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Development of an endoluminal intestinal attachment for a clinically applicable distraction enterogenesis device

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Abstract

Purpose—Previous methods of distraction enterogenesis have relied upon blind-ending intestinal segments or transmural device fixation, requiring multiple operations and potential bowel injury. We hypothesized that using a novel attachment would allow reversible device coupling to the luminal bowel surface, achieving effective endoluminal distraction.

Methods—A telescopic hydraulic device was designed with latex balloon attachments covered with high-friction mesh and a dilating fenestrated elastic mask (DFM attachment), allowing mesh-to-mucosa contact only with inflation. Yorkshire pigs underwent jejunal Roux-en-Y limb creation and device placement via jejunostomy. Devices underwent 3 cycles of balloon inflation and hydraulic extension/retraction per day for 7 days and then explanted and studied for efficacy.

Results—DFM attachment allowed reversible, high-strength endoluminal coupling without tissue injury or reduction in bowel perfusion. After 7 day implant, distracted bowel achieved a $44 \pm 2\%$ increase in length vs. fed, non-distracted bowel, corresponding to a gain of 7.1 ± 0.3 cm. Distracted bowel demonstrated increased epithelial cell proliferation vs. control bowel. Attachment sites demonstrated villus flattening, increased crypt depth, thicker muscularis mucosa, and unchanged muscularis propria thickness vs. control.

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Conclusion—Novel high-strength, reversible attachments enabled fully endoluminal distraction enterogenesis, achieving length gains comparable to open surgical techniques. This approach may allow development of clinically applicable technology for SBS treatment.

Keywords

distraction enterogenesis; pediatric device; mechanotransduction; short bowel syndrome

BACKGROUND

Short bowel syndrome (SBS), the most common cause of pediatric intestinal failure, results from insufficient intestinal absorptive capacity due to the loss of small bowel length (1). Despite advances in the medical and surgical management of patients with SBS, morbidity and mortality remain considerable (2–4). While surgical lengthening procedures have been developed (5, 6), these are highly invasive and many patients are not candidates due to unfavorable anatomy (7–9). The majority of SBS patients therefore receive supportive therapy with parenteral nutrition (PN), which carries risks such as metabolic abnormalities, hepatic dysfunction, and sepsis (1). The ability to wean off of PN is predicted by increased bowel length (2–4).

Distraction enterogenesis, or the use of longitudinal mechanical force to induce small intestinal elongation, may provide a novel therapeutic option for SBS (10–12). Using various methods of applying controlled tension on the bowel, distraction enterogenesis has been shown in animal models to lead to multi-fold lengthening with normal intestinal function, and sustained lengthening after device removal (13–15). While various methods of generating longitudinal force have been successful, including osmotic distension, spring devices, and hydraulic pistons, these have all been limited by the method of force transmission to the intestinal wall. This has remained a significant obstacle in the translation of these experimental approaches to a clinically applicable technology.

Prior distraction enterogenesis approaches have required the surgical creation of blind-ending intestinal segments (10, 11), or the placement of transmural sutures or circumferential vessel loops (16, 17). These intestinal attachment approaches all require open surgical device placement and re-operation for removal and restoration of intestinal continuity. This may lead to significant intestinal length loss, increases the risk of surgery-related injury to the intestine, and adds considerable risk given the elevated systemic inflammatory response of SBS patients to laparotomy (18, 19). We have thus sought to create a method of distraction enterogenesis using a fully endoluminal intestinal lengthening device, which would allow trans-stomal placement, distraction, and removal without the need for surgical intervention. A double balloon catheter designed for this purpose was limited by insufficient device attachment to the bowel wall, as maximum balloon pressure without inducing ischemia still resulted in device slippage (20). In this study, we describe a novel expandable mesh attachment. We hypothesized that this attachment would allow high-strength, reversible device coupling to the bowel wall, achieving fully endoluminal distraction enterogenesis.

METHODS

Device design

A hydraulic-driven concentric piston device (Fig 1) was designed as previously described (21) and adapted for linear actuation and inclusion of novel attachments. Briefly, this device consisted of a 10 cm long reciprocating single-stage stainless steel linear pump that allowed 1.1 cm of linear extension with infusion of 1 ml of water. Two latex balloons (30Fr, 5cc) were mounted on the ends of the device and served as the basic uncoated balloon attachments. Subsequent attachment modifications were made on top of these balloons. The device was controlled using four tubes that were extended through the intestinal lumen and accessible via a stoma: one hydraulic drive line, two air injection lines for balloon inflation, and one flush lumen that allowed injection of water between the two balloons. This removed pleats in the bowel during device cycling. The distal end of the device was modified to include a 10 cm latex taper in order to distribute force from the functional tip of the device along the curvature of the bowel, preventing perforation.

Attachment design

To provide a high-friction surface, a knit nylon/polyester mesh (3M, St. Paul, MN) was applied to balloon surface (balloon + friction mesh attachment). This was further modified by overlaying the friction mesh material with a mask of 0.040 inch diameter elastic bands spaced 0.12 inches apart (dilating fenestrated mask [DFM] attachment; Fig 1). In the deflated state, the elastic bands prevent mesh-mucosa contact. With balloon inflation, however, the bands separate, exposing the friction mesh to allow coupling to the intestine. With device cycling, deflating the balloon again contracts the elastic mask, de-coupling the device from the bowel wall.

Acute attachment test

To characterize coupling strength and reversibility of the attachments, an acute tension test was performed using fresh porcine jejunum. Each of the three attachment types – plain latex balloon, balloon + mesh attachment, and DFM attachment – was tested by inserting the attachment into the jejunal segment. A tension gauge was used to measure the tangential displacement force at which attachment slip occurred (slip force), during balloon inflation and deflation.

Acute tissue perfusion assessment

At the time of implantation into a pig, blood flow to the bowel wall was measured using a Lisca PIM II Laser Doppler Perfusion Imager (Perimed AB, Stockholm, Sweden), placed 10 cm above the antimesenteric surface of the intestine at the attachment site. Perfusion patterns were analyzed using LDPIwin 2.3 software (Perimed AB) as previously described (22), using triplicate measurements of a 1 cm² tissue plane. Sequential measurements were taken at the same site with balloon inflation and deflation.

Animal model

The device using DFM attachments was tested using our previously described swine model (13). 30–40kg female Yorkshire pigs were used (n=4, 2 acute and 2 chronic), and all procedures were approved by the University of Michigan Animal Use Committee (#PRO00005005). Via a midline laparotomy, a jejunal Roux limb was created 90 cm distal to the ligament of Treitz and brought out as an end jejunostomy (Fig 1D). Intestinal continuity was restored with an end-to-side anastomosis to form a Roux-en-Y jejuno-jejunostomy. The device was inserted via the jejunostomy such that the proximal balloon rested 10cm deep to the stoma. The drive lines were sutured to the abdominal wall as they emerged from the stoma. Silastic markers (vessel loops) were placed along the antimesenteric border of the Roux-limb at 2 cm intervals. These allowed for accurate measurement of gain or loss of intestinal length at harvest. A 12 cm segment was selected 10 cm distal to the jejuno-jejunostomy as a fed control, and this was similarly marked at 2 cm intervals. This allowed paired analysis of lengthening between the distracted and fed control segment from each animal. The abdomen was then closed in standard fashion. All animals were fed a regular solid diet on the first postoperative day until explant. After a 24 hour recovery period, the device was cycled every 4 hours during the day, with a 12 hour rest overnight. Cycling consisted of balloon deflation, hydraulic aspiration (resetting the device), flushing to remove any pleating of the bowel wall, inflation of both balloons, and hydraulic device expansion. Overnight bowel rest consisted of balloon deflation, hydraulic aspiration, and flushing only.

Tissue assessment

After 7 days, a re-laparotomy was performed and the device was removed from the jejunostomy. Intervals between antimesenteric silastic markers were measured along the Roux limb and the control segment. The Roux limb was inspected grossly for evidence of mucosal damage or perforation. Full-thickness samples of the Roux limb at attachment sites, at the device midpoint, and fed control were resected and fixed in 10% formalin overnight, followed by paraffin embedding. Of note, the recycling nature of this device allowed the attachments re-attach to new areas of the mucosa, either due to device movement or as the intestine between attachments increased in length. Attachment site samples were therefore taken at the midpoint of the mucosal region of attachment contact as evident at explant. Hematoxylin and eosin (H&E) staining was performed for histologic examination. Slides were visualized using a Nikon A-1 confocal microscope and assessed qualitatively for evidence of mucosal compromise, as well as quantitative measurements of villus height, crypt depth, muscularis mucosa thickness, and muscularis propria thickness. PCNA staining was performed to measure epithelial cell proliferation and expressed as the percent of PCNA positive crypt cells, as previously described (23).

Analysis

All longitudinal growth measurements were made along the experimental Roux limb relative to a fed control segment. This allowed correction for the confounding effects of post-laparotomy inflammation on bowel length. Paired t-test was used to compare results from

distracted and control segments from matched animals. Results were expressed as mean $\pm$ standard deviation unless otherwise specified. $P < 0.05$ was considered significant.

RESULTS

Attachment strength

Acute attachment strength was assessed by determining the maximum longitudinal force applied before device slippage (Fig 2). The uncoated latex balloon had low attachment strength of 120 gram-force (gf) with inflation and allowed ready detachment with < 20 gf upon deflation. The balloon + friction mesh attachment demonstrated high attachment strength of > 500 gf, but with deflation failed to readily detach, requiring 200 gf to slip. The DFM attachment demonstrated similar coupling strength of > 500 gf upon inflation, with ready detachment at 80 gf upon deflation. The DFM attachment was used for all subsequent experiments given its favorable attachment strength and reversibility.

Device safety

Laser Doppler assessment demonstrated no significant decrease in intestinal tissue perfusion with the DFM attachment (0.21 ± 0.07 perfusion units [PU] vs. 0.30 ± 0.09 PU; inflation vs. deflation; $p = 0.46$). PU is a dimensionless unit used for laser Doppler measurement. After 7 days of distraction, no device-related intestinal obstruction, perforation, or anastomotic complication occurred. Gross inspection of the mucosa at attachment sites remained intact without ulceration.

Lengthening

After 7 days of distraction, the cumulative percent growth of the bowel in contact with the device relative to fed control was $44 \pm 2\%$ (Fig. 3A). The net gain in length is dependent upon the length of bowel which is exposed to distractive force, with notable variation in the percent length gain achieved at different points along the device. Therefore, the cumulative distance from the stoma to each marker along the distracted segment was measured and compared to the group of fed control segment marker intervals at explant. This was extrapolated over the same number of markers (20), yielding a total increase in length of 7.1 ± 0.3 cm vs. fed control (Fig 3B). The increase in length exceeded the 1.1 cm stroke length of the device, indicating multiple-payout distraction.

Epithelial cell proliferation

PCNA staining of unfed distracted bowel (mid-device) without attachment contact demonstrated increased epithelial cell proliferation vs. fed control ($53.4 \pm 11.5\%$ vs. $41.0 \pm 6.2\%$; $p = 0.04$; Fig 4). Attachment sites similarly demonstrated an elevated proliferative index vs. fed control ($60.0 \pm 9.4\%$; $p < 0.01$), though not significantly greater than mid-device bowel ($p = 0.26$).

Histologic changes

H&E staining of attachment sites demonstrated loss of villus height ($265.3 \pm 15.7 \mu\text{m}$) compared to fed control ($535.2 \pm 33.4 \mu\text{m}$; $p < 0.01$) and mid-device bowel ($341.3 \pm 38.6 \mu\text{m}$;

$p < 0.01$; Fig 5). Attachment site crypt depth was increased ($594.3 \pm 33.1 \mu\text{m}$) vs. fed control ($546.3 \pm 15.8 \mu\text{m}$; $p = 0.01$) and mid-device bowel ($519.7 \pm 68.4 \mu\text{m}$; $p = 0.04$). Muscularis mucosa thickness increased at attachment sites ($57.7 \pm 6.3 \mu\text{m}$) vs. fed control ($41.3 \pm 9.4 \mu\text{m}$; $p < 0.01$) and mid-device bowel ($40.9 \pm 6.0 \mu\text{m}$; $p < 0.01$). On the other hand, muscularis propria thickness was not significantly different between the attachment sites ($534.2 \pm 37.4 \mu\text{m}$), fed control ($559.0 \pm 16.9 \mu\text{m}$; $p = 0.17$), and mid-device bowel ($551.0 \pm 20.1 \mu\text{m}$; $p = 0.36$).

DISCUSSION

While the efficacy of distraction enterogenesis has been demonstrated in experimental models, the translation of this approach to clinical utility has been limited by the challenge of maximizing bowel length gain while limiting the risks of distraction therapy itself (10–16). The endoluminal approach to distraction enterogenesis remains an attractive strategy, as it would allow the application of distractive force using a device that may be placed via a stoma or trans-orally. This may obviate the need for multiple operations. Attempts to employ fully endoluminal distraction, however, have been limited by the lack of effective endoluminal device attachment, with atraumatic balloon-based approaches failing to provide the attachment strength required for enterogenesis (20). Other strategies such as self-expanding metal stents (SEMS), while relatively safe for prolonged implant, are designed to be not readily detached (24). In addition, they are not designed to withstand high longitudinal force as required for distraction enterogenesis. Further, because of their hourglass shape which grasp the bowel at both ends, there may be a high likelihood of perforation with an applied distractive force.

This study demonstrates a novel attachment design that provides high-strength, reversible coupling of an endoluminal device within a compliant tube – the small intestine. With expansion, a high-friction mesh coated balloon allowed the application of over 500gf of longitudinal distraction without slip, well exceeding loads that have previously produced intestinal lengthening (20). Given the high compliance of the small intestine, however, device uncoupling failed to occur with balloon deflation using a simple high-friction balloon, still requiring excessive tension of 200gf to slip. This would make device implantation and removal difficult, and exceeds the safe upper limit of distraction before perfusion compromise as previously shown (25). By covering the high-friction mesh with a fenestrated elastic mask, the DFM attachment ensures separation of the compliant bowel wall from the attachment surface, uncoupling the device and reducing the tension required to slip to a safe 80gf. Such attachment dynamics may have applications in other contexts where reversible endoluminal fixation is required, such as in the treatment of long-gap esophageal atresia.

A potential benefit of reversible endoluminal attachment is that distraction force may be applied in a cyclic manner. As shown in this 7-day implant series, the DFM attachment was successfully employed for 12 hours per day in 4 hour cycles. At each device recycle, the DFM attachments were uncoupled from the bowel and re-applied after flushing out folds in the bowel. Although such attachment re-setting was not directly observed in this model, the fact that net length gain of distracted bowel exceeded the gain in length of the device itself at full extension indicates that this indeed occurred. Prior techniques of distraction

enterogenesis have employed fixed attachment sites such as staple lines, sutures, or surgically placed vessel loops (10, 11, 16, 17). These approaches require single-stroke distraction, with length gain limited to the maximum length of the device at full extension. This requires surgical device replacement for multiple rounds of distraction, which may be required for patients with <10% of expected bowel length who have the greatest need for intestinal lengthening (2). Potentially, multiple endoluminal device cycles over several months could be used for those with severe SBS, without requiring multiple operations. In addition, by intermittently deflating the attachments during cyclic distraction, prolonged obstruction of luminal contents would be prevented during a clinical implant.

Future work may investigate how changing the frequency and duration of cyclic distraction may impact the efficacy of DE. In this study, 4 hour cycles were used with 12 hours of bowel rest overnight, when the device was uncoupled from the intestine and no distractive force was applied. This study was not designed to demonstrate a benefit to this cycling pattern or the need for bowel rest. Prior approaches have employed continuous distraction without rest or cycling and achieved safe DE. In vitro data from epithelial cell monolayers suggests, however, that cyclic distraction may produce a more robust cellular proliferative response than static pressure (26). It is possible that an optimal cycling pattern, prolonging the duration of therapy, or adding trophic growth factors may produce more efficient enterogenesis (23).

After 7 days of cyclic endoluminal distraction, this device produced $44\pm2\%$ growth versus fed non-distracted bowel. This degree of lengthening is actually quite comparable to the primary STEP procedure, which produces between 22–43% bowel lengthening per operation (27–29). While bowel lengthening operations such as STEP create length gains at a single setting, however, distraction enterogenesis produces lengthening over the period of time during which distraction is applied. Therefore, results were measured relative to control bowel after the same period rather than comparing to the same segment of intestine at the time of device implant.

Tissue analysis of lengthened jejunum demonstrated characteristic findings of mechanically lengthened bowel, including increased crypt depth and increased epithelial cell proliferation (12, 15, 17). In contrast to prior approaches to distraction enterogenesis, we found no significant increase in muscularis propria thickness in distracted bowel (10). The clinical significance of this is unclear. A possible explanation for the lack of muscular hypertrophy using the current approach is non-continuous pattern of force application, with 12 hour intervals during which no distraction occurred. This regular period of bowel rest may have allowed for the restoration of normal muscular architecture.

The safety of the DFM attachment was characterized acutely using laser Doppler assessment of tissue perfusion, showing no significant decrease with attachment inflation. As laser Doppler flowmetry was only possible during laparotomy when the serosal surface of the bowel was exposed, perfusion assessment was not possible in the chronic setting. After 7 days of distraction, however, no evidence of ischemia or perforation was evident at the attachment sites, making chronic ischemia unlikely. Histologic examination of attachment sites showed loss of villus height, which may indicate mild mucosal injury from the DFM

attachment versus simple villus atrophy from lack of enteral nutrition in the unfed Roux limb.

A limitation of this study was the inability to quantify the distractive force being applied to the bowel during chronic implant. For clinical adoption, safe parameters of distraction will need to be defined, and direct feedback of applied tension would aid the clinician in guiding safe distraction. A future challenge in the development of a clinically applicable device will therefore be the incorporation of a sensor in the device to allow continuous calibration of distractive force during therapy. Another limitation was the requirement of a laparotomy to place bowel markers for growth measurement. The use of contrast studies might obviate the need for this and allow fully trans-stomal device placement. In clinical use, such an approach to distraction enterogenesis may be employed via an enterostomy, gastrostomy, or possibly transorally.

In summary, this study demonstrated a high-strength, reversible endoluminal attachment, allowing effective distraction enterogenesis. This approach may allow the development of a minimally invasive, clinically applicable device for the treatment of SBS.

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Fig. 1.

(A) The hydraulic distraction enterogenesis device with a tapered tip (triangle) to prevent perforation and a hydraulic line (arrow) that allowed trans-stomal control. (B) High-friction mesh coated balloons with dilating fenestrated elastic masks for reversible attachment. (C) Device implanted in the jejunum, actuated and producing longitudinal distractive force. (D) Schematic of the Roux-en-Y construction and device implantation via jejunostomy. The device is actuated via an external hydraulic drive line, and lengthening outcomes compared between antimesenteric markers along the Roux and fed control segments.

Fig. 2.

Acute endoluminal attachment strength measurements. The tangential force at which device slip (loss of coupling to intestinal wall) occurred with balloon inflation (I) and deflation (D) for three attachment types.

Fig. 3. Lengthening results. (A) The % increase in distance from the stoma to each marker along the distracted segment, relative to fed control. (B) The increase in distance from the stoma to each marker for the distracted segment relative to fed control. Control segments were extrapolated over the same number of markers to compare total bowel length gain. Each marker was initially placed 2 cm apart.

Fig. 4.

Epithelial cell proliferation was measured as the percent of PCNA-positive cells per crypt (A). Representative immunofluorescence images of intestinal crypts from the DFM attachment site (B), mid-device (C), and fed control (D) after 7 days of distraction. PCNA=green, DAPI=blue. Scale = 50 μ m. * $p<0.05$, ** $p<0.01$

Fig. 5. Histologic changes. Villus height (A), crypt depth (B), thickness of muscularis mucosa (C) and thickness of muscularis propria. (D) at the DFM attachment site, mid-device, and fed control segment after 7 days of distraction. (E) Representative hematoxylin and eosin-stained section of the DFM attachment site demonstrates villus flattening with crypt preservation. Scale=400 μm . * $p < 0.05$, ** $p < 0.01$