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Developing a novel ambulatory total parenteral nutrition dependent short bowel syndrome animal model

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Abstract

Background: Short Bowel Syndrome (SBS) results from extensive bowel resection. Patients with SBS require Total Parenteral Nutrition (TPN) for survival. Understanding mechanisms contributing to TPN-associated liver injury and gut atrophy are critical in developing SBS therapies. Existing SBS models using tethered animals have significant limitations and are unlike ambulatory human SBS patients. We hypothesized that we could induce SBS in piglets and develop an ambulatory TPN-SBS model.

Material and Methods: 18 neonatal pigs received duodenal and jugular catheters. They were fitted with a jacket holding TPN and a miniaturized pump. 6 piglets had 90% small bowel resection and catheter placement (SBS group). Non-SBS piglets were randomized into enteral nutrition (EN) or TPN.

Results: Bowel resection was successfully accomplished in SBS animals. Weight gain was similar in all groups. SBS animals had increased serum bilirubin compared to EN. Mean conjugated bilirubin ± SD was 0.045 ± 0.01 for EN, (p=0.03 EN vs TPN and p=0.03 SBS vs EN) and 1.09 ± 1.25 for TPN, (p=0.62 TPN vs SBS). Gut density was reduced in the TPN group compared to EN and SBS groups. Mean gut density ± SD was 0.11 ± 0.04 for TPN (p=0.0004 TPN vs SBS and p=0.00007 TPN vs EN) and not statistically different for EN vs SBS (p=0.32).

Conclusion: We created a novel, ambulatory TPN-SBS model using piglets, mimicking longterm TPN delivery in human SBS patients. Our model demonstrated TPN-related conjugated

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Author Contribution:

Ajay Kumar Jain contributed to the conception/design of the research. All authors contributed to acquisition, analysis, or interpretation of data as well as drafting the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work and approved the final manuscript.

Conflict of Interest:

AKJ serves as a consultant and speaker for Alexion Pharmaceuticals; however this association is not relevantto the current manuscript. "The authors declare that there is no conflict of interest regarding the publication of this paper."

hyperbilirubinemia and compensatory gut hypertrophy, as noted in humans with SBS. This model holds great potential for future research.

Keywords

Model; Animal; TPN; Short Bowel Syndrome; Ambulatory; Cholestasis; Gut atrophy

INTRODUCTION:

Short Bowel Syndrome (SBS) is an often debilitating condition that results from bowel resection usually secondary to necrotizing enterocolitis, gastroschisis, inflammatory bowel disease, ischemic injury or trauma[1]. Patients with SBS require Total Parenteral Nutrition (TPN) for survival[2,3].

TPN is known to cause liver injury as well as significant morbidity and mortality in adult and pediatric populations[4,5], the mechanisms of which remain elusive and are the major focus of ongoing research[6,7].

Efforts to understand mechanistic pathways contributing to TPN associated injury as well as the development of ameliorative and preventative strategies are critical in the ongoing care for such patients[8,9]. A key component of such endeavors is the availability of model systems replicative of human SBS.

Testing systems using a tethered animal with indwelling catheters are not ideal due to short duration TPN therapy secondary to animal stress from a lack of free mobility[10,11]. Animal stress has been shown to cause alterations in hepatobiliary receptors as well as intestinal motility, ion secretion and intestinal permeability, [12]. Additional concern is the viability of long term indwelling catheters, which are prone to dislodgement in traditional fixed tethered systems. Conversely, in human SBS patients, TPN can be delivered long term in an unobstructed, ambulatory manner[13-15]

Hypothesis:

Given this predicament, we hypothesized that we could develop an ambulatory model of short bowel syndrome utilizing neonatal pigs that undergo 90% surgical bowel resection. Such animals would be maintained on TPN, infused via secured catheters using miniaturized infusion pumps carried by the animal thus permitting completely untethered animal mobility and nutrition delivery. This would be a significant step forward in establishing a robust model to test SBS and a platform for future mechanistic studies.

METHODS AND MATERIALS:

Animal procurement:

Saint Louis University (SLU) is a registered research facility with the United States Department of Agriculture. The study was initiated upon approval by the Institutional Animal Care and Use Committee of SLU (SLU No. 2657, US Department of Agriculture registration 43-R-011) and conducted in accordance with the *Guide for the Care and Use of Laboratory Animals*.

Seven to ten day old, term neonatal pigs were used for this study. Animals were procured from an approved Class A vendor. Animals were identified by ear tags. Upon arrival they were immediately placed in heated cages.

Acclimatization and Housing:

In accordance with University guidelines, animals were acclimatized for three days upon arrival. Piglets were fed *ad lib*, swine milk replacer formula (LitterLife; Merrick's Inc, Middleton, WI, USA) with close monitoring of their daily intake. All animals were kept in a thermally controlled environment for the duration of the study at temperatures mandated by the facility's veterinarian.

Surgery and Catheter Placement:

Following three days of acclimatization, the piglets underwent surgery for creation of iatrogenic short bowel syndrome and placement of both jugular and duodenal catheters. Each piglet was taken to the veterinary operating room and placed in an individual chamber containing 3% to 5% isoflurane for anesthetic induction. Subsequently the animal was transferred to a heated surgery table. Using a cone mask, appropriate anesthesia was maintained (2%-4% isoflurane). Oxygen saturation, body temperature, heart rate and the respiratory rate were continuously monitored throughout the surgical procedure. Once deeply anesthetized, the neck and abdomen were surgically prepared and draped for aseptic surgery.

Jugular Catheter Placement:

Jugular catheters were placed in the right and left jugular vein by a vascular cut-down technique. The catheters were secured to the vessel via a purse string suture. Patency was confirmed by injecting 3mL heparinized saline. The catheters were subsequently tunneled subcutaneously to exit the skin just caudal to the scapulae. The catheter was then sutured to the skin via a catheter flange. In order to limit catheter slide, medical grade silicone glue was applied to additionally secure the catheter.

Duodenal Catheterization:

A midline 5 inch abdominal incision was made cranial to the umbilicus. Placement of a catheter into the duodenal lumen was performed as previously published[10]. Once the catheter was secured and tunneled, we proceed with 90% mid-small bowel resection.

Creation of Short Bowel:

A 50 cm segment of the bowel proximal to the ileocecal valve as well as a 50cm segment distal to the ligament of Treitz was identified. We measured the bowel using sterile silk ribbon placed along the anti-mesenteric border of the gently stretched small intestine. Using doyen-clamps the proximal and distal ends were clamped to prevent gross contamination. The small bowel in between these two segments was resected using electrocautery and measured outside of the piglet (Figure 1A).

Once the resected segment was freed from the mesentery, the doyen-clamped ends of each remnant bowel section (jejunum and ileum) were brought together. Stay sutures at the

mesenteric and anti-mesenteric borders were used to ensure correct apposition. To ensure 90% resection we measured the entire length of resected bowel and if necessary, we made adjustments by resecting further bowel (Figure 1B). Luminal continuity of the two remnant sections was restored by jejunoileal side to side (functional end to end) stapled (Just Right® 5 mm Stapler) anastomosis (Figure 1C).

The anastomosis was copiously washed in a bowl of warm saline before being returned to the abdomen. The abdominal incision was closed in two layers with 2.0 Vicryl (absorbable; all layers of abdominal wall except skin) and staples. Piglets were administered buprenorphine (0.1 mg/kg, subcutaneously) for postoperative pain relief and monitored until full recovery.

Jacket Placement:

Animals were fitted into a jacket with pockets on both sides. An ambulatory, miniaturized battery-operated infusion pump (Orchestra 500) was placed in the right pocket. Nutrition bag tubes were placed in the left pocket. Both of the jugular catheters were sieved through the left pocket fabric. While one was heparin locked, the other was connected to the pump via a PEGA tube mechanism.

Subsequently, the TPN solution (Clinimax E and Intralipid) in EVA bags (EVA, code 66050; Medtec Medical, IL, USA) was placed in the left pocket. This was connected via cannula clamps to the tubing supplying the pump. All piglets were closely monitored by veterinary staff until fully recovered.

Animal Monitoring:

Animals were weighed each morning and examined by a veterinary doctor. Additionally, they were monitored with scheduled visits by the research personnel in accordance with the Institutional Animal Care and Use Committee and the Guide for the Care and Use of Laboratory Animals.[16]

Group allocation and Statistical Analysis:

After 48-hour post-surgery recovery, 18 animals were randomly assigned to three experimental groups (Table 1). The EN animal group (n=6) received enteral nutrition via the duodenal catheter and no TPN. The TPN animal group (n=6) received no enteral nutrition but were provided TPN via the jugular catheter. The SBS animal group (n=6) underwent 90% bowel resection and received TPN via the jugular catheter but no enteral nutrition. Mean and standard deviation were calculated for each group for the weight gain, serum bilirubin and the gut density. The student’s t test was used for statistical analysis. All tests were 2 sided using a statistical significance level of 0.05.

Nutrition Intake:

Isocaloric and isonitrogenous nutrition was provided to all animals for a period of approximately 3 weeks. The EN group received the swine replacement formula LitterLife (Merrick's Inc). Enteral nutrition was delivered via the duodenal catheter at a rate of 260 mL

kg–1 d–1 with 25 g/kg lactose, 12.4 g/kg protein, and 5 g/kg fat along with electrolytes, trace minerals, and vitamins, for a total of 187 kcal kg–1 d–1.

Total parenteral nutrition piglets received the commercially available parenteral nutrition preparation (Clinimix E; Baxter, IL, USA;) via the jugular catheter. This provided fluids at 260 mL kg–1 d–1 with 26 g/kg dextrose, 11.05 g/kg protein, and 5 g/kg fat along with electrolytes, trace minerals, and vitamins, for a total of 182 kcal kg–1 d–1 via the jugular catheter.

The TPN or EN was placed in nutrition bags (EVA, product code 66050; Medtec Medical) with nutritional constituents as seen in table 2. All nutrition bags were replaced every 12 hours using aseptic precautions.

Animal Euthanasia and Sample Collection:

Blood samples were obtained for conjugated bilirubin prior to administration of euthanasia. Piglets were euthanized using a pentobarbital sodium (100 mg/kg)–based euthanasia solution (Beuthanasia-D; Schering-Plough Animal Health, Kenilworth, NJ, USA) delivered intravenously. Immediately after euthanasia, the abdomen was opened and the liver was procured in its entirety. The proximal and distal segments were identified based on suture location and removed in their entirety. Removed bowel from all groups was immediately flushed with cold saline and weighed.

RESULTS:

A total of 18 piglets were implanted with duodenal and jugular vein catheters. At the time of euthanasia we inspected all bowel anastomosis in SBS animals (Figure 2A), which remained intact (Figure 2B).

Weight gain:

An indicator of adequate caloric intake is weight gain. We evaluated the weight of each animal daily. The daily weight gain was similar for all groups with no statistically significant differences, verifying adequate caloric support using ambulatory pump for nutrition (Figure 3). The mean daily weight gain ± SD was 132.89 ± 29.73 for EN, (p=0.06 EN vs TPN); 105.26 ± 13.72 for TPN, (p=0.31 TPN vs SBS) and 113.15 ± 11.88 for SBS, (p=0.15 SBS vs EN).

Conjugated Hyperbilirubinemia:

Increased conjugated bilirubin level is characteristically noted with TPN therapy. We measured the direct bilirubin fraction prior to animal euthanasia at the completion of the study. As expected, animals on TPN had significant conjugated hyperbilirubinemia in comparison to the EN animal group. The SBS animal group also had significant elevation of serum conjugated bilirubin (Figure 4A).

The mean conjugated bilirubin level ± SD was 0.045 ± 0.01 mg/dL for EN, (p=0.03 EN vs TPN); 1.09 ± 1.25 mg/dL for TPN, (p=0.62 TPN vs SBS) and 0.79 ± 0.09 mg/dL for SBS,

(p=0.03 SBS vs EN). We also measured hepatic cholestatic deposits. While the cholestatic deposits were higher in animals on TPN, this did not reach statistical significance (p=0.87).

Gut Density:

We have previously published gut atrophic changes with TPN[2]. To further quantify the atrophic changes we determined the density of the gut as a measure of weight in grams per centimeter of bowel length. We noted a significant reduction in gut density in TPN animals compared to those on EN. Paradoxically, animals with SBS, despite being on TPN had higher gut density compared to their TPN counterparts with intact bowel. Additionally, there was no statistical difference in the gut density between EN and SBS animals (Figure 4B). The mean gut density ± SD was 0.22 ± 0.02 gm/cm for EN, (p=0.00007 EN vs TPN); 0.11 ± 0.04 gm/cm for TPN, (p=0.0004 TPN vs SBS) and 0.25 ± 0.08 gm/cm for SBS, (p=0.32 SBS vs EN).

DISCUSSION:

Worldwide, every year a large number of patients undergo bowel resection for several disorders, including necrotizing enterocolitis, volvulus, inflammatory bowel disease (IBD), malignancy, mesenteric ischemia, gastroschisis, trauma and others[17,18]. Significant bowel resection compromises digestive and absorptive processes impairing proper nutritional status. These patients thus need nutritional support via the intravenous route – a modality called total parenteral nutrition (TPN)[19,20].

Since TPN associated liver injury[21] can lead to significant morbidity and mortality, weaning from TPN remains a major goal for such patients[22,23]. While significant research is focused in finding preventative or ameliorative strategies to manage the complications associated with chronic TPN, a major limitation in moving the field forward is the lack of a robust SBS animal model replicating human ambulatory TPN infusion. This is a critical step for translational studies.

We hypothesized that we could create an ambulatory SBS piglet model with miniaturized pumps carried by the animal. We developed surgical techniques to resect 90% bowel in neonatal pigls and achieve end to end anastomosis. We were also able to introduce intra-duodenal as well as jugular catheters sieved subcutaneously to exit at the animals dorsal with minimal complications. Subsequently, using miniaturized ambulatory pumps we were able to successfully deliver TPN to these animals and such placement facilitated animal mobility.

We demonstrated equal weight gain in short bowel animals compared to animals without bowel resection on TPN as well as those on enteral nutrition indicating adequate nutrition delivery with our new model.

A key component of liver injury that occurs in patients with SBS on TPN is jaundice which is a clinical manifestation of hyperbilirubinemia[24]. Validating this aspect of hepatocellular injury, we noted significantly higher conjugated bilirubin level in animals on TPN.

Recent evidence also points to atrophic changes in the gut while on TPN. This is believed to occur due to a lack of trophic signals secondary to a lack of luminal nutrients[2,5]. As

expected animals on TPN had gut atrophic changes as documented by a reduction in the gut density. Interestingly, the gut density in animals with SBS was higher. We speculate that this response was due to gut adaptation secondary to the extensive bowel resection and mechanisms driving such gut growth would be an important research area.

Our model demonstrated that the establishment of an ambulatory SBS model with TPN is feasible and replicates the physiopathology of SBS in humans. This model is promising in many ways since it may allow experimental evaluation of the gut and liver alterations with SBS, as well as could prove critical in the development of novel therapies for SBS.

Emerging data supports the use of bile acids[25] to ameliorate TPN associated liver injury via activation of gut derived signals which modulate the gut-liver crosstalk[2,26,27]. An important use of our model would be therapeutic drug testing, as well as to further define mechanistic links mediating such crosstalk. Given its ambulatory nature, our SBS model poses minimal animal stress in comparison to the tethered animal models and thus long term effects of TPN infusion could be ascertained and tested.

CONCLUSION:

We created a successful short bowel syndrome animal model using neonatal pigs and delivered TPN using miniaturized pumps in an ambulatory fashion. We believe this model recapitulates long-term ambulatory TPN delivery in human SBS patients. Our TPN-SBS model, with significant bowel resection shows the classical hyperbilirubinemia as well as compensatory gut hypertrophy noted with significant bowel resection and thus validates key injury elements noted in human short bowel syndrome. This model holds great potential for translational research supporting drug development and in our understanding of SBS as well as complications of TPN.

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ABBREVIATIONS:

TPN	Total Parenteral Nutrition
JV	Jugular Vein
DC	Duodenal Catheters
USDA	United States Department of Agriculture

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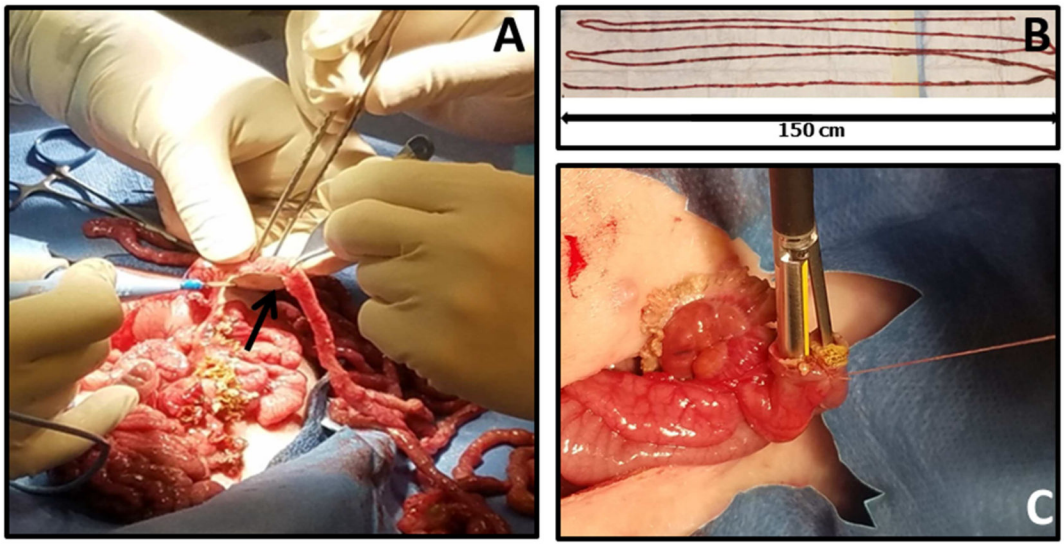

Figure 1:
(A) Electrocautery is used to obliterate the mesentery to accomplish the resection. (B) Resected bowel is measured to confirm 90% resection. (C) Jejuno-ileal side to side stapled anastomosis (Just Right® 5 mm Stapler)

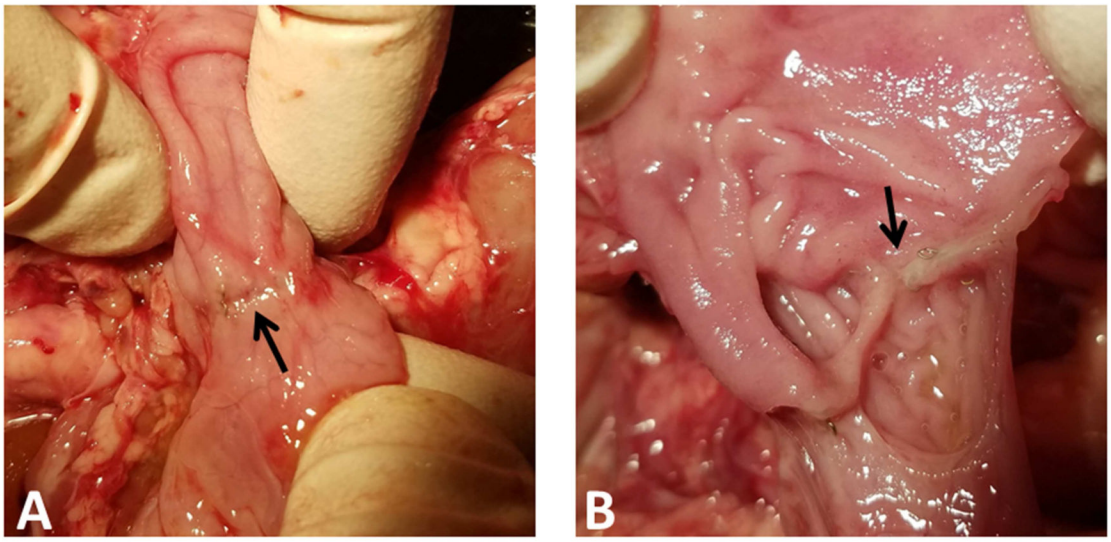

Figure 2:
(A) Intact anastomosis on serosal surface (arrow marks staples). (B) Anastomosis has been divided, intact mucosa is visualized.

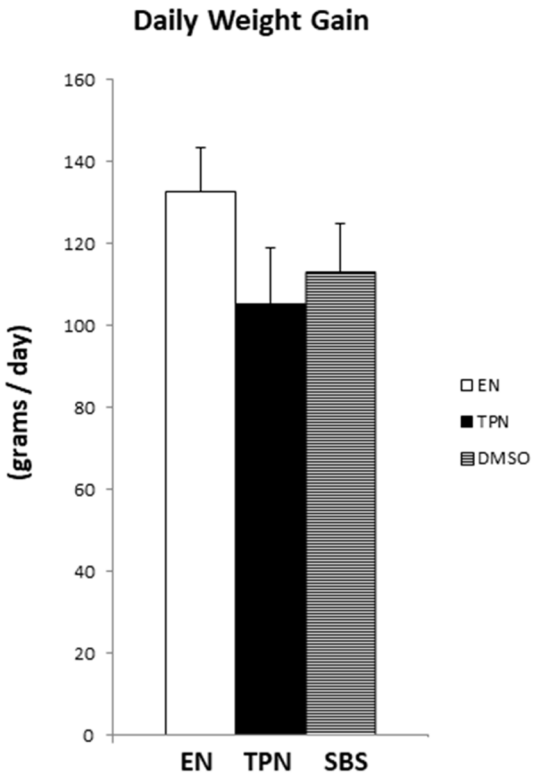

Figure 3:

Daily weight gain in each group. Each column reflects the mean for that group. Error bars represent standard error. Differences between groups are based on the T test. All test were 2 sided using a significance level of 0.05. Note: No difference in daily weight gain between the groups.

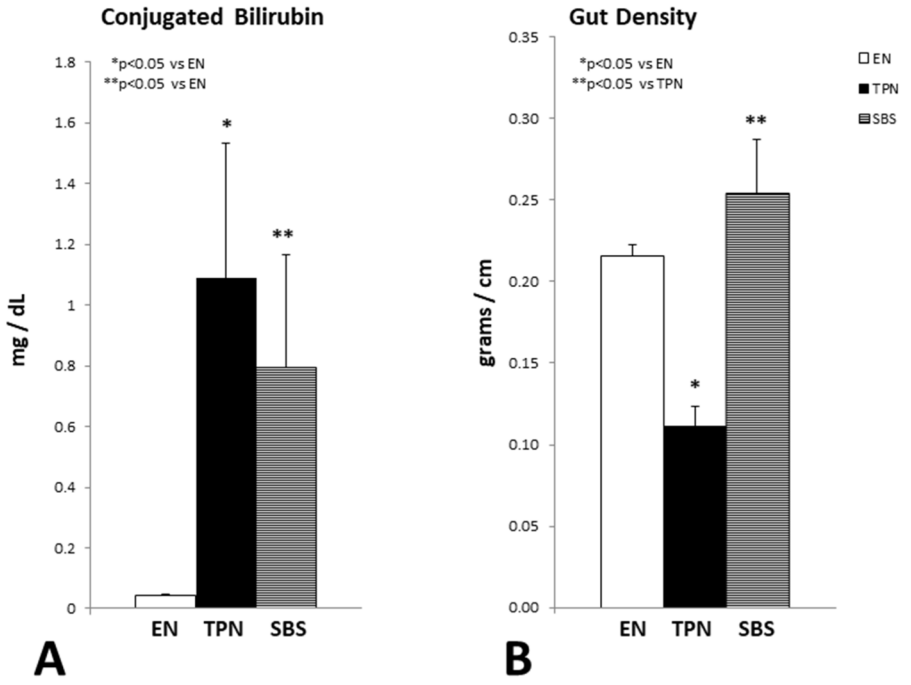

Figure 4.

(A): Serum conjugated bilirubin. Each column reflects the mean for that group. Error bars represent standard error. Differences between groups are based on the T test. All test were 2 sided using a significance level of 0.05. Note: Significant elevation of bilirubin in the TPN and SBS group vs EN. No statistical differences in serum bilirubin were noted between TPN and SBS. (B) Gut density as measured in grams per centimeter. Each column reflects the mean for that group. Error bars represent standard error. Differences between groups are based on the T test. All test were 2 sided using a significance level of 0.05. Note: Significant reduction of gut density with TPN vs EN. SBS had the highest gut density, likely secondary to gut adaptation.

Table 1:

Group Allocation

Group	Assigned Treatment
EN Group	Animal with catheter placements and abdominal incision but no bowel resection. Animals received regular enteral nutrition but no TPN.
TPN Group	Animal with catheter placements and abdominal incision but no bowel resection. Animals received TPN but no enteral nutrition.
SBS Group	Animal with catheter placements and abdominal incision with 90% bowel resection. Animals received TPN but no enteral nutrition.

Table 2:

Nutritional Constituents

Total Parenteral Nutrition	Enteral Nutrition
Ingredients: Leucine, Isoleucine, Valine, Lysine, Phenylalamine, Histidine, Threonine, Methionine, tryptophan, Alanine, Arginine, Glycine, Proline, Serine, Tyrosine, Sodium, Potassium, Magnesium, Calcium, Acetate, Chloride, Phosphate, Dextrose) and Intralipid (Fresenius Kabi, Germany, Ingredients: Soybean Oil, Egg Yolk Phospholipids, Glycerin and Water.	Ingredients: Dried Whey Protein Concentrate, Animal Plasma, Animal and Vegetable Fat preserved with BHA, Dried Lactose, Lecithin, Dicalcium Phosphate, Magnesium Sulfate, Manganese Sulfate, Ferrous Sulfate, Zinc Sulfate, Cobalt Sulfate, Copper Sulfate, Calcium Iodate, Sodium Selenite, Vitamin A Acetate, d-Activated Animal Sterol, Vitamin E Supplement, Menadione Dimethylpyrimidinol Bisulfite, Choline Chloride, Riboflavin Supplement, Calcium Pantothenate, Niacin Supplement, Vitamin B12 Supplement, Biotin, Ascorbic Acid, Yucca Schidigera Extract, Natural and Artificial Flavors.