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Short-Bowel Syndrome in Children – An Update in Management Strategies

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<http://dx.doi.org/10.5772/59313>

1. Introduction

Pediatric short bowel syndrome (PSBS) is usually defined as a devastating condition that results from massive intestinal resection due to congenital or acquired lesions and is associated with inadequate absorption of enteral nutrients [1-2]. Additionally, PSBS is accompanied by the loss of the immune capacity and secretion of the intestinal hormones and regulating enteral peptides [3]. Children with PSBS are usually dependent on parenteral nutrition (PN) to compensate fluid, electrolyte and energy requirements [1]. The causes of PSBS vary according to age; in neonates, predominant causes include necrotizing enterocolitis, small bowel atresia and gastroschisis, complicated meconium ileus, and midgut volvulus [4-6]. According to most studies, necrotizing enterocolitis is the most common cause of PSBS in the neonatal period, particularly among extremely premature infants, with an incidence rate ranging from 14% to 43% [4, 7]. In older children, PSBS may be ascribed to Crohn's disease, abdominal tumors, radiation enteritis, trauma, malignancy, iatrogenic lesions and adhesive obstruction [8, 9]. Intestinal motility disorders (total or subtotal aganglionosis) and mucosal enteropathies have also been implicated [10, 11].

There are no accurate data in the literature for the incidence of PSBS [5]; it is based mainly on prematurity and low birth weight [1]. In a large cohort study performed by Cole et al [12], the reported incidence of PSBS among very low birth-weight infants was 0.7% and 1.1% among extremely very low birth-weight infants. Wales et al [13] conducted a retrospective cohort study involving 175 surgical neonates with PSBS, and reported an overall incidence of 22.1/1000 neonatal intensive care unit (NICU) admissions (95% CI=15.3, 28, 9) and 24.8%/

100.000 live births (95% CI=12.1, 36.9). Again, PSBS was higher among premature infants (43.6 of 1000 vs. 3.1 of 1000 admissions).

The mortality rates for PSBS vary extensively between studies and depend on the definitions and causes of PSBS. In general, mortality rates vary from 15% to 40% [13-16]. It is thought that the main risk factors for the high mortality of PSBS include the length of the remaining small bowel, catheter-associated bloodstream infection, loss of ileocecal valve and liver failure due to the prolonged duration of parenteral nutrition [17-21]. Earlier studies concerning PSBS and successful outcome were based on the remaining bowel length after resection and the presence of ileocecal valve (ICV). Wilmore [21] reported a successful outcome of 50% in infants with at least 15cm to 25 cm of residual bowel and an intact ICV, but there were no survivors among those with a residual bowel of 15 cm. However, in a retrospective review of 80 pediatric patients, Spencer et al [22] reported that only cholestasis and the length of the age-adjusted small bowel length can be considered as the strongest predictors of mortality in PSBS. Septic episodes, the presence of ileocecal valve, and the etiology of SBS were not predictive.

The management of PSBS remains a challenge and needs a careful individual curative approach. The aim of the present study is to provide an update of the current therapeutic methods and future aspects in the treatment of PSBS. To this end, PubMed was searched for relevant articles using as key words "short bowel syndrome", "children", "management", "surgical treatment", "medical management", "small bowel transplantation", "tissue engineering", and "experimental approach". The retrieved articles were further screened for additional studies. Articles published in a language other than English were excluded. A brief reference to the pathophysiological changes following intestinal resection is also cited.

1.1. Pathophysiological consequences of PSBS

There are three dominant anatomical anastomoses depending on the extent of the resected bowel: 1) jejunioileal anastomosis, 2) the jejunocolic anastomosis, and 3) end-jejunostomy [23]. Patients of the first group rarely display considerable electrolyte or nutrient imbalance because the residual ileum and the intact colon can balance the absence of the resected bowel [23], due to a) the presence of the less permeable tight junction of the ileum [9] and b) the capacity of the colon for fluid absorption [24]. However, partial resection of the jejunum may impair the secretion of the regulatory hormones produced by jejunal cells. Loss of cholecystokinin released with secretin when food from the stomach reaches the first part of the duodenum may lead to gastric acid hypersecretion due to abolition of the feedback inhibition mechanism that regulates gastrin and gastric acid secretion. This discrepancy may cause an increase in the pH of the proximal small bowel that leads to denature of the pancreatic enzymes and impairment of digestion [25-27]. Experimental studies have shown that patients with jejunocolic anastomosis have more severe disease because the jejunum has reduced adaptive ability as compared to the ileum [28, 29]. Usually, the ICV has also been resected in such cases. The following alterations in the absorption, secretion of fluids, bile salts, lipids and adaption in hormonal mediators due to resection of the ileum may be seen: a) extensive diarrhea due to decreased

water reabsorption by the distal small intestine [9], b) malabsorption of vitamin B₁₂ because of the deficiency of receptors of B₁₂ localized to the distal ileum [30], c) reduced absorption of bile salts, which in turn may lead to deficiency in fat-soluble vitamins, steatorrhea, and diarrhea [9,30,31], d) up-regulation of glucagon-like peptides 1 and 2 and peptide YY, all of which are produced by enteroendocrine L cells of the distal ileum and colon of patients with ileum resection but with a preserved colon [32, 33]. The net result leads to normal gastric emptying and intestinal transit time for solid foods, less gastric hypersecretion and increase in villus height, crypt cell proliferation, and inhibition of enterocyte apoptosis [23, 34-39]. The loss of both ileum and colon in patients undergoing end-jejunostomy leads to severe dehydration, and electrolyte depletion [23]. Additionally, colon resection results in further depletion of energy as studies have shown that the colon can absorb up to 15% of energy requirements [40-41]. Furthermore, patients with end-jejunostomy display increased gastric emptying and intestinal transportation [42] due to the lack of the protective effect of hormonal mediators such as GLP-1, GLP-2, and peptide YY [23]. Studies in adults have shown that the presence of little or no colon and less than 50-100 cm of jejunum results in permanent parenteral nutrition [43, 44]. However, the results are inconclusive for infants and children, and it seems that colon loss is not a strong predictor for weaning off parenteral nutrition [22, 45, 46].

1.2. Management of PSBS

The current management of patients is multifaceted and includes surgical modification techniques and medical approaches, which will be discussed below. Tissue engineering is also reviewed; this novel strategy, currently in its exploratory phase, aims to build a new small bowel [47].

2. Surgical techniques to treat PSBS

A substantial number of surgical techniques have been described in order to address the two main problems of PSBS: the loss in absorptive surface and dysmotility of the residual above the anastomosis. These procedures pertain to autologous methods of intestinal reconstruction and could be categorized further into two subgroups: I) lengthening of the residual short bowel to provide satisfactory nutrient amount [48,49], and II) slowing of the intestinal transit [4]. Small bowel transplantation represents a separate option and has been proposed as an alternative for children with permanent intestinal failure and no longer tolerated parenteral nutrition (PN) [11, 50].

2.1. Surgical techniques for lengthening of the residual short bowel

- a. *Bianchi's procedure.* In 1980, Bianchi was the first to apply the longitudinal intestinal lengthening and tailoring (LILT) technique in an animal model [48]. In brief, this technique consists of a construction from a segment of small intestine of two isoperistaltic hemiloops of half the original diameter. The two hemiloops are then positioned in a circular manner,

and an end-to-end anastomosis is performed between them. Subsequently, the new segment is reconnected with the remaining bowel. This allows the doubling of the entire length of the original segment to be performed. Data from the literature suggest that successful outcome is achieved when the following anatomical conditions are met [7]: a) an intestinal diameter > 3 cm; b) a residual small bowel length > 40cm, and c) a dilated bowel length > 20 cm. However, another study by Bianchi [51] of 20 children (aged 7 weeks to 92 months) undergoing LILT, suggested that the favorable outcome (9/20 survivors, 45%) was associated with the presence of >40cm of the residual dilated small intestine and minor hepatic dysfunction. Age, the presence of ICV and the length of the residual colon did not affect survival. In conclusion, LILT seems to increase the function of the residual small bowel; survival rates reach as high as 100% (range 30% to 100%), improvement is noted in intestinal transit, stool frequency, intestinal absorption, weight gain and, in 50% of cases, weaning off parenteral nutrition is observed [51, 52-56].

- b. *Kim's procedure*. Serial transverse enteroplasty (STEP) was introduced by Kim et al [49] in 2003 in an experimental study. The technique was performed using a GIA stapler to create a zig-zag channel with a diameter of 2-2.5cm at the mesenteric site. The staples were placed from the 90° and 270° positions at the mesenteric site of the intestine, using the mesentery as the 0° reference point. The basic results showed that the technique is easy to perform, avoids anastomoses, carries a low risk of intestinal ischemia, can be used repeatedly, and could almost double the length of the residual intestine [1].

Recently, Frongia et al [57] compared the above mentioned lengthening techniques in a systematic review. After analyzing the results of 39 articles (LILT: 24, STEP: 15) including 472 patients (LILT: 363 patients, STEP: 109 patients), they concluded that both methods are thought to be acceptable. However, STEP seemed to have a more favourable outcome : LILT 30.2% mortality rate vs. STEP 14.3%. Similar results were reported in a retrospective study by Jones et al [58] who pooled data from the International STEP Data Registry involving the long-term follow-up of 97 patients, aged 2.4 months to 37.8 months, who had undergone STEP. An overall mortality of 11% was recorded. More recently, at small cohort study of 12 children (aged 0.9 to 19 months) was conducted by Wester et al [59]; a t median follow-up of 37.2 (3.0 to 87.5) months, no deaths were recorded.

- c. *Cherni's procedure (experimental)*. Recently, Cherni et al [60] used a new technique called spiral intestinal lengthening and tailoring (SILT), as an alternative method to LILT and STEP. In brief, spiral incision lines are drawn with a sterile pen to the longitudinal axis of the dilated bowel segment at 45° to 60°. The dilated bowel is then incised along the marks, and the bowel is stretched longitudinally and sutured along the incision line. The purpose of this technique was to minimize injury of the vascular supply of the intestine, as could occur with the LILT procedure, and preserve the anatomy of circular and longitudinal muscle fibers which could be destroyed by the stapler in the STEP technique [59]. The first histopathological results were promising and showed no signs of ischemia and collagen accumulation, while the myenteric, mucosal plexuses and Cajal cell network were normal.

2.2. Surgical techniques to slowing the intestinal transit

- a. *Anti-peristaltic segments.* Surgical reconstruction of the residual small bowel using anti-peristaltic jejunal segments has been recommended for patients with a resected ileum and ICV [61]. In summary, the technique includes excision of a small segment (10-15cm in length for adults and 3cm for children) of the distal intestine with its mesenteric blood supply rotation over 180° degree of the distal intestine, and an end-to-end anastomosis between the reversed intestinal segment and the proximal jejunum and distally to the remaining colon [61]. Although, studies in adults [62,63] have shown beneficial results regarding an increase in absorption and weaning from PN, the procedure may be ineffective in the case of an insufficient length of the reversed segment [64]
- b. *Colon interposition.* This surgical technique has been used as an adjuvant method in cases of medical management failure. Studies in adults have shown that after interposition, the colon behaves in a similar way to the reversed small intestinal segment [4]. The technique may be performed iso-or antiperistaltically [65]. Glick et al [66] used an isoperistaltic colon interposition in six infants with PSBS refractory to medical management. The authors reported a reasonable survival rate of 50% and weaning off total PN. However, this surgical option needs additional studies with a large number of patients to support its effectiveness.
- c. *Intestinal valves.* Based on the observed importance of the ICV in the outcome of children with PSBS [21], various techniques have been described for the construction of similar valves. The simplest techniques include the installation of sutures or external Teflon around the circumference of the bowel [67]. Another option involves the creation of small intussusceptions by everting a segment of small bowel [68]. Georgeson et al [69] reported a series of six children in whom a small nipple valve was initially created to provide temporary partial obstruction and thereby induce dilatation and lengthening of the proximal small intestine. In a second stage, they performed an intestinal lengthening procedure. Several of these patients improved and weaned off PN. However, clinical experience of this technique is limited, and the results are based on small series.
- d. *Recirculating loops.* Few discouraging results including increased morbidity and mortality have been reported in the literature concerning the use of recirculation loops in the management of PSBS [69]. In addition, improvement of absorption was limited [68].
- e. *Tapering enteroplasty.* Tapering enteroplasty is another option in the management of PSBS and involves reducing the caliber of the dilated intestinal segment in patients with PSBS. Usually, this portion exhibits low contraction resulting in stasis, malabsorption and bacterial overgrowth [68]. As patients with PSBS have a short residual intestine, excision of the dilated intestine may be not reasonable. The reduction could be performed either by excising the antimesenteric portion of the dilated segment or by the folding and placcation of the intestine [67]. Thomson et al [70] reported a large series of 160 patients including 11 children, aged 6 months to 9 years. All these children had dilated intestinal segments and residual bowel length no longer than 30 cm. Successful enteroplasty with complete weaning from PN was reported in nine (81.8%) children. A drawback to this

method is the possible breakdown of the sutures lines with recurrence of dilation and functional obstruction of the bowel [68].

2.3. Intestinal transplantation

Small bowel transplantation is considered the definitive treatment in the management of PSBS. It is indicated in patients with failure of intestinal improvement after various surgical techniques, and in those with no possible feeding tolerance, irreversible hepato-intestinal disease, recurrent sepsis, and failure of their central venous sites [1]. In neonates and small children, liver-intestine or multivisceral transplantation (stomach, pancreaticoduodenal complex, and small intestine) are the choice of treatment [1]. In older children, isolated intestinal transplantation may be used as a further option [1, 11]. Rayes et al reported a one-year patient survival rate of 70% and graft survival rate of 65% [71]. More recently, Lao et al [72] studied the outcome of 852 patients (aged from 1 to 21 years) who had undergone intestinal and/or liver transplantation for short bowel syndrome for various reasons including gastroschisis, necrotizing enterocolitis, volvulus, and others. They found that the relative risk ratio for death was higher among the necrotizing enterocolitis group ($p:0.015$), lower in those with PSBS for atresias, inflammatory bowel diseases, arterial or venous thrombosis ($p:0.001$), and not statistically significant in the volvulus group ($p:0.094$). The authors concluded that underlying disease may influence the outcome of patients. Complications include acute cellular rejection (fever, nausea, vomiting, abdominal distention), graft vs. host disease, and post-transplant lymphoproliferation disorder [11]. The introduction of novel immunosuppressive agents may further improve the outcomes of intestinal transplantation.

3. Medical enhancement of intestinal function

Several peptides, hormones and growth factors have been studied in animal models of SBS the last 20 years. However, few have been investigated in adult patients, and hardly any in children. The most common agents used to alter nutrient absorption will be discussed briefly.

3.1. Epidermal growth factor (EGF)

EGF is a low-molecular-weight polypeptide which enhances cellular proliferation, differentiation, and survival [73]. Sham et al in an experimental study showed that EGF improves carbohydrate absorption and intestinal permeability and reduces weight loss [74]. Possible mechanisms of action include a reduction in apoptosis of intestinal cells, increased expression of the anti-apoptotic gene *bcl-w*, and decreased expression of the pro-apoptotic gene *bax* [75]. Several authors have investigated the synergistic role of EGF in experimental studies along with other factors such as interleukin-11, bombesin and neurotensin, and found that they further enhance the adaptive action of EGF [76-78]. Promising results with the use of EGF were reported in a pilot study by Sigalet et al [79] who investigated the effect of enterally administered recombinant EGF on nutrient absorption and tolerance feeding in infants with severe PSBS (<25% bowel length for predicting age). EGF was given orally with foods in a daily dose

of 100 µg/kg for six weeks. The results showed improvement in nutrient absorption, increased tolerance with enteral feeding and possible improvement of infection rate. In contrast, Lukish et al failed to observe any changes in the small bowel epithelium after an experimental massive intestinal resection and utilization of EGF [80].

3.2. Growth hormone (GH)

GH is a single chain protein comprising 191 amino-acids and is produced in the pituitary gland [81]. Receptors of GH have been found throughout the intestine, including muscularis propria, submucosa muscularis, lamina propria, muscularis mucosa and intestinal epithelium [82]. Laboratory studies have shown that GH causes mucosal hyperplasia and increases the adaptive capacity after small resection [83, 84]. Other actions of GH include enhancement of the villus height and crypt depth, positive nitrogen balance and bowel growth when rats were given GH combined with glutamine and/or a diet high in protein [85,86]. Studies in children with PSBS showed a reduction in PN [87], but after cessation of GH the positive response could not be preserved [88]. The results in adults are controversial. For example, Scolapio et al [89] reported no benefits from the administration of recombinant human GH (rhGH) in adult patients with SBS. On the contrary, Seguy et al [90] showed a significant increase in absorption rates, followed by a decrease in PN requirements.

3.3. Glucagon-Like Peptide 2 (GLP-2)

GLP-2 is a 33-amino acid peptide that is secreted by enteroendocrine L-cells which are found mainly in the terminal ileum and colon [91]. Release of GLP-2 is stimulated by food input, directly or indirectly promoting intestinal growth and nutrient absorption [91, 92]. Patients who had undergone ileal resection and jejunostomy have a diminished secretion of GLP-2 [93], while those submitted to ileal resection but with preservation of colon in continuity have elevated levels of GLP-2 at baseline, compared with the control group, which remain high following a meal [32]. Teleglutide is an analog of GLP-2 with a longer half-life which encourages villus height and increases crypt depth, improving nutrient absorption, gastric emptying and body weight [94]. Using an animal model with preterm pigs, Vegge et al [95] recently showed that GLP-2 enhances rapid digestion adaptation and improves digestion function in preterm pigs with jejunostomy.

3.4. Insulin-like Growth Factor-1 (IGF-1)

IGF-1 is secreted primarily by hepatocytes, and activated by GH [96]. A review of Bordvedt et al [97] provided strong evidence that IGF-1 mediates growth effects of GH and GLP-2 on the intestine or continuous growth in experimental models of bowel resection or Crohn's disease, besides the perception that these hormones or IGF-1 may reinforce further growth if given shortly after bowel resection. Similarly, using a rat model, Chen et al [98] demonstrated that IGF-1 may prevent mucosal atrophy, enhance gut metabolism, and protect the intestinal barrier against sepsis. Furthermore, Barksdale et al [99] showed that children with PSBS demonstrated growth failure despite adequate nutritional support. Serological tests for GH,

IGF-1, and thyroid function showed that only IGF-1 and IGFBP-3 correlated with growth failure.

3.5. Hepatocyte Growth-Factor (HGF)

HGF is secreted by mesenchymal cells and carries trophic properties [96]. Laboratory studies have demonstrated that HGF enhances small intestine growth and absorptive function regarding carbohydrates and amino-acids. However, there are no clinical data on human beings.

4. Tissue Engineering Small Intestine (TESI)

TESI comprises a new complex field in the management of PSBS. In order to build a viable and functional small intestine, the armamentarium of TESI includes sophisticated materials, human pluripotential stem cells, and biopharmaceutical means [100].

Salerno-Gonsalves et al [101] designed an organotypic model consisting of fibroblasts, lymphocytes, epithelial and endothelial cells, in order to create a comparable and functional structure to human intestinal mucosa. Their concept based on previous observations showed that the culture of endothelial and epithelial cells under microgravity could self-organize into structures resembling native tissues. [102-105]. Although their results showed differentiated cell-types and villus-like structures, the mesenchyma was absent.

Human pluripotent cells [both embryonic and induced pluripotent stem cells], in vitro, have been shown to differentiate in tissues resembling those of the fetal bowel with secretory and absorptive properties [106]. Although these mesenchymal markers detected the presence of a mesenchymal layer, the structures lacked blood vessels and nerves; hence, these strategies could not be used for correct growth of a full thickness intestine.

Promising results may derive from plugs of full thickness intestine called organoid units. Studies have shown that organoid units, placed on a coated scaffold implanted in the omentum of rats, acquired vessels and developed a cyst-shaped structure resembling a small intestine [107]. After placement in continuity with the small intestine, rats returned to their preoperative weight [108, 109].

A number of proteins or nucleic acid, known as biopharmaceuticals, have been used either in clinical trials or in vitro [110]. Available biopharmaceuticals products include IGF-I, IGF-II, EGF, TNF-a, etc. However, a substantial number of these products are currently not used in clinical practice or in TESI.

5. Conclusion

The management strategies of PSBS have expanded over the last 20 years. New surgical techniques and innovative medical and nutritional inventions are used to improve survival

and quality of life in patients with PSBS. Research of new fields, such as TESI and biopharmaceutical agents, could lead to a more successful and definite treatment of PSBS.

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