JOURNAL OF SURGICAL RESEARCH 195 (2015) 433–443

Available online at www.sciencedirect.com

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Intestinal lengthening and reversed segment in a piglet short bowel syndrome model

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ARTICLE INFO

Article history:
Received 15 March 2014
Received in revised form
7 December 2014
Accepted 11 December 2014
Available online 29 December 2014

Keywords:
Short bowel syndrome
Longitudinal intestinal lengthening procedure

ABSTRACT

Background: Treatment of short bowel syndrome (SBS) remains difficult, entailing severe morbidity and mortality. Accepted surgical treatment modalities for SBS are the Bianchi intestinal lengthening procedure and reversed-segment procedure. We seek to investigate the short-term effects regarding growth, nutrition, and microscopic and functional adaptation after the intestinal lengthening and RS procedures in a piglet SBS-model.
Material and methods: Twenty-four piglets (Sus scrofa, ±30 kg) were divided into four groups ($n = 6$ each) as follows: sham, SBS, Bianchi lengthening procedure (BIA), and reversed-segment (RS). At day one either sham laparotomy (sham) or 75% small bowel resection (SBS, BIA, and RS) was performed. After 2 wk sham laparotomy (sham and SBS), BIA, or RS procedure was performed. After 8 wk all animals were terminated. During the experimental time course, the following parameters were assessed: body weight, intestinal length, diameter, and weight, fat absorption, and biochemical parameters from serum and urine. Citrulline was used as a marker of absorptive enteral mass to demonstrate massive functional bowel loss. Intestinal biopsies were obtained for histologic analysis and electrophysiological measurements to analyze glucose absorptive capacity.
Results: Eight weeks after bowel resection, piglet growth was reduced in SBS, BIA, and RS piglets as demonstrated by reduced weight (51 ± 4 kg, 47 ± 2 kg, and 53 ± 1 kg, respectively) compared with sham (69 ± 3 kg; $P < 0.01$), with no demonstrable difference between SBS and treatment groups. Malabsorption and malnutrition occurred in SBS, BIA, and RS piglets reflected by increased fecal fat loss per 24 h (35 ± 4%, 30 ± 2%, and 32 ± 4%, respectively *versus* 18 ± 1% in sham; $P < 0.01$) and reduced serum albumin levels (24 ± 1 g/L, 22 ± 1 g/L, and 24 ± 1 g/L, respectively *versus* sham 33 ± 1 g/L; $P < 0.01$), but there was no significant difference between SBS and treatment groups. Serum citrulline levels reflected massive functional bowel loss (SBS 36 ± 7 μmol/L, BIA 23 ± 1 μmol/L, and RS 24 ± 2 μmol/L) compared with sham (64 ± 5 μmol/L; $P < 0.01$). Electrophysiological measurements demonstrated reduced glucose absorption after intestinal resection, which did not return to base levels within the experimental time course. However, the intestine of BIA and RS piglets adapted more profoundly than SBS piglets, as reflected by a greater crypt depth

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0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2014.12.024

(490 ± 25 μm and 492 ± 21 μm *versus* 388 ± 20 μm; $P < 0.01$); and BIA piglets showed greater villus length (884 ± 58 μm) than RS or SBS piglets (715 ± 30 μm and 737 ± 64 μm, respectively; $P < 0.01$) after 8 wk.

Conclusions: Despite increased histologic intestinal adaptation, neither intestinal lengthening nor RS procedure demonstrated significantly improved absorption, nutrition, or weight gain for the treatment of SBS during the study period. Reduced glucose uptake on electrophysiology measurements and persistent low levels of citrulline may indicate reduced small bowel enterocyte functioning during the initial phase of intestinal adaptation.

1. Introduction

Therapy of short bowel syndrome (SBS) is aimed at optimizing enteral and parenteral nutrition (PN) therapy, but also at prevention, early detection, and treatment of complications of PN such as cholestasis and central venous catheter-related infections [1,2]. In the long term, achieving enteral autonomy should be the primary objective. When first line therapy, including surgical interventions such as restoring bowel continuity and adhesiolysis, is inadequate to achieve this goal, further surgical therapy may be indicated.

Various surgical therapies have been developed to treat SBS symptoms and accelerate adaptation. These may generally be divided into autologous intestinal reconstruction procedures and bowel transplantation. Bowel transplantation has demonstrated great improvements in survival but is still associated with severe morbidity and mortality. Furthermore, application is constrained by the limited number of donors, especially in pediatric patients [3]. Autologous procedures may offer better long-term results with reduced morbidity and mortality [4]. The longitudinal intestinal lengthening procedure, as originally described by Bianchi [5], is one of the most widely applied autologous surgical procedures for pediatric SBS [6,7]. Another older, less complex procedure is the reversed-segment (RS) procedure [8], sometimes used in combination with the Bianchi procedure. Over the last years, the STEP (serial transverse enteroplasty) procedure [9] has also gained popularity.

The Bianchi longitudinal intestinal lengthening procedure makes use of the bifurcated vascularization of the intestine. It uses sequential longitudinal transection and bowel anastomosis, with serial anastomosis to double remaining intestinal length (Fig. 1). Thereby, it increases intestinal length and reduces intestinal diameter with resultant increased transit time and chymal-mucosal contact.

The antiperistaltic reversed segment (RS), reduces transit time by surgical isolation of an intestinal segment, 180° rotation, and anastomosis; thus creating an antiperistaltic segment (Fig. 2). RS thereby increases the nutrient load, and thus possibly enhances adaptation.

Both procedures have shown clinical value [4–10]. A recent systematic review described that some 70% of children could be weaned from PN after the Bianchi procedure, while an overall intestinal lengthening of 1.48 fold (range 1.25–2.0) could be achieved [9]. For the RS, 45% of adult patients achieved intestinal autonomy, whereas remaining patients showed a reduction in PN dependency in the largest reported clinical series ($n = 38$) using this technique [10].

Despite such promising clinical results, the working mechanism of both procedures requires further elucidation. We present an experimental study in a validated porcine model for SBS [11] investigating growth and nutritional status, as well as early microscopic and functional changes of the intestine after longitudinal lengthening and antiperistaltic RS.

2. Material and methods

Twenty-four piglets (Sus scrofa, female, ±30 kg, aged 8 wk) were included after 1-wk acclimatization and divided into four groups ($n = 6$ each) as follows: SBS, sham, Bianchi lengthening procedure (BIA), and RS; (Table 1). The pigs were housed in individual pens, side by side, on a grid floor. Room temperature was maintained at 20°C, with light–dark cycles of 12 h. Animals were fed 1.4 kg of standard grower feed per day (Hope Farms, Woerden, the Netherlands, 9.34 MJ/1000 g, 17.5% protein, 4.5% fat, and 4% fiber) with water *ad libitum*, except postoperatively. The protocol was approved by the Animal Ethics Committee of Amsterdam (the Netherlands).

All animals were handled in accordance with the guidelines prescribed by Dutch legislation and the International Guidelines on the protection, care, and handling of laboratory animals.

On day one, surgery was performed, either a sham laparotomy (sham-group), or creation of the SBS by means of 75% small intestinal resection (remaining groups). Surgical intervention occurred again after 2 wk, either sham operation (sham group and SBS group), or Bianchi lengthening procedure (BIA group) or reversed segment (RS group) in the experimental groups; with termination in all groups after 8 wk.

2.1. Surgical procedures

Creation of the SBS has been described previously [11,12]. Briefly, animals were fasted for 12 h, then analgesia (flunixinum 2 mg/kg and buprenorphine 0.01 mg/kg) was administered. Anesthesia was induced with midazolam (1 mg/kg), ketamine (10 mg/kg), and atropine (0.02 mg/kg). An endotracheal tube was inserted and anesthesia maintained by ventilation with isoflurane (1.5% by volume) and O_2/N_2O, with sufentanil (15 mg/kg) ketamine (15 mg/kg), and clonidine (0.5 mg/kg). Pancuronium (0.1–0.5 mg/kg) was given for muscle relaxation. Perioperatively, antibiotics (ceftriaxone 30 mg/kg and ampicillin 15 mg/kg) and analgesia (flunixinum 2 mg/kg and buprenorphine 0.01 mg/kg) were administered.