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ORIGINAL ARTICLE

Simultaneous Serial Transverse Enteroplasty (STEP) in Size Mismatch Small Bowel Transplantations

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Abstract

Background Small bowel transplantation (SBTX) in children receiving larger grafts from adults can be challenging because of size mismatch. The aim of the present study was to assess whether a simultaneous serial transverse enteroplasty (STEP) can address the problem of size mismatch.

Methods Three different size ratio groups between donors and recipients were compared in a porcine model with a 14-day follow-up. The groups were size matched, size mismatched (1:3.8 weight ratio), and size mismatched + STEP (each $n = 8$).

Results It was technically feasible to simultaneously perform a STEP and SBTX of a mismatched intestinal segment. The postoperative clinical course was uneventful. No signs of bleeding, leakage, stenosis, or ileus were observed and the intestinal segment was well perfused at relaparotomy. Body weight decreased in all groups, but the percentage decrease was lowest in the mismatched + STEP group. Vital enterocyte masses were similar in all the groups (citrulline levels) and the nutritional status was best in the STEP group (transferrin levels, $p = 0.04$).

Conclusions We have demonstrated that a simultaneous STEP and SBTX procedure is technically feasible and clinically useful in overcoming the challenges associated with size mismatched SBTX. Our short-term findings justify further investigation in a larger series to elucidate the long-term outcomes of this procedure.

Keywords Intestinal transplantation · STEP · Living donor · Size mismatch · Children

Introduction

Intestinal rehabilitation programs and parenteral nutrition are effective therapies for children affected by intestinal failure and short bowel syndrome (SBS).[1] Small bowel transplantation (SBTX) is the standard therapy for patients that do not respond well to these interventions.[2–6] Improved patient selection, surgical techniques, and perioperative management for SBTX together with advances in immunosuppression have considerably increased patient and graft survival.[7–11] Following SBTX, most patients resume oral nutrition and enjoy an improved quality of life. Adult recipients are likely to reintegrate into social and working life and pediatric recipients resume normal growth.[12–16]

The overall scarcity of organs for transplantation, particularly size matched organs, represents a significant challenge in pediatric SBTX. Living donor transplantation has been successfully implemented and may be a feasible solution to organ scarcity.[17–20] However, similar to cadaver grafts, all living donor organs offered for pediatric transplantation come from adults. This creates anatomical size mismatch challenges as the adult donor organs are usually larger than those required by the recipient.

Transplanting an entire adult intestine into a child is not feasible because the recipient may not be able to sufficiently perfuse the large graft. In addition, complications with

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abdominal wound closure might occur. To overcome these issues, shorter intestinal segments from adults are transplanted into children.[19] However, shortening the length of the intestinal graft concomitantly reduces the resorptive capacity of the transplanted organ. Moreover, the larger diameter of an adult intestine might compromise bowel function after transplantation into a child.

Improving the size mismatched SBTX procedure may deal with the problems of larger intestinal diameter and reduced resorptive capacity. Surgically tailoring and lengthening the intestinal segment intended for SBTX may be a suitable approach. Serial transverse enteroplasty (STEP) is a widely accepted autologous intestinal reconstruction procedure that enhances enteral autonomy by surgically tailoring and lengthening an intestinal segment.[21] STEP partially transects the intestinal lumen by placing staples sequentially at alternative sides of the bowel using a linear GIA stapler.[21] The intestine length can be increased 1.63-fold (1.4–2.2) and the intestine diameter can be reduced by 50% using this method.[22] Lengthening the graft in this way may adjust the difference in intestinal diameter between donors and recipients and enhance the resorptive capacity of the transplanted intestine segment.

We hypothesized that STEP can be performed simultaneously with SBTX to deal with the size mismatch challenge. To date, STEP has not been performed simultaneously with a SBTX in a size mismatch setting, and no data regarding the outcome of such a procedure is currently available. Therefore, the aim of present work was to study the feasibility of this approach in a porcine model of size mismatched SBTX.[23–27]

Materials and Methods

Animal Ethics

This study was performed in accordance with the National Research Council's principles for the care and use of laboratory animals. The Animal Ethics Review Committee of the Regional Commission (Karlsruhe, Germany) approved the study protocol. This study was performed in accordance with the National Research Council's guidelines and the EU Directive 2010/63/EU for animal experiments. Animals received humane care in compliance with institutional guidelines.

Study Groups

Twenty-four female German landrace pigs were used. All recipients had a body weight of approximately 25 kg. In the *size matched* group, the donors had a body weight of approximately 25 kg, while in the *size mismatched* and in the *size mismatched + STEP* group, the donors had a body weight of approximately 96 kg. Three experimental SBTX groups were created according to the body weight of the donors and recipients: *size matched* ($n = 8$), in which donors were size matched to the recipient and each had a body weight of approximately 25 kg; *size mismatched* ($n = 8$), in which the body weights of donors and recipients were mismatched by a size ratio of approximately 1:3.8; *size mismatched SBTX + STEP* ($n = 8$), in which animals were mismatched by a size ratio of approximately 1:3.8 and received a STEP of the intestinal segment used for SBTX.

Small Bowel Graft Procurement

Anesthesia, intraoperative monitoring, and central venous catheter implantation were performed as previously described.[27] A 60-cm segment of the terminal ileum, including the last branch of the supplying superior mesenteric artery and vein (SMA and SMV), was dissected from the donor 15 cm proximal to the ileocecal valve. The thickness of the intestinal wall of the large donors was approximately 3 mm. Heparin (200 IU/kg) was administered to the donor by cannulating the infrarenal vena cava. After arterial and venous dissection, the intestinal graft was perfused with 60-ml histidine-tryptophan-ketoglutarate (HTK) solution (Custodiol, Dr. F. Kohler Chemie GmbH, Alsbach-Hahnlein, Germany) for 2 min over the supplying superior mesenteric artery. The graft was preserved in HTK solution in a plastic bag on ice. The donors were sacrificed under deep anesthesia with a fast infusion of 2 mmol/kg potassium chloride (B. Braun, Melsungen, Germany).

STEP Procedure

The STEP procedure was performed before donor heparinization and graft harvesting, while blood was still supplied to the intestinal segment by the donor. For STEP, staples were sequentially placed at alternative sides of the bowel using a linear GIA stapler (Medtronic, Neustadt, Germany). Each staple was placed 180° from the previous staple according to the initial technical description.[21] The staples were closed with a continuous single layer suture using a resorbable 5–0 monofilament (PDS, Ethicon, Norderstedt, Germany) (Fig. 1).

Recipient Native Enterectomy

In recipients, the native enterectomy was performed as previously described.[27] Fifteen centimeters of jejunum following the ligament of Treitz and 15 cm of ileum preceding the ileocecal valve were preserved to facilitate a tension-free intestinal anastomosis with the graft.

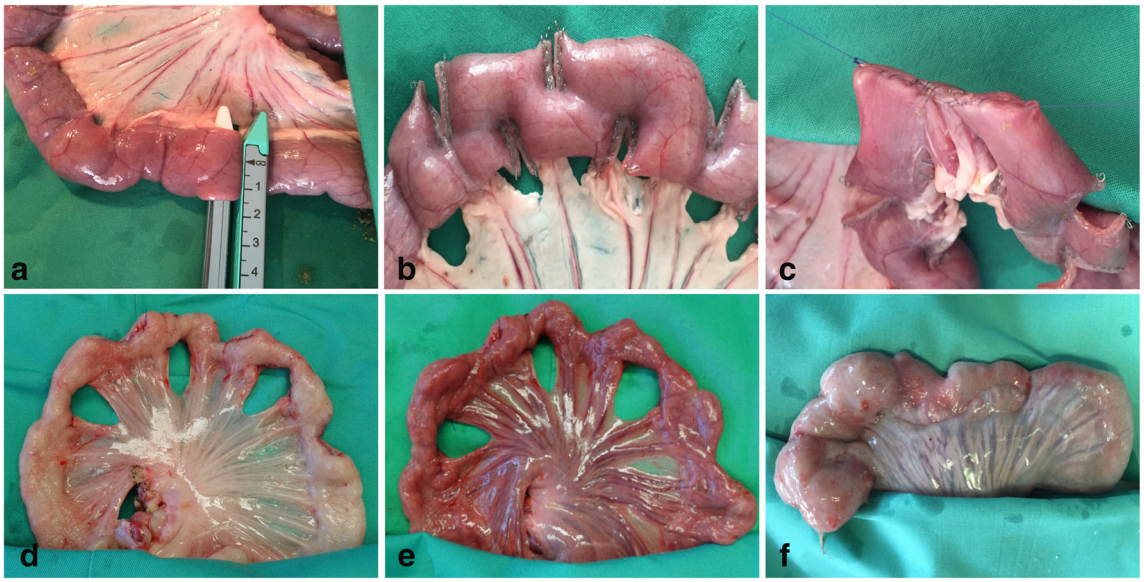

Fig. 1 Simultaneous STEP and SBTX in a size mismatch setting, transforming a size mismatched intestinal segment to a size matched segment using STEP followed by SBTX. For STEP, staples were sequentially placed along the intestinal segment using a linear GIA stapler on alternative sides and perpendicular to the previous staple (**a**), resulting in a tapered and lengthened zig-zag intestinal segment (**b**). The stapler lines were each sewed over with a continuous single layer suture (**c**). After implantation into the recipient, the intestinal segment is shown before reperfusion (**d**), after reperfusion (**e**), and at postoperative day 14 (**f**)

Implantation of the Graft

The supplying SMA branch of the graft was anastomosed end-to-end to a recipient SMA branch of the same caliber (approximately 4 mm diameter each) by interrupted sutures using 7–0 monofilament (Prolene, Ethicon, Norderstedt, Germany). The SMV branch of the graft was anastomosed end-to-end to a recipient SMV branch (approximately 6 mm diameter each) of the same caliber using a continuous suture with 5–0 monofilament (Prolene, Ethicon, Norderstedt, Germany). The proximal and distal intestinal anastomoses between the graft and recipient were performed in an isoperistaltic side-to-side fashion using a continuous double-layer suture with a resorbable 5–0 monofilament (PDS, Ethicon, Norderstedt, Germany) as previously described.[28]

Immunosuppression

The recipient received induction therapy with 0.5 g methylprednisolone (Sanofi-Aventis, Frankfurt, Germany) 5 min before graft reperfusion. Recipients also received postoperative immunosuppressive monotherapy with 0.05 mg/kg/day Tacrolimus (Astellas, Munich, Germany).

Postoperative Management

After surgery, animals had immediate access to water. Postoperative nutrition consisted of 1000 g yoghurt per day for the first two postoperative days, and dry chow thereafter (SAF 130P, Raiffeisen, Keil am Rhein, Germany). Each animal received similar amounts of chow. The central line inserted intraoperatively into the jugular vein was maintained postoperatively to allow intravenous medication and blood sampling. In addition to immunosuppressive therapy, pigs received the following daily intravenous postoperative medication for the entire observation period: 5000 IU heparin (200 IU/kg/day); 1.5 g ampicillin/sulbactam (Pfizer, Berlin, Germany) and 0.5 g metronidazol (Sanofi-Aventis, Frankfurt, Germany) as antibiotic prophylaxis; 20 mg/day pantoprazole (Takeda, Konstanz, Germany) as a stress ulcera prophylaxis; and 0.04 mg/kg/day buprenorphine (Reckitt Benckiser, Slough, England) and 25 mg/kg/day metamizole (Sanofi-Aventis, Frankfurt, Germany) as analgesia every 12 h. After the first 48 h, buprenorphine was given only if required, while metamizole was administered for the entire postoperative observation period.

Evaluation of Postoperative Outcome Parameters

The postoperative outcome was evaluated by clinical, biochemical, and functional parameters during the 14-day observation period and by relaparotomy on postoperative day (POD) 14.

Clinical Outcome

The general condition of the animals, clinical signs of abdominal swelling, and stool output and consistency were monitored daily. Recipient body weight was monitored at POD 14 using a calibrated weight scale (Bizerba-Sauter, Albstadt, Germany).

Biochemical Outcome

Serum albumin and total protein levels in recipient blood samples were measured at our central laboratory. Recipient blood was collected over the central line directly before reperfusion during the SBTX and at POD 14. Serum levels of the short-term nutritional marker transferrin[28] were determined by Western blot as previously described.[28] Citrulline serum levels (a marker of vital enterocyte mass[29]) were determined by tandem mass spectrometry, as previously described.[28]

Functional Outcome

A D-xylose test was performed to quantify intestinal resorption capacity at POD 14 as previously described.[28] Briefly, D-xylose (0.5 g/kg) was dissolved in 50-ml saline solution and administered intragastrally through an orogastric tube. Serum D-xylose levels were measured in blood samples collected in sodium fluoride sampling tubes through the central venous catheter before and 180 min after D-xylose administration.

Evaluation at Relaparotomy

After the D-xylose test, an explorative laparotomy was performed to macroscopically examine the graft and to search for intraabdominal complications, such as anastomotic insufficiencies and abscess formation. Following relaparotomy, animals were sacrificed with a fast infusion of 2 mmol/kg potassium chloride (B. Braun, Melsungen, Germany) under deep anesthesia.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 for Windows (SPSS Corp., Chicago, IL, USA). A one-way ANOVA was conducted to compare the effect of the different surgical approaches on the postoperative outcome parameters. In cases where a significant difference was found, a post hoc comparison using the Scheffé test was also performed. A *t* test for paired variables was used to compare changes in weight within the groups. A p value of < 0.05 was considered significant. Data are expressed as mean ± standard deviation.

Results

Group Characteristics

The recipient's body weight and cold and warm ischemia times during SBTX were similar between the groups (Table 1). The donors' weights differed significantly between the three groups according to ANOVA ($p < 0.001$). Post hoc comparison using the Scheffé test revealed that the differences in body weight were significant between the *matched* and the *mismatched* group ($p < 0.001$), the *matched* and the *mismatched* + *STEP* group ($p < 0.001$), but not between the *mismatched* and the *mismatched* + *STEP* group ($p = 0.759$).

Technical Feasibility

During the STEP procedure, the intestinal segment was tailored from approximately 4 to 2 cm and lengthened from 60 ± 0 to 93.2 ± 4.4 cm (1.55-fold). Intraoperatively, no major complications occurred. In particular, no bleeding was observed from the incision border after graft reperfusion following SBTX.

Clinical Outcome

Postoperatively, no morbidity, bleeding, intestinal leakage, intestinal insufficiency, stenosis, ileus, or mortality was observed in any group. All animals had an uneventful stepwise transition to a normal diet. After initial persistent or recurrent diarrhea, all animals produced solid or semi-solid stools from POD 8 on. We observed similar postoperative weight loss in all animals. Weight loss was marginally less pronounced by POD 14 in the STEP group, but was not significantly lower than in the other groups.

Relaparotomy Results

At relaparotomy performed on POD 14, all transplanted intestinal grafts were well perfused with no signs of early necrosis, stenosis, leakage, or acute rejection. No abscess formation or indirect signs of infection were observed (Table 2). For STEP-operated segments, the stapler line sutures were intact throughout the segment and healed with a preserved zig zag-shaped intestinal channel (Fig. 1).

Biochemical Outcome

Mean levels of the short-term nutritional marker transferrin at POD 14 were significantly higher in the *mismatched* + *STEP* group compared with other groups ($p = 0.049$). Post hoc comparison revealed significantly higher transferrin levels in the *mismatched* + *STEP* group compared with the *matched* group (4.1 ± 0.9 vs. 1.6 ± 0.1, $p = 0.049$). Transferrin levels were also higher in the *mismatched* + *STEP* compared with the *mismatched* group (4.1 ± 0.9 vs. 2.5 ± 1.0, $p = 0.283$), and in the *mismatched* group compared with the *matched* group (2.5 ± 1.0 vs. 1.6 ± 0.1, $p = 0.613$). However, these differences were not statistically significant. Serum levels of the long-term nutritional markers albumin and total protein were not significantly different between the groups. Citrulline serum levels were also similar between the groups (Table 2).

Table 1 Animal study group characteristics at SBTX

	Matched $n = 8$	Mismatched $n = 8$	Mismatched + STEP $n = 8$	p value
Body weight				
Donor (kg)	25.7 ± 1.1	96.0 ± 0.3	96.8 ± 0.3	< 0.001
Recipient (kg)	25.8 ± 0.9	26.7 ± 0.6	25.6 ± 0.6	0.480
Ischemia time				
CIT (minutes)	121.3 ± 8.4	121.3 ± 6.0	103.3 ± 6.5	0.185
WIT (minutes)	89.4 ± 7.7	94.3 ± 8.7	87.5 ± 5.3	0.821

CIT cold ischemia time, *WIT* warm ischemia time

Functional Outcome

The mean serum levels of D-xylose were not significantly different between the three groups at the 180-min endpoint (Table 2).

Discussion

In the present experimental study, we demonstrated for the first time that it is technically feasible to perform STEP and SBTX as a one-stage procedure in pigs without any major short-term complications. The approach was functionally feasible based on an uneventful short-term (14 days) postoperative follow-up. Body weight decreased in all animals, probably because of organ-related weight loss caused by enterectomy and experimentally induced SBS.

At relaparotomy, the transplanted intestinal segment was well perfused with no intraabdominal signs of infection or abscess formation. Therefore, the STEP procedure appears to be feasible on an intestinal graft intended for transplantation, at least in the short term. No differences were detected in serum albumin and total protein during the postoperative follow-up. However, albumin has a half-life of around 20 days; therefore, more long-term measurements are necessary to draw firm conclusions regarding nutritional status. Transferrin is a more sensitive indicator of nutritional status because it has a shorter half-life of a few days and it has been used to assess the nutritional status of adults and children.[29] We observed a significantly higher transferrin level in the STEP group and similar vital enterocyte masses (determined by citrulline levels) between the groups. This might indicate an improved nutritional status in animals receiving size mismatched intestinal segments that were modified by STEP. However, this positive effect was not confirmed by the D-xylose resorption test; this confirmation may be possible with more long-term follow-up.

We were able to perform STEP and SBTX simultaneously without modifying the original STEP technique.[23] We performed STEP before organ procurement to shorten the warm ischemia time and achieve similar warm ischemia times in all groups. The shorter warm ischemia time might explain the positive postoperative results. The staple-suture lines are a common pitfall for STEP because they can cause adhesions and increase the risk of leakage if a gap is present at the conflation point between two staple lines. These complications can be more serious after SBTX when the recipient is immunosuppressed and wound healing is compromised. To

Table 2 Postoperative body weight and biochemical and functional outcome

	Matched $n = 8$	Mismatched $n = 8$	Mismatched + STEP $n = 8$	p value
Body weight				
Absolute at POD14 (kg)	20.6 ± 0.6	20.6 ± 0.7	21.5 ± 1.1	0.696
Percentage change from surgery to POD14 (%)	− 20.2	− 22.8	− 19.1	
Biochemical outcome				
Transferrin (%)	1.6 ± 0.1	2.5 ± 1.0	4.1 ± 0.9	0.049
Albumin (g/l)	33.1 ± 1.5	33.5 ± 1.7	29.9 ± 1.5	0.276
Total protein (g/l)	58.7 ± .2	61.9 ± 4.4	63.0 ± 3.0	0.669
Citrulline (μmol/l)	16.6 ± 2.1	13.7 ± 1.1	15.5 ± 2.4	0.548
Functional outcome				
D-xylose (180 min)	81.3 ± 10.3	70.9 ± 5.9	58.5 ± 2.4	0.149

POD postoperative day

avoid this potential complication, we sewed over the stapler sutures with a continuous single layer suture. These sutures secured the staple lines and closed the gap between them. This approach stabilized the staple lines after transplantation, despite continued immunosuppression, as shown by an uneventful postoperative clinical course in all animals, with no signs of leakage or peritonitis.

Altering the anatomy of normal intestine with a STEP would not improve the overall performance of the adjusted bowel segment. However, this is not necessarily the case when transplanting it into a child whose residual intestine has a smaller diameter. In such a case, resorption-related complications are conceivable. We examined this in the present study and our data suggests that STEP has positive effects on short-term nutritional status in a porcine model of size mismatched intestinal transplantation. This is a first indication that altering the anatomy of normal intestine to be transplanted with a STEP may be advantageous. While the vital enterocyte mass (determined by citrulline levels) was similar between the groups, the final length of the transplanted bowel was significantly longer in the *mismatched + STEP group* than the other two groups. Therefore, we assume that the observed improvement in nutritional status (transferrin levels) in the *mismatched + STEP group* is due to the intestinal lengthening by STEP and not to differences in enterocyte absorption capacities.

Postoperative intestinal redilation occurs in 30–67% of pediatric patients following STEP.[30,31] Redilatation of the operated intestinal segment is a serious complication because it may regress the bowel to a dysfunctional status. In addition, it significantly lowers weaning rate from parenteral nutrition and increases the mortality rate.[31] However, it remains unclear whether postoperative intestinal redilation indicates failure of the surgical procedure or is part of the natural adaptation of the intestine.[31] Indeed, a repeated STEP procedure on the same intestinal length may be important to further enhance intestinal function.[32–36] However, this remains to be determined. Nonetheless, redilation with overgrowth, dysmotility, and need for a repeat STEP procedure are common problems and are associated with important complications, such as a lower weaning rate from parenteral nutrition and a higher mortality rate.[31] It has not been proven that size mismatched organs cause dysmotility or bacterial overgrowth. Our finding that simultaneous STEP and SBTX is technically feasible and clinically useful needs to be investigated further in larger cohorts with a longer follow-up to determine the long-term desired and undesired effects of STEP.

The primary aim of the described technique is to surgically adapt intestine diameter between the donor and recipient and to enhance intestinal resorption by extending the contact time of passing nutrients with the intestinal mucosa. From a technical point of view, tapering is a much easier way to reduce intestinal diameter than STEP. With this procedure, the antimesenteric border of a dilated bowel is longitudinally resected, thereby reducing the intestinal circumference. To achieve a 100-cm-long intestinal segment allograft with 2 cm in diameter from a larger donor intestine with 4 cm in diameter, different initial intestinal allograft segment lengths are needed, depending on the technique. With the STEP option, we initially used a 60-cm segment that was lengthened to approximately 100 cm, while using the tapering option, we would initially necessitate a 100-cm segment, as no lengthening is achieved by the tapering procedure. In both cases, the achieved intestinal segment allograft has a length of 100 cm and a diameter of 2 cm. Therefore, the inner volume, the outer volume, and the inner surface (resorptive mucosal layer) of the final intestinal allograft segment will be the same for both options (respectively, 324.2 cm^3, 530.9 cm^3, and 634.2 cm^2), and none of both options has an advantage in this regard. In contrast, the total volume of the allograft (intestinal segment + mesenterial tissue, including fat and lymphatic and blood vessels including vessels) will be larger for the tapering, as the mesenterial tissue will be larger in a longer segment needed for the tapering compared to the shorter one needed for STEP. An increase of the total allograft volume by 40% is conceivable, analogously to the increase in segment length. The necessity of a 40% longer donor intestinal might raise the risk of complication and burden for the living donor and limit the total number of intestinal segment graft available from each cadaveric donor. The increase of the total allograft volume by estimated 40% could additionally lead to a higher abdominal pressure in the recipient in the context of a size-mismatched intestinal transplantation, which could likely cause complications regarding the abdominal wound closure and organ perfusion. Therefore, we consider STEP to be more adequate to cope with the size-mismatch difficulties in the context of an intestinal transplantation. STEP tailors and lengthens the intestine without reducing enterocyte mass. Due to the antimesenteric resection, tapering is associated with a considerable loss of enterocyte mass, which might further speak for the STEP in the context of a SBTX to treat a SBS. A further advantage is that no intraoperative compromise of intestinal blood supply has been reported for STEP.[22] During the STEP procedure, the dilated bowel lumen is partially transected using a linear GIA stapler in a side-to-side manner, with each staple placed 180° from the previous one. Blood supply comes from the mesenteric border and crosses the bowel remaining perpendicular to its long axis; therefore, blood is supplied to the bowel by vessels between the staple lines.[21]

The main drawback of this study is the short-term follow-up of only 14 days. However, this was a first demonstration of the technical and short-term clinical feasibility of simultaneous STEP and SBTX in a size mismatch setting; therefore, we consider this short-term follow-up adequate for this purpose. Future studies with a longer follow-up are required to determine whether short-term effects of the simultaneous approach are maintained in the long term and how potential complications (including poor motility, staple line ulcers/bleeding/leakage, and intestinal redilation) affect the overall outcome.

The impact of STEP on inflammation may increase the risk of fibrosis or rejection and should also be evaluated by future studies. STEP did not interfere with baseline or hormonally stimulated motility within the small bowel in a porcine SBS model.[37] However, preserving allograft motility following transplantation and simultaneous STEP is important and needs to be addressed.

The transferrin levels at POD 14 were significantly higher in the *mismatched + STEP* group compared with the *matched* group. While higher transferrin levels in the *mismatched + STEP group* suggest improved nutrition, presumably due to better nutrient absorption, the serum levels of D-xylose at 180 min were lowest in the STEP group (although this difference was not significant); therefore, the improved nutritional status needs to be confirmed in future studies. In addition, future studies should confirm whether the positive short-term effects are maintained in the long term using sensitive long-term indicators of nutritional status, such as serum albumin. Moreover, it has to be evaluated whether these effects are clinically important. The present feasibility study provides a useful basis for future studies.

If a simultaneous STEP and SBTX procedure can be confirmed in the long term, then this approach may increase the success of pediatric SBTXs and promote the use of size mismatch living donor transplantation, for example between parents and children. Performing a simultaneous STEP in a living donor transplantation setting, e.g., between parents and children, might further profit of reduced ischemia times and immunological problems associated with living donor transplantations,[20] thereby improving the overall outcome of the transplantation. The method described here surgically optimizes larger allografts for transplantation into smaller recipients and may increase the number of allografts available for transplantation. Although size matched organs are preferable, this approach allows the use size mismatched organs in urgent cases when size matched organs are not available and may help increase organ availability in countries where appropriate organs are scarce.

Our findings justify future long-term investigations to fully assess whether simultaneous STEP and SBTX can promote the success of size mismatched SBTX for longer clinically relevant periods. Furthermore, this simultaneous approach needs to be validated for similar techniques, such as Spiral Intestinal Lengthening and Tailoring (SILT).[26–29,38,39]

Author's Contributions Study conception and design: Frongia G; Mehrabi A.

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Analysis and data interpretation: Frongia G.

Drafting of the manuscript: Frongia G.

Critical revision: Günther P; Vianna R; Mehrabi A.

Compliance with Ethical Standards

Animal Ethics This study was performed in accordance with the National Research Council's principles for the care and use of laboratory animals. The Animal Ethics Review Committee of the Regional Commission (Karlsruhe, Germany) approved the study protocol. This study was performed in accordance with the National Research Council's guidelines and the EU Directive 2010/63/EU for animal experiments. Animals received humane care in compliance with institutional guidelines.

Conflict of Interest The authors declare that they have no conflicts of interest. No funding was received.

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