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New insights and interventions for short bowel syndrome

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Abstract

Purpose of review—This review summarizes recent innovations in the treatment of patients with short bowel syndrome.

Recent findings—The use of surgical procedures, growth factor stimulation, and bioengineering approaches to increase absorptive surface area of the intestine is examined. While the morphology of the intestine is clearly altered by these interventions, it is less clear that the overall function of the intestine is improved.

Summary—Continued innovations will likely bring about new therapeutic options for patients with short bowel syndrome. Careful evaluations of the impact of these interventions await controlled clinical trials.

Keywords

teduglutide; intestinal lengthening; distraction enterogenesis; tissue engineering

Introduction

Short bowel syndrome (SBS) is a congenital or acquired condition affecting the small intestine, hallmarked by loss of intestinal absorptive capacity with resultant malabsorption, dehydration, and malnutrition. This is due to the loss of absorptive surface area, as the human intestinal tract requires a massive surface area to effectively absorb nutrients to support a growing and living organism. Common etiologies of congenital or acquired SBS include intestinal atresias, massive intestinal resection due to infarction from abdominal wall defects, necrotizing enterocolitis, volvulus, or extensive aganglionosis. The incidence of SBS is approximately 25 per 100,000 live births per year in the United States [1]. However, the combined health expenditure per year in the United States for patients with SBS is in excess of \$500,000 per patient for the first year of diagnosis, and greater than \$200,000 for each year thereafter [2].

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Conflict of Interest

Joshua D. Rouch and James C.Y. Dunn declare that they have no conflict of interest

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Historically, the mainstay of treatment for SBS was the use of parenteral nutrition in order to sustain children without sufficient small intestine. Other therapies met with limited success included transit slowing and bowel lengthening surgical procedures, as well as small bowel transplantation. Thus far, these have all carried significant risk of sepsis, intestinal failure associated liver disease, and mortality. Recently, there have been surgical and biochemical therapies employed to increase options for the clinical treatment of SBS, in order to avoid the morbidity of parenteral nutrition. Although no therapies have been shown to be curative for SBS, there are exciting new treatment strategies in the realm of surgical treatment, biochemical modification, and bioengineering that may show promise for the future treatment of SBS.

This review highlights the recent literature focused on new burgeoning therapies for the debilitating and highly morbid disease of SBS. These therapies range from increased experience with bowel lengthening surgical procedures, introduction of new pharmacologic therapies to enhance adaptation, and the exploration of bioengineering concepts including devices that employ distractive force and the creation of intestinal tissue. New formulations of the lipid component of parenteral nutrition used in the prevention and treatment of intestinal failure associated liver diseases have extended the time frame for the support of patients with SBS. Collaborative work combining elements from multiple categories has also shown synergistic promise for treatment of this complex problem, often employing elements of both increased absorptive surface area and absorptive efficiency.

Recent Overview

New therapies for SBS exist in three distinct areas: surgical treatments, biochemical modification, and bioengineering. The topic of lipid composition in the management of SBS will not be reviewed here.

Surgical Treatment

Non-transplant, surgical therapy for SBS has been hallmarked by two main classes of procedures, bowel lengthening and transit slowing procedures. A combination of lengthening techniques along with transit slowing efforts may be considered for gastrointestinal reconstruction [3]. Transit slowing procedures have been largely abandoned. The two most common bowel lengthening procedures include the Bianchi longitudinal intestinal lengthening and tailoring (LILT) procedure and the serial transverse enteroplasty (STEP) procedure [4]. Each procedure has not been shown to help wean SBS patients from parenteral nutrition in carefully controlled trials. The LILT procedure has been criticized due to its technically challenging nature and the lack of adjustability since it always reduces the diameter by half and doubles the length. The STEP procedure is technically easier and more adjustable, but it alters the physical structure of the muscularis and may contribute to further gastrointestinal dysfunction [4].

Typically, STEP is used in patients who suffer from intestinal failure and bacterial overgrowth that is refractory to optimal medical management. Recent literature in the arena of surgical gastrointestinal reconstruction has focused on compiling long term data on each

of these procedures to estimate the ability to wean patients from parenteral nutrition [5–7]. In one center's experience, out of 20 patients undergoing STEP, five patients were able to achieve complete enteral autonomy, with ten others who increased their enteral feeding tolerance [5]. Looking broader, a meta-analysis examining the ability of achieving enteral tolerance compiled seven case series with a total of 86 children who had undergone STEP procedure [6]. They found that after STEP, mean percent of enteral feeding tolerance increased from 35.1 to 69.5%, and that 87% of children sampled had at least some increase in their tolerance to enteral nutrition [6]. These results should be interpreted with caution, as the patients in these series are heterogeneous in terms of their underlying diagnoses and residual small intestinal lengths. Consequently, it has been difficult to compare the outcome of these patients to a control group of patients who are supported by contemporary medical therapy. The potential benefit of STEP also needs to be weighed against the operative risks, including infectious complications and further intestinal dysfunction.

STEP is also used in neonates with congenital SBS who have very short bowel segments with extreme proximal dilatation. A retrospective series examined 15 patients undergoing primary STEP for congenital SBS as a safe means to limit the need for stoma creation, which may help limit further bowel length reduction that comes with repeated ostomy takedowns, bowel resection and anastomoses [8]. They found that primary treatment with STEP was able to increase intestinal length by 50%, and led to complete enteral autonomy in two of the 15 patients [8]. Because the neonatal bowel has tremendous potential for growth and adaptation, it is unclear whether such patients could have been weaned from parenteral nutrition without STEP.

Biochemical modification

Following from surgical therapy, a whole new line of work has focused on the efficacy of pharmacologic therapy for the treatment of SBS. Teduglutide, a recombinant analogue of the human glucagon-like peptide-2 (GLP-2) is an emerging clinical adjunct for patients with SBS [9–11]. A hormone that alters the proliferation and function of gastrointestinal cells, GLP-2 has been a helpful adjunct to promote bowel adaptation through increases in absorptive capacity due to its associated increase in villus height and crypt depth as well as its slowing effect on motility [10].

Two recent randomized controlled clinical trials, STEPS-004 and STEPS-020, have evaluated the effect of teduglutide on adults with SBS [12,13]. They were each double-blinded, multi-center studies in 2011 and 2012 involving adults dependent on parental nutrition, and the use of teduglutide was associated with a greater ability to partially wean from parenteral support as compared to placebo. They found that 63% vs. 30% of patients were able to achieve at least 20% weaning from parenteral support [13]. A 2016 evaluation has expanded upon these studies, providing adults on parenteral support with 2 years of teduglutide at 0.05mg/kg/day [14]. They found that 26% of adults were not able to complete the study, most often due to abdominal pain or catheter related problems. Of the remaining 74%, there was a sustained ability to wean from parenteral support associated with the duration of teduglutide supplementation [14].

One important limitation of teduglutide as an adjunct for bowel adaptation is its association with abdominal complaints [10]. Some SBS patients are on narcotics for their motility slowing effects. Two recent randomized controlled trials have assessed whether the combination of narcotic use and teduglutide leads to abdominal complaints such as pain, distention, nausea or vomiting [12,13]. Another group reviewed and compiled these two trials, and concluded that teduglutide does not have a significant increase in these adverse clinical effects, and that most of the adverse abdominal complaints relate to underlying intestinal dysfunction [15].

These findings are all encouraging for pharmaceutical stimulation as a means to treat patients with SBS. However, there are no studies yet published that have definitively evaluated the use of teduglutide in children. There is a current clinical trial underway that plans to replicate the methodology of the STEPS trials in pediatric patients up to 17 years of age.

Biongeneering

Recent developments in bioengineering have focused on both lengthening the existing bowel and creating new bowel using tissue engineering concepts. The two areas of greatest work have been in distraction enterogenesis and in tissue engineered small intestine (TESI) as novel means to increase intestinal tissue [16,17].

Distraction Enterogenesis

Distraction enterogenesis is a process by which mechanical forces are applied to the intestine to achieve greater length and surface area [18]. Multiple labs have worked to demonstrate the feasibility of this technique in small and large animal models, using various devices to achieve distraction.

Small animal models of distraction enterogenesis have explored intraluminal and extraluminal methods of lengthening [18–20]. These methods have included fluid injections, hydraulic pistons, extracorporeal screws, and metallic springs. However, each of these models has had multiple limitations. Recent work in the small animal model has focused on device optimization, as well as biochemical synergism. In 2014, Sullins *et al.* described a novel biodegradable spring device that could be placed within the bowel to effect lengthening; this was a step beyond nitinol springs, which would require repeat procedures to retrieve implanted devices [16]. The new spring device was made from poly-caprolactone, a food and drug administration approved material that can degrade in the body [21]. This was expanded upon, whereby springs were placed repeatedly in a rodent model, which showed the capacity for intestinal segments of rodent to lengthen repeatedly [22]. Other work to overcome repeated bowel manipulation led one group to develop an extraluminal system of bowel lengthening, whereby a radially expanding shape-memory polymer was applied to the outside serosal surface of a Roux-en-y configured bowel reconstruction [23,24].

Synergism between mechanical lengthening and biochemical modification has been another area of work that has sought to bring this novel technique to clinical application. One group

analyzed the biochemical changes brought about by intestinal lengthening, demonstrating the role of several known mechano-transductive cell signaling pathways that are activated during the process, including the focal adhesion kinase pathway [25]. This provided the insight that taking advantage of biochemical signaling could in fact enhance the process of distraction induced intestinal growth. A concurrent study showed that the provision of GLP-2 to murine subjects undergoing distraction enterogenesis with injected polyethylene glycol had increased epithelial cell proliferation [26]. Another group demonstrated that sustained release basic fibroblast growth factor enhanced length and vascularization of distracted segments of bowel [27].

While significant, the previous mentioned work was performed in small animal, rodent models. Small animals are especially useful for biochemical studies in distraction enterogenesis, but fail to sufficiently model the size and weight characteristics of human patients. Thus, large animal models have developed to better approximate device specifications to human subjects. Demerhi *et al.* showed that a novel device using hydraulic force to apply distraction can reliably lengthen porcine bowel in experimental settings [28–30]. This relied on a system where two balloons were placed within the bowel, which could be inflated to oppose the intestinal wall, and hydraulic distractive force was instilled in between these to achieve lengthening. In this model, balloons were then let down to allow for forward flow of intestinal contents, an important novel development that showed the feasibility of in-continuity lengthening. Previous to this, all procedures had relied on de-functionalized loops of intestine to lengthen. A limitation of this technique was again the need for repeated surgeries to deploy and safely remove the hydraulic device. Another laboratory showed the feasibility of in-continuity lengthening with self-expanding spring devices [31]. They also characterized a scalable factor that could be used for spring size and force dimensions for application to differing size human intestine [32]. Further work is focusing on ways to provide better bowel wall coupling to facilitate lengthening, followed by degradation and passage of the biodegradable spring. Taken together, distraction enterogenesis shows promise as a translatable therapy for human patients with SBS in the near future.

Tissue Engineered Small Intestine (TESI)

Another novel treatment direction that utilizes a multidisciplinary approach to solve the problem of insufficient bowel absorptive surface area is TESI. Many prior studies have explored the feasibility of growing the different cells of the intestinal tract and loading these cells on biomaterials in the physical shape of intestine for *in vivo* implantation [17,33,34]. The concept is to utilize autologous tissue to obviate the need for immunosuppression. A recently published review article specific to TESI highlights our current understanding of the morphologic and molecular fundamentals of TESI [33]. One group that has previously shown that human and murine TESI possess histologic features of small bowel has demonstrated the functional capacity of their TESI constructs [17]. They show that both human and murine TESI grown in the peritoneal cavities of mice form what could become an intestinal tube with the ultra-structural components microvilli and tight junctions, as well as functional brush border and digestive enzymes [17]. This insight shows the capacity for

postnatal human intestinal cells to generate functional, implantable TESI, which brings this therapy one step closer to human application.

A limitation of this as a translatable concept has been the cell source. In order to produce TESI, the starting cells would sacrifice too much of the already ‘short’ bowel in these patients. Therefore, one recent study proved the ability to convert small jejunal biopsies into sufficient cellular material to load onto a scaffold to create TESI [34]. Thus, the process of cellular expansion sufficient to generate new bowel is becoming possible from limited starting material. Another significant limitation to the current TESI is the lack of peristaltic movement. While the formation of a rudimentary muscularis has been observed, effective peristalsis of TESI remains to be demonstrated.

Another landmark work demonstrated that it is possible to develop human intestinal organoids *in vitro* and *in vivo* from embryonic stem cells and induced pluripotent stem cells [35]. They showed that their transplanted intestinal tissue was morphologically similar, and capable of participating in digestive function [35]. This study may pave the way for future modeling of intestinal diseases, and with refinement may bring us closer to personalizing the treatment of SBS patients. Further developments for bringing TESI to the translatable forefront include surface optimizations of the scaffolds, enhancements made to the cell cultures, and vascular integration of TESI with existing *in vivo* intestine [36,37].

Conclusions

In the past decade, new forms of therapy are emerging for the treatment of SBS. While all of these approaches change the quantity of the small intestinal tissue, it is essential to keep in mind that the quality of the intestinal tissue must be evaluated. Although the name SBS implies intestinal length to be the dominant determinant, the function of the intestine is likely more important than its length. There are numerous patients with less than 20 cm of intestine who could be weaned from parenteral nutrition, yet there are others with over 80 cm of intestine who still depend on parenteral nutrition. Therefore, it is more appropriate to call this condition dysfunctional bowel syndrome rather than SBS. As one strives toward the development of new therapies, it is crucial to keep in mind that improved function of the intestine must be demonstrated along with morphological changes of the intestine in these approaches.

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**of major importance

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