC) in both pig and human jejunum.

Materials and methods—SEC was made using 80% corn syrup. Ten cm pig and human intestinal segments had a spoke-shaped 2.2cm coupling adaptor sutured in place intraluminally. The adaptor had a flow-through area of 33.6mm². SEC was pumped into the proximal part of the intestinal segment at 0.083mL/sec. The times to first passage of SEC through the coupler (first drop), 10mL and 20mL of SEC eluted from the distal end were recorded.

Results—Mean time to first drop elution was 155±38 seconds with pig, and 149±22 seconds with human bowel (p = 0.8). This corresponded to a hydrostatic pressure of 37.5mmHg before the initial drop passed through. Mean flow rates were 0.094mL/sec in pig bowel and 0.084mL/sec in human bowel (p=0.09). To account for occlusion from luminal debris, a 75% occlusion of coupler holes was studied in the smaller pig bowel to investigate if reductions in flow-through area could be tolerated. Mean time to first drop increased slightly to 171±15 seconds, and the elution rate stayed the same (p=0.5).

Conclusions—After a physiological level of initial pressure buildup allowing the first drop of SEC to pass the coupling adaptor, our prototype intestinal coupling adaptor did not obstruct flow-through of SEC, even after a 75% decrease in flow-through area. This type of attachment represents a viable approach to placing a device in-continuity without obstructing flow of enteric contents.

Keywords

Distraction enterogenesis; short bowel syndrome; simulated enteric contents; viscosity; flow-through

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Introduction

Short bowel syndrome (SBS) is a highly morbid condition in which patients have insufficient small bowel length for proper nutritional absorption. Patients with SBS require supplemental parenteral nutrition, and often suffer complications including cholestatic liver disease, central line infections, and bacterial overgrowth.[1] Despite promising new advancements in the treatment of SBS, such as the advent of intestinal lengthening procedures (e.g. serial transverse enteroplasty)[2] and improved survival after intestinal transplantation,[3] SBS still remains a very difficult process to treat.

The prognosis of patients with SBS is known to be dependent on remaining bowel length. Patients with less than 10% of predicted small bowel length have little to no chance of weaning off of parenteral nutrition.[1] It therefore stands to reason that therapies which can increase small bowel length hold promise in improving the treatment of SBS patients. Previously, investigators have successfully achieved small bowel lengthening in a rat model, and showed that its histology was not compromised and enzymatic functions increased.[4, 5] Our group has successfully induced longitudinal growth in porcine small bowel.[6] Through the application of mechanical distractive forces, a 45% increase in longitudinal bowel length was achieved over a 10-day period. The lengthened intestine showed increased rates of epithelial cell proliferation, consistent with true growth due to mechanotransductive mechanisms. This bowel also demonstrated intact epithelial barrier function and transmucosal uptake of nutrient substrate. Such a rapid form of intestinal growth may offer a unique approach to treat SBS.

Previous strategies employed in our laboratory to apply distractive forces have used surgically isolated segments of bowel[6]. Two issues with this type of implantation are that the device will need to be implanted by open invasive surgery, and the stretched isolated segment will eventually require a reanastomosis. To overcome these issues, we developed a prototype of an intestinal lengthening device that can be implanted in-continuity with the rest of the bowel. This novel approach has the advantages of requiring minimal bowel manipulation (including no need to re-anastomose intestine), and having the future potential to be placed endoscopically with improvements in bowel attachment techniques.

An obvious concern upon implementing this type of device is the risk of causing a small bowel obstruction. Both benign (e.g. intramural hematoma[7]) and malignant (e.g. metastatic disease[8]) natural space-occupying processes are known to cause bowel obstructions, but the extent to which such lesions must occupy luminal space before producing symptoms has not been fully evaluated. The larger the device can be, the more structural support it can have, and the easier it would be to engineer parts. However, a larger device is more likely to cause obstructive problems than a smaller device.

The purpose of this study is to test the ability of simulated small bowel enteric contents (SEC) to flow through the diminished area of the intestinal attachments of this new device in both pig and human jejunum. Tests were conducted to assess the initial resistance of the attachment to flow-through of SEC, and also to determine if the diminished flow-through area altered the speed of elution once SEC passed through the attachment. To further evaluate other factors that may impede flow-through ability, tests were repeated with 75% of the elution holes in the attachment plugged, and with SEC with particulate matter added. We performed these experiments to assess the feasibility of an in-continuity distraction enterogenesis device in future live animal models.

Materials and methods

Bowel samples

Pig bowel was obtained from adult female Yorkshire swine immediately after their death. Bowel segments were cut into ~30cm segments, and were immediately frozen in a -80°C freezer until they were used. Human jejunal segments were obtained from organ donors in coordination with the Gift of Life Michigan.

Approval for tissue usage was obtained from the University Committee on the Use and Care of Animals (protocol 09026), Gift of Life Michigan, and the Institutional Review Board (HUM00023670) at the University of Michigan.

Prototype of intraluminal in-continuity intestinal lengthening device

Figure 1a shows a schematic of our prototype in-continuity intestinal lengthening device. The disks at both ends of the device are designed to act as attachments of the device to the bowel. The central tube contains a shape-memory alloy powered ratcheting system that allows for extension of the device and longitudinal intestinal growth. Details of the workings of this device can be found in Utter et al[9]. The largest cross-sectional diameter (22mm) is present at the attachment rings on both ends of the device. The total cross sectional flow through area is 33.6mm² divided in 8 arced slots spaced equally (Figure 1b). Therefore, to test the ability of enteric contents to flow through the device, we specifically tested the ability of simulated enteric contents to flow through the attachment (Figure 1c).

Simulated small bowel enteric contents (SEC)

Pig cecal content viscosity has been described between 0.1 and 1.0 Pa-s over a range of shear rates[10]. Cecal contents will have a lower water content, hence a higher viscosity than small bowel contents, but we attempted to create a fluid with a similar coefficient of viscosity in order to be more rigorous with our testing. Varying dilutions of dark Karo corn syrup (ACH food companies, Cordova, TN) were measured using a falling sphere viscometer shown in Figure 2. A steel sphere was dropped from the top of the fluid column, and the terminal velocity of the sphere (of radius r in Figure 2) was measured by calculating the time it took for the sphere to drop a pre-defined distance (d in Figure 2). The coefficient of viscosity (μ) was calculated using the following formula:

$$\mu = 2r^2g^*(\rho_p - \rho_f)/(9v)$$

where r is the radius of the steel sphere, g is the gravitational constant (9.8m/s²), ρ_p is the density of the steel sphere, ρ_f is the density of the tested fluid, and v is the measured terminal velocity of the sphere falling through the fluid.[11]

Using this methodology, 80% corn syrup diluted in water was found to have a viscosity coefficient between 0.29 and 0.61 Pa-s; therefore this solution was used as SEC. The density of this fluid was 1.33 grams per mL.

Flow-through setup

For this part of the experiment, thawed bowel was cut into 10cm segments, and its inner circumference was measured by splaying open a small segment of bowel radially, and measuring the length of the mucosa. This circumference was used as a surrogate for inner bowel diameter because bowel is deformable. The spoke-shaped attachment (Figure 1 d and e) was sutured in place 3cm from the distal end of the bowel segment. SEC was pumped into the proximal part of the intestinal segment at 300mL/hr (0.083mL/sec) using a Hospira

Gemstar® infusion pump (Lake Forest, IL) or a Harvard Apparatus syringe infusion pump (Holliston, MA). A goal for fluid passage was determined to be a rate of 300mL/hr (or 0.083mL/sec). This was derived from the known volume of 7L of fluid secreted by the average adult human stomach and small bowel daily (7000mL/24hr = 291.6mL/hr).[12]

The times to first drop, 10mL and 20mL of SEC elution from the distal end were recorded. First drop elution was defined as the time when the first drop of SEC to elute out of the distal end of the bowel segment landed into the measuring cylinder below the bowel (Figure 1e). Similarly, 10mL SEC elution was defined as the time at which 10mL of SEC accumulated in the measuring cylinder below the tested bowel segment. The time to first drop elution was measured as a surrogate for how much pressure (if any) needs to build up in order for viscous SEC to push through the small flow-through holes. The times to 10mL and 20mL elution compared to the fixed inflow rate would capture if there is any catch-up flow rate, or if there is an impeded flow rate due to the coupling device. Each experiment was repeated with 3 different pieces of bowel unless otherwise specified.

Statistical analysis

Comparisons between groups were done using the unpaired t-test. A cutoff of $p < 0.05$ was used for statistical significance. All results are reported as mean $\pm$ standard deviation unless otherwise specified.

Results

Bowel dimensions

Relaxed inner diameter was 1.7 ± 0.8 cm for pig bowel and 2.6 ± 0.7 cm for human bowel ($p < 0.001$).

Flow-through of SEC through pig bowel

Mean time to first drop elution was 155 ± 38 seconds (accumulation of 12.9 ± 3.2 mL prior to the first drop passing through). The accumulation of 12.9mL of fluid is equivalent to 37.5mmHg of pressure over the area of the holes on the coupling adaptor. This was calculated from the formula (pressure) = (force)/(area). The area of flow-through is 33.6 mm^2 or $3.36 \times 10^{-5} \text{ m}^2$, and (force) = (weight of fluid column) * $g = 12.9 \text{ mL} * 1.33 \text{ g/mL} * 1 \text{ kg/1000g} * 9.8 \text{ m/s}^2 = 0.168 \text{ Newton}$. $0.168 \text{ Newton} / 3.36 \times 10^{-5} \text{ m}^2 = 5004 \text{ Pa} = 37.5 \text{ mmHg}$. Mean time from first drop elution to 10mL elution was 106 ± 2.7 seconds, and mean time from 10mL elution to 20mL elution was 108.7 ± 0.5 seconds. This translates to a mean flow-through rate of 0.094 mL/second for the first 10mL and 0.0924 mL/second for the next 10mL.

While the viscosity of our SEC is similar to pig cecal contents, we performed two additional experiments to simulate potential issues that we may encounter *in vivo*.

First, we added mucosal scrapings from pig small bowel to the previously formulated SEC to simulate the presence of particulate matter (including sloughed epithelial cells). We used a glass slide to scrape off mucus and epithelial cells from pig bowel. We added 1 gram of mucosal scrapings per 10mL of SEC, and repeated the flow-through study once. Times to first drop elution, first drop to 10mL elution and 10mL to 20mL elution were 122 seconds, 112 seconds and 115 seconds respectively.

In the second follow-up experiment, we plugged 6 out of the 8 holes with clay to simulate an *in vivo* situation where for any reason (e.g. plugging from enteral feedings), a majority of the holes became non-functional. Mean time to first drop elution was 171 ± 15 seconds

(14.2±1.2mL). Mean time from first drop to 10mL elution was 100.6±27 seconds (0.099mL/second), and mean time from 10mL elution to 20mL elution was 112.8±14.6 seconds (0.089mL/second). None of these values were significantly different from the control run of the experiment ($p = 0.53, 0.73$ and 0.65 , respectively).

Finding no significant difference in first drop elution time even after adding particulate matter and decreasing flow-through area, we analyzed if there was any correlation between bowel diameter and mean time to first elution. We hypothesized that perhaps the compression of the bowel against the part of the adaptor proximal to the actual attachment itself might be causing a resistance to flow-through. Data from all of the above trials were pooled together as there were no statistically significant differences in first drop elution time between the three experiments. After analysis by linear regression, there was no correlation between bowel diameter and time to first elution ($r^2 = 0.08, p = 0.54$, Figure 3).

Flow-through of SEC through human bowel

Mean time to first drop elution was 149±22 seconds (12.4±1.8mL) ($p=0.8$ compared to pig bowel). Mean time to 10mL elution was 119±9.4 seconds, and mean time from 10mL elution to 20mL elution was 102.4±8.6 seconds. Mean flow-through rate for the first 10mL was 0.084mL/second and 0.098mL/second for the second 10mL ($p=0.09$ and $p=0.3$ respectively compared to same time frame in pig bowel). A summary of the human and pig flow through data is shown in Table 1.

Discussion

To our knowledge, this prototype device is the first intestinal lengthening device designed to be placed in-continuity with the flow of enteric contents. Previously described animal models of distraction enterogenesis used externally mounted screws[13], continuous saline infusions[5] or isolated segments of bowel with drains[6]. While all of these models have merits, none of these devices offer the possibility of inducing bowel growth without disrupting the pre-existing continuity of the intestine. Although this current prototype is too long and rigid to allow it to be placed endoscopically, we believe that with sufficient modification, including miniaturization and a more sophisticated attachment method, endoscopic placement will be feasible; thereby opening exciting new avenues of treatment for SBS via distraction enterogenesis. These future projects notwithstanding, the *ex vivo* experiments performed in this manuscript were designed to address the concerns of obstruction associated with the placement of an intraluminal device.

The first challenge was to develop a suitable substitute for enteric contents. While using freshly harvested small bowel contents would have been the best, a more readily accessible source of enteric contents that would obviate the need for sacrificing multiple animals was needed. The most important characteristic to capture in a simulated enteric content is its viscosity. As previously published by Takahashi et al[10], the viscosity of pig cecal contents was described between 0.1 and 1 Pa-s over a range of shear rates between 1 s^{-1} and 450 s^{-1} . Therefore, we proceeded to create a fluid with a viscosity between 0.1 and 1 Pa-s. The rheological properties of syrups have been well described[14, 15], and for low cost and ease of handling, a diluted corn syrup mixture was used. While small bowel fluid viscosity may be lower than that found in the cecum, it was felt that using a higher viscosity challenge would allow us to test the system more rigorously.

A valid question at this point is whether 80% corn syrup alone is truly a viable simulation of enteric contents. For example, corn syrup does not have any sloughed epithelial cells seen in enteric contents. To address this concern, we added 1 gram of mucosal scrapings (containing mucus and epithelial cells) per 10mL of SEC. This amount was chosen because we obtained

approximately 1 gram of mucosal scrapings from 10cm of pig small bowel – the approximate length of the full prototype device. Importantly, the addition of mucosal scrapings did not alter the time to first drop elution compared to run of SEC without mucosal scrapings. We did not test flow through with larger particles as it is anticipated that future animals will be fed a liquid diet while the device is implanted, and therefore the only particulate matter seen in the lumen would be mucosally-derived. Even if larger particles reached the attachment and plugged some of the flow-through holes, our testing of the device with 6 out of 8 holes plugged showed that SEC will still flow through.

Our data demonstrates that once the SEC gets past the coupling adaptor, the flow rate is essentially constant, and slightly faster than the inflow rate. The elution rate being faster than the inflow rate can be explained by the initial buildup of fluid behind the adaptor prior to the first drop coming through. If the adaptor added no resistance to flow-through, the time to first drop elution would be on the order of a few seconds (the time it takes for SEC to pass through 5cm of small bowel). However, it took between 2 and 3 minutes before the first drop came through which implies a significant impediment to flow-through caused by the coupling adaptor. The mean amount of SEC accumulation before first drop elution was 12.9mL, the equivalent of 37.5mmHg of hydrostatic pressure accumulating prior to first drop elution. Normal human jejunum generates pressures up to 50mmHg[16] which would mean that peristalsis alone will be able to generate sufficient pressure to push through the enteric contents in an *in vivo* setting. Another factor that appeared to be linked to the initial resistance to flow-through was bowel diameter. However, no statistically significant correlation was found, implying that the flow through area is more likely the limiting factor in SEC flow-through. Human bowel, which had a significantly larger diameter than pig bowel, also showed similar flow-through characteristics to that of pig bowel. This gives further support to the concept that the flow-through area (not the size of the “tube”) is the limiting factor in determining if enteric contents can pass through the coupling adaptors.

There are a number of limitations to our model. We used through-and-through sutures to secure the attachment to the bowel wall. While this method of securing the adaptor will withstand forces above 100 gram force (a previously defined threshold for safe load application[17]), there is concern that this may predispose to abscess formation or leakage at the attachment site. Unfortunately, this can only be tested in an *in vivo* model. Also, flow through was tested with fluid traveling in the direction of gravity. In the *in vivo* setting, the bowel will be going in all different directions, and there may be a lower force pushing the content through the small adaptor holes. However, our cadaveric bowel does not have any peristaltic activity, another factor that can only be tested in an *in vivo* model. Despite these limitations, we believe the data from our experiments indicates that these attachments to the small bowel using this design of adaptors represent a viable model for future live animal studies and possibly clinical translation.

In summary, our prototype intestinal coupling adaptor allowed SEC to flow through with physiologic levels of pressure, and once flow-through occurred, the coupling adaptor did not significantly alter the flow-through rate of SEC, even with a 75% decrease in flow-through area. Further safety testing of this device will need to be done in live animal models. This type of attachment, however, represents a viable approach to placing a device in-continuity without obstructing flow of enteric contents.

References

1. Spencer AU, Neaga A, West B, et al. Pediatric Short Bowel Syndrome: Redefining Predictors of Success. *Annals of Surgery*. 2005; 242:403–412. [PubMed: 16135926]

2. Kim HB, Lee PW, Garza J, et al. Serial transverse enteroplasty for short bowel syndrome: a case report. *Journal of Pediatric Surgery*. 2003; 38:881–885. [PubMed: 12778385]
3. Vianna RM, Mangus RS, Tector AJ. Current status of small bowel and multivisceral transplantation. *Adv Surg*. 2008; 42:129–150. [PubMed: 18953814]
4. Chang PC, Mendoza J, Park J, et al. Sustainability of mechanically lengthened bowel in rats. *J Pediatr Surg*. 2006; 41:2019–2022. [PubMed: 17161196]
5. Puapong DP, Wu BM, Lam MM, et al. Distension enterogenesis: increasing the size and function of small intestine. *J Pediatr Surg*. 2006; 41:763–767. [PubMed: 16567190]
6. Spencer AU, Sun X, El-Sawaf M, et al. Enterogenesis in a clinically feasible model of mechanical small-bowel lengthening. *Surgery*. 2006; 140:212–220. [PubMed: 16904972]
7. Cheng J, Vemula N, Gendler S. Small bowel obstruction caused by intramural hemorrhage secondary to anticoagulant therapy. *Acta Gastroenterol Belg*. 2008; 71:342–344. [PubMed: 19198584]
8. Dite P, Lata J, Novotny I. Intestinal obstruction and perforation--the role of the gastroenterologist. *Dig Dis*. 2003; 21:63–67. [PubMed: 12838002]
9. Utter, B.; Brei, D.; Luntz, J., et al. Preliminary *in vivo* experimental validation of SMA based bowel extender for short bowel syndrome; Conference on Smart Materials Oxnard, CA: Adaptive Structures and Intelligent Systems; 2009.
10. Takahashi T, Sakata T. Viscous properties of pig cecal contents and the contribution of solid particles to viscosity. *Nutrition*. 2004; 20:377–382. [PubMed: 15043855]
11. Sutterby. Falling sphere viscometer. *Journal of Physics E: Scientific Instruments*. 1973; 6:1001.
12. Brunicki, FC. Schwartz's Principles of Surgery. New York: McGraw-Hill Companies; 2005.
13. Safford SD, Freerman AJ, Safford KM, et al. Longitudinal mechanical tension induces growth in the small bowel of juvenile rats. *Gut*. 2005; 54:1085–1090. [PubMed: 15840689]
14. Haynes, WM. Handbook of Chemistry and Physics. Boca Raton: CRC-Press; 2010.
15. Ngadi MO, Yu LJ. Rheological properties of Canadian maple syrup. *Canadian Biosystems Engineering*. 2004; 46:15–18.
16. Bjornsson ES, Abrahamsson H. Comparison between Physiologic and Erythromycin-Induced Interdigestive Motility. *Scandinavian Journal of Gastroenterology*. 1995; 30:139–145. [PubMed: 7732336]
17. Miyasaka EA, Okawada M, Utter B, et al. Application of distractive forces to the small intestine: defining safe limits. *J Surg Res*. 2010; 163:169–175. [PubMed: 20605600]

Figure 1.

a. Schematic of the prototype in-continuity intestinal lengthening device. The attachment coupling rings are indicated by the arrows. b. Axial view of the attachment coupling ring. 8 slots with a total flow through area of 33.6mm^2 are seen. c. Photograph of the attachment coupling. d. Setup of bowel attachment and simulated enteric content (SEC) flow. A 10cm segment of bowel was used. The attachment coupling was sutured in place 3cm from the distal end of the bowel, and the IV tubing dispensing the SEC was placed 5cm from the proximal end of the bowel. e. Photograph of experimental setup with measuring cylinder placed beneath the tested bowel segment.

Figure 2.

Setup of falling sphere viscometer. A cylinder of diluted corn syrup and a steel ball with a radius r are prepared. The sphere is dropped into the corn syrup, and after the sphere reaches terminal velocity, its velocity is calculated by measuring the time it takes for the sphere to fall the distance d .

Figure 3.

Linear regression analysis of bowel diameter against time to elution of the first drop of SEC. Data was pooled from all the trials using pig bowel. No significant trend was seen ($r^2 = 0.08$, $p = 0.54$).

Table 1

Summary of human and pig flow-through data

	Mean (s)	Volume and/or Rate	SD (s)	p compared to pig control
Human				
Time to first drop	148.9	12.4 mL	22.4	0.83
Time from first drop to 10mL	119.2	0.084 mL/s	9.4	0.09
Time from 10mL to 20mL	102.4	0.117 mL/s	8.6	0.27
Pig				
Time to first drop	154.7	12.9 mL	38.4	-
Time from first drop to 10mL	106.5	0.094 mL/s	2.7	-
Time from 10mL to 20mL	108.7	0.092 mL/s	0.5	-
With 6/8 holes plugged				
Time to first drop	171.1	14.3 mL	15.4	0.53
Time from first drop to 10mL	100.6	0.099 mL/s	27.1	0.73
Time from 10mL to 20mL	112.8	0.089 mL/s	14.6	0.65
With particulate matter				
Time to first drop	122.1	10.2 mL	-	-
Time from first drop to 10mL	111.5	0.090 mL/s	-	-
Time from 10mL to 20mL	114.9	0.087 mL/s	-	-

Summary of time until first drop of SEC made it through the adaptor, elution of 10mL and the elution of the next 10mL in pig and human bowel samples. The volume and/or rate column shows the volume (in mL) of SEC that accumulated before first drop elution or the rate of fluid elution (in mL/second) for the listed timeframe (i.e. 0 to 10mL or 10 to 20mL). SD – standard deviation.