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Development of a novel approach to safely couple the intestine to a distraction-induced device for intestinal growth: Use of reconstructive tissue matrix

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Abstract

Background—Distraction-induced intestinal growth may be a novel treatment for short bowel syndrome. Longitudinal, distractive tension created by the application of force creates a significant challenge: to produce adequate force, yet not cause perforation at the fixation points. This paper describes our development of a coupling strategy to allow for successful bowel lengthening.

Methods—A curvilinear hydraulic device was implanted in an isolated Roux limb of small bowel in young Yorkshire pigs. Bowel was lengthened over a 2 week period. Study groups included: Group 1: Twelve silk transmural anchoring sutures into an engineered-coupling ring at each device end. Group 2: Addition of felt pledgets to the coupling rings on the serosal surface of the small bowel. Group 3: Extraluminal use of either thin AlloDerm®, thick AlloDerm®, or Strattice™ mesh to anchor the device.

Results—Group 1 (suture-only) resulted in a gradual pulling through of the suture with increasing tension and no lengthening. Felt pledgets eroded in a similar fashion, causing abdominal sepsis. Thin AlloDerm® failed to prevent erosion, however it protected against gross contamination. Animals in which either thick AlloDerm® or Strattice™ mesh was used survived complication-free to the study endpoint. Both thick AlloDerm® and Strattice™ prevented erosion and perforation allowing for an average of 10.85-cm expansion.

Conclusion—This study demonstrates use of either thick AlloDerm® or Strattice™ reconstructive tissue matrix allows for safe and effective coupling. Further, we suggest this approach could be an adjunct to esophageal lengthening procedures.

Keywords

short bowel syndrome; mechanotransduction; intestine; distraction-induced growth; reconstructive tissue matrix

INTRODUCTION

There are numerous cellular responses induced by mechanical stress including the conversion of mechanical force into chemical signals that stimulate growth. Mechanotransduction is evident in embryonic growth, development of a child[1, 2], adult

physiology[3], and pathophysiology of disease[4, 5]. Therapies based on this principle are currently in use to treat bone and soft tissues disorders. Notable examples of this are distraction osteogenesis[6], soft tissue reconstruction procedures[7] as well as esophageal lengthening[8]. Mechanistic properties of mechanotransduction are becoming clearer. Physical forces such as tension, shear stress and other mechanical cues, can be transmitted[9] to the nucleus via intracellular proteins[10]. Alterations in the cellular and peri-cellular environment lead to changes in cell shape. Intracellular signal transduction involving RhoA (a small G-protein) and focal adhesion kinase, among others factors, result in an up-regulation of transcription of growth factors [11].

The concept of mechanotransduction has been applied to the gastrointestinal system in the hopes of establishing a novel treatment for short bowel syndrome (SBS). SBS is defined as insufficient surface area to absorb nutrients required for normal growth and development [12]. Despite improved outcomes, there remains a reported 10-30% 5-year mortality rate[13]. The ability to wean off PN is closely dependent on intestinal length [14] and anatomic position [15] of remaining bowel after resection. Those with less than 10% of their predicted small bowel are far less likely to wean from PN compared to those with greater lengths[16]. For those unable to wean from PN, current treatment strategies include administration of growth hormones[17], surgical lengthening of the small bowel[18, 19], and small bowel transplantation[20] with widely variable results. Mechanotransduction may offer new treatment methods for SBS.

Longitudinal, distractive tension created by an intraluminal device has proven to induce functional lengthening in multiple animal models in multiple laboratories [21-23]. Our laboratory recently published our experience in distraction-induced intestinal enterogenesis noting the feasibility of producing functional lengthening in a swine model [21]. In this model, an isolated segment of small bowel was lengthened over time then placed back into intestinal continuity. The function of the lengthened segment of bowel was assessed after re-implantation. Four weeks after implantation there was a return to normal morphologic, epithelial proliferation, permeability, and disaccharidase activity.

While this study provides support in the use of this method as a possible treatment for SBS, there are many difficulties that need to be overcome prior to clinical applicability. Our current model places the device into a Roux-en-Y limb (Figure 1). The challenge in this model is developing a coupling (i.e., fixation) design that will adequately attach a device to the bowel wall to allow for application of distractive forces, yet not cause perforation at the attachment points. Fixation point erosions could lead to stress of the tissue and animal, inadequate distraction and ultimately failed experiments. We hypothesized that trans-mural suture fixation of our devices to bowel wall will allow adequate application of force to stimulate growth.

Methods

We perform experiments on a series of Yorkshire pigs weighing 30-50kg. Through a midline laparotomy incision, a roux limb was created 90 cm from the ligament of Treitz. The proximal end of the distal bowel was brought out in the left lower abdomen where a stoma was matured. This acted as mucus fistula as well as enabled access to the device as the hydraulic line exited the bowel through this stoma. A side-to-side functional end-to-end anastomosis was created to form a standard jejuno-jejunal Roux-En-Y configuration placing the remaining bowel back into continuity. The mesenteric defect was closed to prevent internal hernia. The device was secured into the Roux limb using a variety of coupling methods (Figure 1).

The variability in the five experiments were performed was only with the attachment method. Group 1: Twelve 2-0 silk transmural anchoring sutures were placed in the engineered coupling ring at each end of the device to allow for displacement of distractive forces. Group 2: The addition of felt pledgets to the coupling rings on the serosal surface of the small bowel. Group 3: Extraluminal use of human cadaveric dermis thin (0.23-0.51mm) or thick (1.04-2.28mm) AlloDerm® (LifeCell Corporation, Branchburg, NJ) or extraluminal use of porcine dermal Strattice™ mesh (LifeCell Corp.,) to anchor the device. Experimental protocols for each experiment were otherwise unchanged. Marking stitches were placed 1cm apart at the center of the device and inside each coupling ring on the antimesenteric serosal border on the Roux-limb in order to aid in the identification of growth (i.e., examination of distraction between these markers). The abdomen was then closed in multiple layers. Twenty four hours of recovery was allowed prior to expansion. The device was then expanded with 0.55ml injections of water twice daily via a syringe and hydraulic line. The injection schedule was calculated based on an expected rate of distraction to allow for a 2-fold increase. Tissue harvest was planned after 2 weeks of expansion was completed through a repeat midline laparotomy.

Results

These studies were performed in sequential order and the knowledge gained from the previous animals allowed us to modify to approach in the next group. Our first obstacle was designing an attachment, or end-cap to allow for the placement of transmural sutures to couple a longitudinally expanding device to deliver linear force to the bowel wall. Numerous planning meetings and technical drawings resulted in several prototypes for benchtop and in vivo testing [24] (Figure 2). Considerations for design of these coupling rings were shape, number of suture fixation points, diameter, and porosity to small bowel contents. After selecting an appropriate design a curvilinear hydraulic driven device was constructed (Figure 3A). This initial design was flawed, as it was too thin, and had a low distribution of distractive forces. The next modification (Figure 3B) broadened the distraction across a wider surface area. The final design (Figure 3C) moved to two coupling rings on each end, and moved from 6 suture holes to 12 staggered holes between two attachment rings on each end. This then allowed us to divide the force of tension over this expanded surface area.

The first group, suture only model, resulted in a gradual pulling through of the suture with increasing tension leading to an inadequate coupling and no lengthening. As well, there was a high degree of inflammation concerning for occult leakage of enteric contents. With the next animal, felt pledgets (Group 2) were added to increase the surface area in which force was applied, allowing for a more even distribution of tension. Unfortunately, these eroded in a similar fashion, causing abdominal sepsis (Figure 4A). This animal died secondary to complications prior to study endpoint.

Given failure of the previous models, thick AlloDerm® was attempted to further distribute forces and prevent erosion. This animal survived to the study endpoint with adequate coupling producing effective enterogenesis (Figure 4C). Thin AlloDerm® was used in the subsequent animal as this is a similar product to thick AlloDerm® with lower cost. At harvest, however, the device was noted to have expanded within the lumen of the bowel after erosion of the stitches resulting in no enterogenesis (Figure 4B). While thin AlloDerm® failed to prevent erosion, it did protect against gross contamination seen in previous pigs. Strattice™ mesh was used in the last experiment (Figure 4D). This resulted in prevention of erosion and adequate coupling. Enterogenesis was noted at harvest. Animals in which thick AlloDerm® or Strattice™ mesh were used survived complication-free to the study endpoint.

Both thick AlloDerm® and Strattice™ prevented erosion and perforation allowing for an average of 10.85cm of growth over 2 weeks.

Discussion

Designing a coupling system proved challenging, but insightful. A group effort over several years involving medical personal, engineers and translational researchers has been necessary to produce a working design. In this study, the use of reconstructive tissue matrix allowed for continued research in distraction enterogenesis. Our eventual goal is to induce lengthening of the gastrointestinal system without taking bowel out of continuity. Ideally this could be achieved with endoscopic placement of a device, without laparotomy. While the use of transmural fixation will probably not be feasible for a minimally invasive device, this technique has allowed continued mechanistic research and our ability to test growth characteristics of the intestine. As well, the use of this device coupling approach may be an alternative viable approach to enterogenesis, but will require a repeat surgery to remove the expanded device.

Reconstructive tissue matrix has been used successfully for several years in surgical procedures including complex abdominal wall closure[25]. Grafts composed of acellular collagen provide a scaffold for tissue incorporation[26]. The grafts fused to the serosa of the small bowel. This added reinforcement to the bowel wall which allowed the application of forces necessary to induce growth. However, surrounding tissue and adhesions also fused to the reconstructive matrix making dissection at harvest more difficult. In cases in which AlloDerm® or Strattice™ was used an extensive lysis of adhesions was carried out. While the dissection was more difficult, this did not preclude safety.

As we observed the erosion of sutures through the intestinal wall with the application of force, a similar disease process with this described complication came into discussion. Mechanotransduction has been used in long-gap esophageal atresia with the Foker procedure[8]. In this technique sutures are placed in the atretic proximal esophagus and distal esophageal stump. Gradual tension is applied over a 10 day period or until the two ends of esophagus are close enough for primary repair as measured by contrast studies. There have been reports of these sutures tearing through the esophagus[27]. Pledged sutures have been described but these have also result in tearing. Disruption of the esophagus could result in mediastinitis and need for additional operations. Though our experience is limited in this procedure, it is the authors' contention that the use of regenerative or reconstructive tissue matrix may aid in the application of force to the esophagus. Further, thin AlloDerm®, while not optimal for preventing erosion, may prevent spillage of enteric contents in the event of suture erosion. Use of thick AlloDerm® or Strattice™ could act as a buttress, prevent erosions and allow the required force to be applied, possibly with less suture erosion.

Concluding Remarks

Thick AlloDerm® and Strattice™ reconstructive tissue matrix allowed for adequate distractive tension to induce bowel lengthening in Yorkshire pigs, without erosion or intestinal leakage. We have found great adaptability of the small bowel and are encouraged that our goal of clinical use of such devices may one day offer therapy for children with SBS. In our experience, small bowel lengthening has only been limited by our ability to transfer forces to the bowel. We have not experienced disruption of bowel other than at fixation points. This demonstrates the plasticity of the small intestine further supporting mechanotransduction as a possible SBS treatment.

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Figure 1. Schematic representation of current operative technique. Our enterogenesis device is placed in a 90cm Roux limb. Hydraulic controls to the device pass through a stoma and are secured to the animals back.

Figure 2.

Examples of three coupling rings considered for final device design. A. Disc design with high flow-through capabilities. B. Canister design with range in suture fixation points and flow-through size. C. Dual rings with fixation points through each ring, used with our device after modification.

Figure 3. Current curvilinear hydraulic device model for distraction-induced enterogenesis. A. Device in collapsed position showing tissue coupling rings, hydraulic line and input syringe. B. Close up of distal end coupling ring. Note modification of staggered suture fixation points (black).

Figure 4.

Composite of harvest photographs. A. Pledgeted suture model showing erosion at fixation points with gross spillage of enteric contents. B. Thin AlloDerm® with intraluminal expansion after stitch erosion. C. Thick AlloDerm® and D. Strattice™. Both C and D approaches led to adequate coupling and distraction.