Serial Transverse Enteroplasty Enhances Intestinal Function in a Model of Short Bowel Syndrome

Robert W. Chang, MD, Patrick J. Javid, MD, Jung-Tak Oh, MD, Steven Andreoli, BA, Heung Bae Kim, MD, Dario Fauza, MD, and Tom Jaksic, MD, PhD

Objective/Summary Background Data: Serial transverse enteroplasty (STEP) is a new intestinal lengthening procedure that has been shown to clinically increase bowel length. This study examined the impact of the STEP procedure upon intestinal function in a model of short bowel syndrome.

Methods: Young pigs (n = 10) had a reversed segment of bowel interposed to induce bowel dilatation. Five pigs underwent a 90% bowel resection with a STEP procedure on the remaining dilated bowel while 5 served as controls and had a 90% bowel resection without a STEP procedure. Determinations of nutritional status, absorptive capacity, and bacterial overgrowth were conducted 6 weeks after resection. Statistical comparisons were made by 2-sample *t* test (significance at $P < 0.05$).

Results: The STEP procedure lengthened the bowel from 105.2 ± 7.7 cm to 152.2 ± 8.3 cm ($P < 0.01$). The STEP animals showed improved weight retention compared with controls (mean, −0.5% ± 1.8% body weight versus −17.6% ± 1.5%, $P < 0.001$). Intestinal carbohydrate absorption, as measured by D-Xylose absorption and fat absorptive capacity as measured by serum vitamin D and triglyceride levels, were increased in the STEP group versus controls. Serum citrulline, a marker of intestinal mucosal mass, was significantly elevated in the STEP pigs compared with controls. None of the STEP animals but 4 of 5 control animals were noted to have gram-negative bacterial overgrowth in the proximal bowel.

Conclusions: STEP improves weight retention, nutritional status, intestinal absorptive capacity, and serum citrulline levels in a porcine short bowel model. A salutary effect upon bacterial overgrowth was also noted. These data support the use of this operation in short bowel syndrome.

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Short bowel syndrome is a condition in which the length or function of intestine is inadequate to meet the nutritive and growth demands of the patient. Congenital etiologies of short bowel syndrome include intestinal atresia, gastroschisis, and midgut volvulus from intestinal malrotation, whereas acquired etiologies encompass necrotizing enterocolitis, Crohn's disease, and abdominal trauma. After a significant intestinal loss, the remaining bowel undergoes a process known as adaptation that involves mucosal hyperplasia in an attempt to increase surface area for improved absorptive capacity. However, this process is frequently accompanied by bowel dilatation, dysmotility, and bacterial overgrowth that may significantly decrease intestinal absorption.[1] Current therapy for infants and children with short bowel syndrome consists primarily of supportive measures, most importantly parenteral nutrition, while awaiting adaptation and growth of the remaining bowel.[2] Complications of long-term parenteral nutrition include recurrent sepsis and parenteral nutrition associated liver disease. These are patients that may benefit from some sort of surgical therapy.

The goal of surgical intervention in the management of short bowel syndrome is to increase intestinal absorption by optimizing intestinal function and motility.[3] The most widely used method to date has been the intestinal lengthening procedure originally described by Bianchi.[4] This procedure can result in a doubling of bowel length with a circumference that is reduced by half. The Bianchi procedure has several limitations: it is technically difficult, involves at least one intestinal anastomosis, places the mesenteric blood supply in jeopardy, and is best done if the bowel is symmetrically dilated.

We have recently developed a novel bowel lengthening procedure for children with refractory short bowel syndrome termed serial transverse enteroplasty (STEP).[5] It is based on the anatomic principle that the blood supply to the bowel comes from the mesenteric border and traverses the bowel perpendicular to its long axis. If all staple lines are kept parallel to the blood supply, the intestine should remain well vascularized. Alternating the direction of the stapler from side to side creates a channel of bowel that is both smaller in diameter and longer than the original bowel. (Fig. 1) The degree of bowel lengthening and tapering depends on the distance between stapler applications and the length from the end of the stapler to the edge of the bowel. The result is a channel of bowel that is uniform in diameter, and both longer and narrower than the original bowel. This technique easily accommodates areas of variable bowel dilatation.

From the Department of Surgery, Children's Hospital Boston and the Harvard Center for Minimally Invasive Surgery, Harvard Medical School, Boston, MA.

Reprints: Tom Jaksic, MD, PhD, Children's Hospital Boston, 300 Longwood Ave., Fegan 3, Boston, MA 02115. E-mail: tom.jaksic@childrens.harvard.edu.

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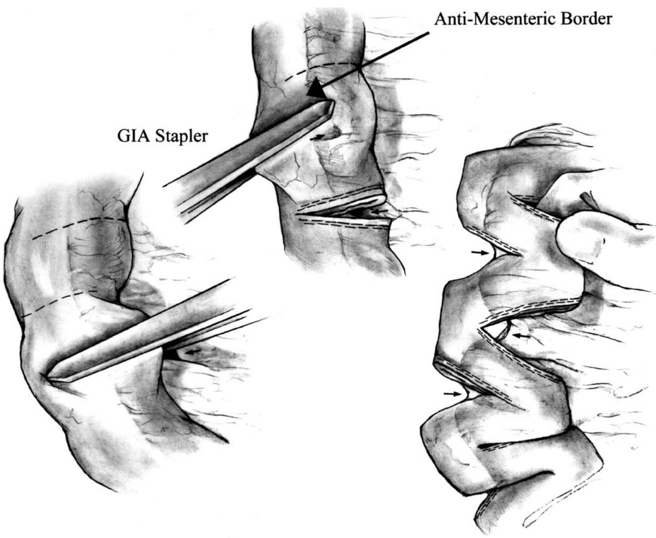

FIGURE 1. In the STEP procedure, all staples lines are kept parallel to the plane of intestinal blood supply. By alternating the direction of the GIA stapler, a channel of bowel is created that is both smaller in diameter and longer than the original bowel.

Preliminary experiments in an animal model demonstrated the safety and simplicity of this procedure.[6] In this study, we sought to examine the nutritional effects of the STEP procedure in a model of short bowel syndrome.

MATERIALS AND METHODS

The Harvard Medical School animal management program is sanctioned by the American Association for the accreditation of Laboratory Animal Care (AAALAC, file #000009) and meets National Institutes of Health Standards as set forth in the Guide for the Care and Use of Laboratory Animals (National Research Council Publication, revised 1996). All experimental protocols for this study were approved by the Harvard Medical School Animal Management Program.

Creation of Intestinal Dilatation

Young domestic pigs (n = 10) were fasted the night before surgery and weighed preoperatively. The animals were given an intramuscular induction agent (Telazol/xylazine) and maintained under general anesthesia using inhaled isoflurane (2–5%). One gram of intravenous cefazolin was administered at the start of the procedure. A midline laparotomy was performed and the bowel was exposed. A polypropylene suture was used to mark an area 125 cm distal to the ligament of Treitz. The bowel diameter was recorded, and a 50-cm segment of bowel was transected and interposed in a reverse peristaltic fashion. Anastomoses were accomplished by a single layer 4-0 running polypropylene suture. The abdomen was then closed in layers, and the animal was awakened from anesthesia. Analgesic medications were administered for the first 3 postoperative days, and pig chow was offered on postoperative day 1.

Creation of Short Bowel Model

After 6 weeks, all animals (n = 10) were anesthetized, prepared for surgery as described above, and weights and baseline blood values were obtained. Following reentry into the abdomen, the entire small bowel length was measured by placing a silk suture along the antimesenteric edge of the intestine from the ligament of Treitz to the ileocecal valve. The small bowel was then resected beginning at the previous proximal anastomosis and ending 25 cm proximal to the ileocecal valve. This left 125 cm of dilated duodenum and proximal jejunum (Fig. 2A) and 25 cm of distal ileum, resulting in an approximate 90% enterectomy. There was no significant difference in the amount of resected intestine among animals. Anastomoses were performed using a single layer of 4-0 running polypropylene suture. Control animals (n = 5) then underwent abdominal closure in layers.

STEP Procedure

The experimental group of animals (n = 5) underwent the STEP bowel lengthening procedure immediately following the 90% enterectomy and reanastomosis. The dilated segment of bowel to be lengthened was measured along its long axis, and a sterile marker was used to indicate the antimesenteric border of the bowel. The STEP procedure was then performed as previously described.[6] Briefly, a reusable GIA stapler (50-3.8 mm loading units, U.S. Surgical Corporation, Norwalk, CT) was applied to the dilated bowel in a sequential fashion, from alternating and opposite directions perpendicular to the long axis of the bowel and parallel to the mesenteric leaves. This was accomplished by placing the lower jaw of the device through small mesenteric defects that were serially placed along the bowel (Fig. 2B). This created a partially overlapping "zig-zag" channel of smaller diameter (Fig. 2C). The operating surgeon determined the number of stapler applications (mean, 17 $\pm$ 2 firings) and the residual channel diameter based on the anatomic presentation of each animal. The extent of bowel lengthening was determined when the diameter of the bowel would not allow adequate stapler application. Following the STEP procedure, the new bowel length was measured and recorded. Animals were then closed in layers and recovered in a similar fashion to the control animals.

Dietary Management

During the period after the first operation and until death, the animals were housed separately and were offered an identical amount of pig chow each morning. The quantity of pig chow given met the requirements of normal growing animals. The pigs invariably consumed all of the pig chow presented each day during the course of the experiment. This obviated the necessity for pair feeding.

Following the second operation, all animals were also administered a daily dose of the H_2-blocker ranitidine (300 mg orally) to prevent gastric ulceration and bleeding.

Absorption Studies

After a 6-week recovery period from the second operation, animals were sedated with intramuscular Telazol (4.4 mg/kg) and xylazine (2.2 mg/kg) IM. They were weighed and

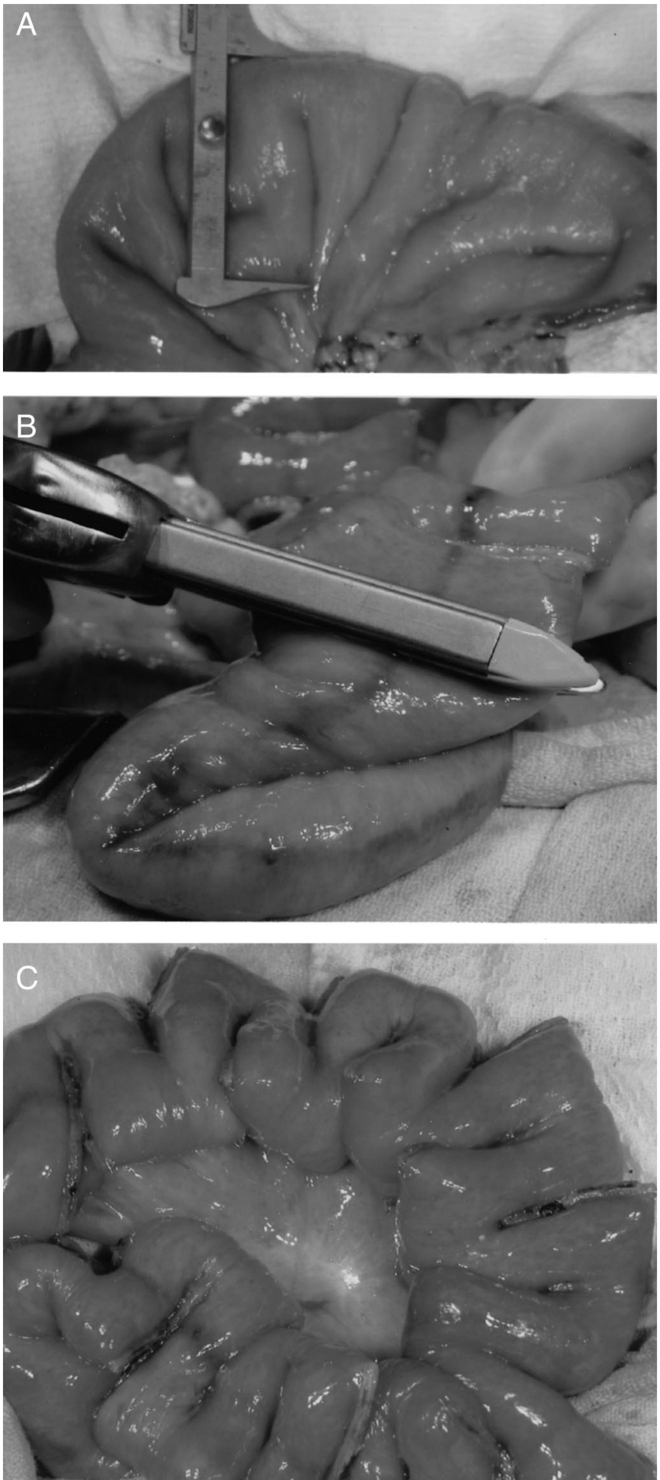

FIGURE 2. Intraoperative photographs of the porcine bowel. A, The dilated proximal small intestine 6 weeks following creation of a reverse peristaltic bowel segment. B, Application of the GIA stapler is performed perpendicular to the antimesenteric border of the small bowel during the STEP procedure. C, The resulting bowel immediately following the STEP procedure demonstrates the classic "zig-zag" appearance.

had baseline hematologic profiles drawn. A 28-Fr orogastric tube was temporarily inserted under direct laryngoscopy, and an aqueous solution of D-Xylose solution (0.5 g/kg, Spectrum Quality Products, New Brunswick, NJ) was given. Serial blood draws were obtained at 40, 60, and 80 minutes following D-Xylose administration. Death was then induced using intravenous Euthasol (aqueous mixture of 390 mg pentobarbital and 50 mg of phenytoin per mL, 2 mL/kg).

Assessment of Intestinal Flora

Immediately following death, a standard midline laparotomy was performed. A 10-cm length of small bowel (beginning at 10 cm distal to the ligament of Treitz) was identified and clamped. The lumen was lavaged with 50 mL of sterile saline, and this liquid was subsequently aspirated into a sterile container.

Total contents of the intestinal segments were vortexed to ensure homogeneous mixing and diluted with normal saline. Total aerobic bacterial counts were obtained by lawn streaking 0.1 mL of undiluted and serially diluted intestinal contents on Chocolate Agar (BD BBL, Sparks, MD). Agar plates were incubated for 24 to 48 hours at 35°C in 5% CO_2. Anaerobic bacteria were plated on *Brucella* agar, placed in an anaerobic gas generating system (Mitsubishi Gas Chemical Company, New York) and incubated for 48 hours at 35°C. All plated bacteria were counted manually in a blinded fashion with total bacteria counts reported as colony forming units/milliliter.

Bacterial overgrowth was defined as gram negative colony counts greater than 10^5 gram negative organisms per mL. Normative data was used to compare flora profiles from nonoperated historical controls to both groups in the study.[7,8]

Histologic Analysis

Upon death, the alimentary tract was removed en bloc from the pylorus to the ileocecal valve. Adhesiolysis was performed, and the length and diameter of the proximal and distal bowel were recorded. Bowel specimens were preserved in 10% formalin, embedded in paraffin, and sectioned for microscopic analysis. These sections were stained with hematoxylin-eosin and reviewed by a gastrointestinal pathologist masked as to whether the samples were obtained from STEP or control animals.

Sample Analysis

Blood samples were obtained from all animals using jugular vein puncture under general anesthesia. Samples were immediately transferred to the Children's Hospital clinical laboratory. All analyses were performed on serum after blood samples were centrifuged using standard technique. Albumin levels were measured with dye-binding technique using bromcresol purple; triglyceride levels were measured by enzymatic oxidation assay; vitamin D was measured using a quantitative chemi-illuminescence reaction; levels of citrulline were measured using high-pressure liquid chromatography; zinc levels were determined by inductively coupled plasma/mass spectrometry; and D-Xylose was measured using spectrophotometric assay.

Statistical Analysis

Statistical analyses were performed using paired sample *t* tests when each animal was considered before and after the second operation. Comparisons between the experimental and control groups were analyzed by 2 sample *t* tests. Significance was set at P less than 0.05. All data were recorded as mean ± standard error of the mean.

RESULTS

There were 3 deaths in the study. One mortality was attributed to technical error following the initial operation, and 2 animals died secondary to massive upper gastrointestinal hemorrhage following the 90% enterectomy. All animals treated with H_2-receptor antagonists (n = 10) survived until the conclusion of the study.

Hematoxylin and eosin-stained slides of the intestine of the STEP and control animals obtained at the end of the experiment demonstrated no significant qualitative structural differences between groups.

A summary of the quantitative findings is seen in Table 1. Prior to the second operation (OR 2), both groups of animals had similar weights. At death, control animals weighed significantly less than STEP animals (46.1 ± 0.8 versus 56.4 ± 0.9 kg, $P < 0.001$). Overall, control animals lost 17.6% ± 1.5% of their body weight following bowel resection, while the STEP group lost 0.5% ± 1.8% ($P < 0.001$, Fig. 3).

The STEP procedure lengthened the small bowel from a mean of 105.2 ± 7.7 to 152.2 ± 8.3 cm, as measured intraoperatively immediately following the procedure ($P = 0.001$). It should be noted that the lengthened bowel did not include the first 20 cm of proximal duodenum (containing the bile duct) and the distal 25 cm of ileum. Thus, immediately after STEP lengthening the total bowel length measured from pylorus to ileocecal valve increased from 150.2 ± 7.7 cm to 197.2 ± 8.3 cm ($P = 0.001$). At death, the total bowel length measured from pylorus to ileocecal valve was found to be significantly greater in the STEP group as compared with controls (229.2 ± 10.6 versus 151.0 ± 4.0 cm, $P < 0.001$). Control animals had significantly greater dilatation in both the proximal bowel (6.0 ± 0.3 versus 3.6 ± 0.2 cm, $P < 0.001$) and distal bowel (4.4 ± 0.2 versus 3.3 ± 0.2 cm, $P = 0.005$) at time of death.

D-Xylose absorption was significantly increased in the STEP group compared with controls at all time points measured after orogastric infusion (Fig. 4). There was a significant increase in serum triglyceride levels of STEP animals between OR 2 and death. (34.4 ± 3.7 versus 90.2 ± 6.5 mg/dL, $P < 0.001$, Fig. 5A) that was not observed in the control group. At death, STEP animals demonstrated higher levels of serum triglycerides (90.2 ± 6.5 versus 39.4 ± 6.3 mg/dL, $P < 0.001$, Fig. 5A), vitamin D (89.3 ± 4.3 versus 64.2 ± 3.3, $P = 0.001$, Fig. 5B), and albumin (1.3 ± .005 versus 0.1 ± .006 g/dL, $P < 0.005$), although both groups demonstrated a decline in serum albumin concentration be-

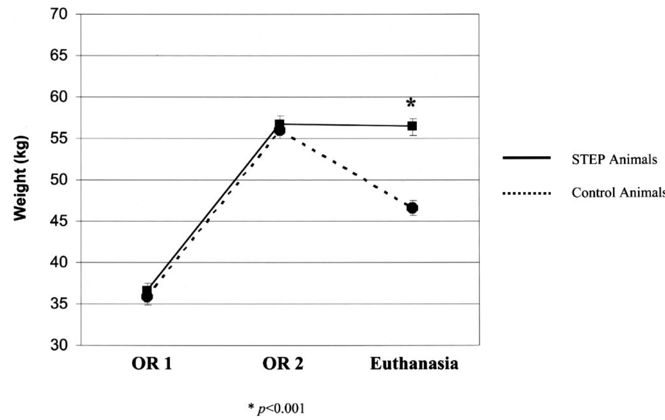

FIGURE 3. Between OR 1 and OR 2, all animals had similar rates of weight gain. Animals that underwent the STEP bowel lengthening procedure maintained their body weight in the 6-week postoperative period, whereas control animals lost 17.6% of their initial body weight ($P < 0.001$). This effect is likely secondary to improved intestinal absorptive capacity in STEP animals.

TABLE 1. Comparison of Data From Experimental and Control Animals

	Control	SEM	STEP	SEM	*P*
Animal weight (kg)					
OR 1	35.8	0.6	36.5	0.5	NS
OR 2	55.9	0.9	56.7	1.4	NS
Death	46.6	0.8	56.4	0.9	<0.001
% loss	−17.6	1.5	−0.5	1.8	<0.001
Total bowel length (cm)					
Pre-STEP	150.0	0	150.2	7.7	NS
Post-STEP	n/a		197.2	8.3	0.001
Death	151.0	4.0	229.2	10.6	<0.001
Bowel diameter (cm)					
Proximal	6	0.3	3.6	0.2	<0.001
Distal	4.4	0.2	3.3	0.2	0.005

STEP indicates serial transverse enteroplasty; SEM, standard error measurement; NS, not significant.

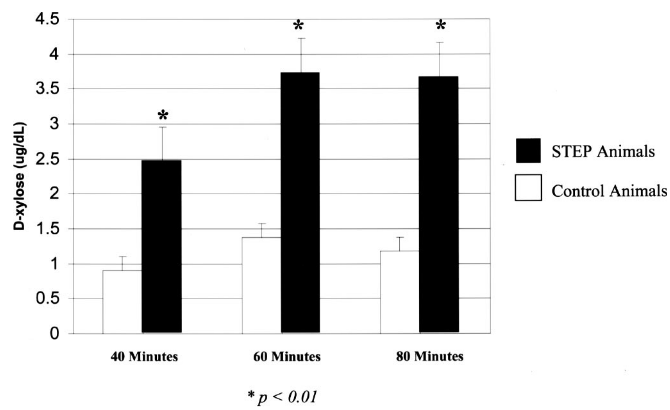

FIGURE 4. At all time points following orogastric administration of D-Xylose, STEP animals demonstrated increased serum D-Xylose levels, implying improved carbohydrate intestinal absorptive function (*$P < 0.01$ for all time points).

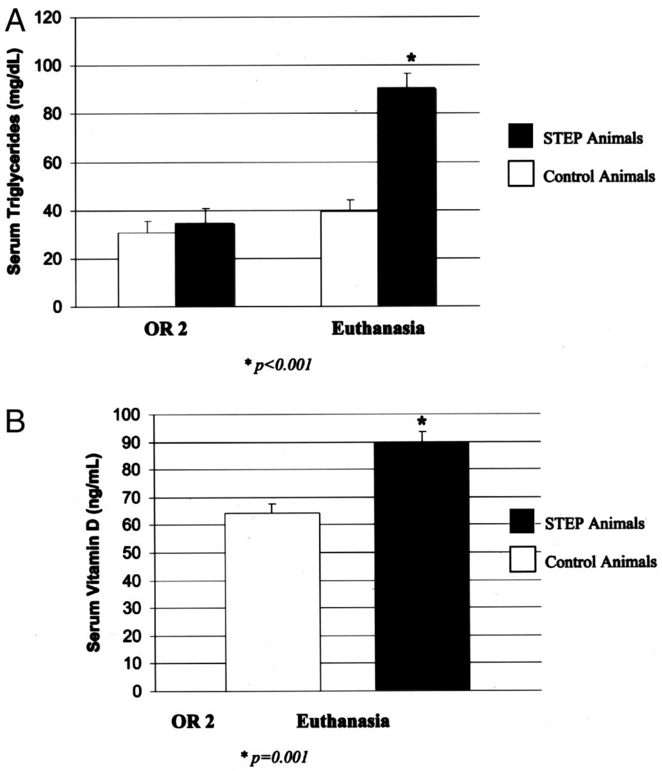

FIGURE 5. A, STEP animals demonstrated a significant increase in serum triglycerides in the 6-week period following bowel resection and STEP procedure that was not observed in control animals ($P < 0.001$). B, Significantly greater serum levels of vitamin D demonstrated in STEP animals as compared with controls ($P = 0.001$).

tween OR 2 and death. There was a trend toward higher zinc levels in the STEP group at death, although this was not statistically significant. STEP animals also exhibited significantly greater serum levels of citrulline, a biochemical marker of intestinal mass at time of death (23.4 ± 1.7 versus 13.8 ± 1.3 μmol/L, $P < 0.01$).

On microbiologic analysis, proximal specimens of STEP animals showed no evidence of bacterial overgrowth. Four of 5 control animals demonstrated abnormally high counts of gram-negative organisms that were identified as *E. coli*, in a concentration greater than 10^5 colony forming units/milliliter. Normative data show no gram-negative bacteria in the proximal bowel of this species under standard conditions.[9]

DISCUSSION

Surgical options for the patient with short bowel syndrome are limited. The most commonly used operation, originally described by Bianchi,[4] has demonstrated some functional improvement in select children.[10] However, this procedure is technically demanding, requires at least one anastomosis, may jeopardize the bowel mesentery, and does not accommodate marked variations in bowel dilatation. In contrast, the STEP procedure is easy to perform, does not require any intestinal anastomoses, and accommodates variations in bowel dilatation with facility.[5] The STEP procedure can be performed as a primary bowel lengthening operation or after a prior Bianchi procedure.

Given the technical success of the STEP procedure in an animal model of dilated bowel, we sought to examine the specific effects of the STEP operation on in vivo intestinal function using a previously established porcine model of short bowel.[6] This model uses a 90% small bowel resection following an initial period of bowel dilatation to produce a replica of short bowel syndrome analogous to the clinical situation. The results from this study demonstrate significant improvement in intestinal function as measured by whole body weight retention, intestinal absorption of carbohydrates and fats, and a decrease in bacterial overgrowth.

The most remarkable effect of the STEP procedure in this study was on the body weight of animals with short bowel anatomy. The experimental group that underwent the STEP procedure was noted to have significantly better weight retention when compared with control animals, which lost approximately 18% of initial body weight (Fig. 3). No external etiologies were observed to explain this weight differential; appetite did not seem to be suppressed in either group, all animals received the same quantity of chow, and individual stall feeders were empty upon morning inspection for all animals. Thus, despite equivalent nutritional intake, STEP animals had significantly greater weight retention. Presumably, this finding is secondary to improved intestinal absorption following the STEP procedure. As weight loss on enteral nutrition is one of the limiting factors in weaning short bowel patients from parenteral nutrition, these weight retention data are encouraging and may have clinical relevance.

This study also sought to measure the absorptive capacity for different classes of common macronutrients. Serum levels of D-Xylose were used as a measure of carbohydrate intestinal absorption. D-Xylose testing is a well-validated proxy for carbohydrate absorption in the gastrointestinal tract of humans.[11] Our data demonstrated an increased D-Xylose absorption at all 3 time-points measured following gastric administration (Fig. 4). Fat absorption was evaluated using serum triglyceride and fat-soluble vitamin levels both before resection and at death. Despite the fact that a portion of the terminal ileum was resected in our animal model, the STEP animals had significantly higher levels of both serum triglycerides and fat-soluble vitamin D. In addition, STEP animals showed a marked accumulation of serum triglycerides during the 6-week post-STEP period that was not observed in control animals. While nutritional indices for protein accretion are difficult to measure in a large animal study, we chose to follow serum levels of albumin for a comparison of protein absorption and overall nutritional status between groups. Albumin levels were noted to be higher in animals following the STEP procedure as compared with controls, although both groups had a decrease in serum albumin following the enterectomy. While albumin is a nonspecific marker for nutritional status, the higher levels in STEP animals may signify improved intestinal protein absorption, less compromised liver function, and a decreased state of metabolic stress.

Previous studies have examined the effects of a 75% intestinal resection on nutritional physiology in a porcine model.[12,13] Significant decreases in macronutrient absorption and postoperative weight loss following resection were noted, and resected animals that subsequently underwent a Bianchi bowel lengthening procedure had significantly improved in vivo fat absorption but no change in carbohydrate and protein absorption. Hence, the current study using the STEP procedure represents the first report that supports improved in vivo lipid, carbohydrate, and protein absorption following operative bowel lengthening in a short bowel animal model.

An intriguing finding in this study was the significantly higher levels of serum citrulline in STEP animals. Citrulline is a serum marker of viable intestinal mass that has been followed clinically in patients following intestinal transplantation.[14] The increase in serum citrulline in the current investigation may imply accelerated intestinal adaptation following a STEP procedure. This hypothesis requires further corroboration by formal morphometric analysis. Interestingly, the control animals also demonstrated a probable intestinal adaptive response as indicated by a significant dilatation of the distal small bowel following the 90% small bowel resection.

Microbiologic data were obtained on bowel specimens from both experimental and control animals to assess any effect of the STEP on bacterial overgrowth. One of the challenges with short bowel syndrome is recurrent bacterial overgrowth in the proximal intestine that may worsen already compromised intestinal absorption and predispose to overwhelming sepsis. While there is no firm mechanism to explain the frequent occurrence of bacterial overgrowth in patients with short bowel syndrome, most authors think it is secondary to poor bowel motility in the proximal dilated intestine.[15] In the data presented here, none of the STEP animals had objective evidence for bacterial overgrowth, whereas 80% of the control animals had culture-proven gram-negative bacterial overgrowth. The beneficial effect of the STEP on bacterial overgrowth may be due to improved bowel motility following the procedure or may be secondary to the procedure's ability to taper the dilated proximal intestine. Indeed, the tapering of dilated bowel has been advocated as a means to improve both motility and bacterial overgrowth in short bowel patients.[16]

Thus, STEP seems to improve weight retention, nutritional status, intestinal absorptive capacity, as well as serum citrulline levels in a porcine short bowel model. A salutary effect upon bacterial overgrowth is also noted. These data support the use of the STEP operation in the treatment of selected patients with dilated bowel and refractory short bowel syndrome.

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