



Does Autologous Gastrointestinal Reconstruction Reduce Catheter-Related Blood Stream Infections? Experience of an Intestinal Rehabilitation Unit

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Abstract

Background and Aims: Catheter-related blood stream infections (CRBSI) occur frequently in Short Bowel Syndrome (SBS) children on parenteral nutrition (PN). Central venous catheter (CVC) complication and complete loss of central venous access are indication for intestinal transplantation. Autologous gastrointestinal reconstruction surgery (AGIR) is mandatory in any chronically PN-dependent patient when there is substantial bowel dilation to reduce bacterial translocation. We reviewed patients who underwent lengthening surgery and calculated the rate of CRBSI pre and post surgery.

Materials and Methods: PN dependent children with SBS were identified. Inclusion criteria were CVC for PN administration pre and post-operatively, CVC removed after weaned off PN and having gained enteral autonomy. CRBSI episodes were defined as temperature above 38.0°C, along with positive blood culture microbiological infection from the CVC.

Results: Nineteen patients were identified (male n=13). Median gestation was 35 (33.5-36.5) completed weeks and birth weight 2080g (1725-2374). Ten patients underwent tapering enteroplasty, eight Longitudinal Intestinal Lengthening and Tailoring (LILT) procedure, and one Serial Transverse Enteroplasty (STEP) procedure. Median duration of PN was 5.3 months (2.9-6.6) pre and 9.0 months (4.2-10.9) post surgery. A total of 115 septic episodes were confirmed (70 prior to surgery and 45 post surgery). The total rate of catheter related sepsis was significantly lower after AGIR compared to before it ($p=0.016$).

Conclusion: CRBSI frequency in PN dependent patients with dilated bowel reduces after AGIR. AGIR appears associated with significantly reduced frequency of CRBSI in PN dependent children with bowel dilatation. These findings warrant further exploration in larger, preferably controlled studies.

Introduction

Catheter-related blood stream infections (CRBSI) occur frequently in infants and children who are dependent on parenteral nutrition (PN) and are a leading cause of morbidity and mortality. Problems with central venous catheter (CVC) access, such as blockage, displacement, venous thrombosis or sepsis (CRBSI), may necessitate CVC replacement, often at a new site. Complete loss of central venous access, due to multiple previous CVC insertions and subsequent thrombosis of central vein sites, is a recognised indication for intestinal transplantation [1]. Minimising CVC morbidity is therefore paramount to the care of PN dependent children and the prevention and treatment of CVC sepsis is an important component of this.

CRBSI are thought to occur through a number of mechanisms including: (i) direct contamination with microorganisms during CVC access or from those of the skin around the exit site; and (ii) translocation of enteric microorganisms from the bowel, through the mucosa into the blood stream [2-4]. Experimental evidence supports the hypothesis that bacterial translocation is frequently related to the presence of dilated and dysmotile bowel that results in stasis of bowel contents and bacterial overgrowth, possibly in conjunction with altered mucosal immunity [5,6].

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Table 1: Primary underlying diagnoses responsible for parenteral nutrition dependence before and after lengthening procedure.

Patient	Sex	Diagnosis	CRBSI All organisms		CRBSI Enteric organisms	
			Before	After	Before	After
1	M	Multiple atresia	0.52	0.00	0.26	0.00
2	M	Multiple atresia	1.00	0.33	1.00	0.22
3	F	Malro/Volvulus	0.33	0.15	0.00	0.08
4	F	Gastroschisis	0.60	0.00	0.60	0.00
5	M	Gastroschisis	0.33	0.09	0.16	0.00
6	M	Gastroschisis	1.42	0.09	0.00	0.00
7	M	NEC	1.45	0.41	0.00	0.00
8	M	Volvulus	0.00	1.34	0.00	0.45
9	M	Gastroschisis	0.00	0.23	0.00	0.23
10	M	NEC	1.13	0.00	0.23	0.00
11	M	Gastroschisis	0.20	0.34	0.15	0.11
12	M	Gastroschisis	0.50	0.00	0.33	0.00
13	F	Gastroschisis	0.71	0.42	0.42	0.33
14	F	Gastroschisis	0.66	0.72	0.51	0.48
15	M	Jejunal Atresia	0.20	0.11	0.20	0.00
16	F	NEC	0.38	0.00	0.38	0.00
17	M	Multiple atresia	0.17	0.23	0.00	0.23
18	M	Anorectal malformation	0.08	0.21	0.08	0.21
19	F	Gastroschisis	0.49	0.00	0.35	0.00
Median			0.49	0.15	0.20	0.00

In order for intestinal function to improve so that PN dependence resolves and enteral autonomy is gained, the intestine must adapt to its diseased state (whether this state be one of abnormal structure e.g. short bowel syndrome or one of abnormal function e.g. dysmotility). When the bowel is dilated, one strategy to facilitate bowel adaptation and expedite enteral autonomy is autologous gastrointestinal reconstruction surgery (AGIR) [7-9]. AGIR aims to reduce bowel dilatation and hence improve mechanical function: some forms of AGIR also increase bowel length. In a comprehensive review of this type of surgery, Thompson and Sudan recommended that 'surgical bowel lengthening be considered in any chronically PN-dependent patient when there is substantial bowel dilation, regardless of remnant bowel length [10]. Given that: (i) AGIR aims to restore motility and decrease stagnation through a change in bowel shape; (ii) AGIR has been shown to reduce bacterial overgrowth in an animal model; and (iii) small bowel length has been shown to inversely relate to CRBSI frequency, we hypothesised that this surgery may also reduce the risk of catheter sepsis (CRBSI) [4,11]. In order to test this hypothesis we reviewed a cohort of patients who had undergone this surgery and calculated the rate of CRBSI pre and post surgery.

Materials and Methods

A retrospective case series analysis from a prospectively collected database was performed.

PN dependent children treated at Royal Manchester Children's Hospital UK between 2001-2010 with AGIR. Patients were included in the study if they had undergone AGIR; had a CVC for PN administration pre and post-operatively and had their CVC removed after being weaned off PN, having gained enteral autonomy.

CRBSI episodes were defined as a temperature above 38.0°C,

along with microbiological confirmation of a positive blood culture taken from the CVC. Episodes of CRBSI were identified by, searching a prospectively compiled electronic microbiological database for each patient and cross-referencing this with nursing temperature charts for that time point. The rate of septic episodes per calendar month of PN treatment was calculated pre and post bowel lengthening surgery. CRBSI were characterised as being 'enteric related' or not: sepsis due to the following organisms was regarded as enteric related: *Klebsiellapneumoniae*, *Enterococcus faecalis*, *Escherichia coli* and *Candida parapsilosis complex*. Infections with the following organisms were not considered enteric related: coagulase negative *Staphylococcus* species, *Staphylococcus aureus*, *Micrococcus* species and *Streptococcus viridans*. *Streptococcus viridans* was not considered enteric related as it is a commensal of the mouth and therefore unlikely to be impacted by bowel dilatation or AGIR. If a septic episode was caused by multiple microorganisms and one of them was enteric related, the episode was regarded as being enteric related. Bowel dilatation necessitating AGIR was defined pragmatically, either from the lead surgeon's judgement intra-operatively or a radiologist's report of contrast study images.

Data were analysed using SPSS Statistics 18.0 (IBM). Continuous data were analysed for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests and homogeneity of variance using Levene's test. Non-parametric data were compared using the Mann-Whitney U test. Data are expressed as the median and interquartile range (IQR). Statistical significance was defined as $p < 0.05$.

Results and Discussion

Nineteen patients with complete data were identified and included in the study (male $n=13$, 65%). Median (IQR) gestation was 35 (33.5-36.5) completed weeks and birth weight 2080g (1725-

2374). The primary underlying diagnoses responsible for parenteral nutrition dependence are listed in Table 1. Ten patients underwent tapering enteroplasty, eight a Longitudinal Intestinal Lengthening and Tailoring (LILT) procedure, and one a Serial Transverse Enteroplasty (STEP) procedure. The 8 LILT's patients had a median pre-operative length of 32.5cm (IQR 20.09-38.91), and a median post-operative of 57 cm (IQR 37.21-73.29). The overall increase in length was 89.5 % (IQR 79.23-96.77), the pre-operative bowel dilatation was 5 cm (IQR 4.65-5.84) and the post operatively the bowel had a 2.5 cm diameter (IQR 2.39-2.92). One patient had the STEP procedure. The pre-operative bowel length was 69cm; the post-operative was 80 cm with an increase of 16%. The pre-operative dilatation was 7 cm and the post-operative bowel diameter was 3.5 cm. ten patients underwent tapering enteroplasty. The median pre-operative length was 62.5 cm (IQR 44.11-108.3) with a 5 cm (IQR 4.27-5.52) pre-operative dilatation. The final bowel diameter after surgery in this group was 2.75 cm (IQR 2.20-3.72).

Median duration of PN was 5.3 months (2.9-6.6) pre and 9.0 months (4.2-10.9) post surgery. Age at reconstructive surgery was approximately equal to the duration of PN pre surgery, since PN was commenced early in the neonatal period in most cases.

A total of 115 septic episodes were confirmed in these patients (70 prior to surgery and 45 post surgery); the isolated organism comprised enteric related species in 57 cases (44 pre and 13 post surgery). The large majority of non-enteric related episodes were due to coagulase negative *Staphylococcus* species. The most common enteric related bacteria implicated were *Klebsiellapneumoniae*, *Enterococcus faecalis* and *Escherichia coli*. Overall, the total rate of catheter related sepsis was significantly lower after reconstructive surgery compared to before it ($p=0.016$). The rate of CRBSI due to enteric-related organisms was also lower after AGIR than before it, but this did not reach statistical significance ($p=0.118$).

We have shown that AGIR appears associated with significantly reduced frequency of CRBSI in PN dependent children with bowel dilatation: given the short and long term risks of CRBSI e.g. overwhelming sepsis or loss of CVC access respectively, this is a significant, novel finding. The possible underlying mechanisms for this observation will now be considered.

One explanation for the reduced rate of CRBSI post surgery may relate to decreased CVC usage (reduced access frequency) and therefore reduced risk of direct contamination of the CVC. This explanation correlates with high rates of infection due to skin commensals e.g. coagulase negative *Staphylococcus* species pre surgery and a subsequent reduction post surgery, as well as our nutritional profile data (unpublished) that demonstrates an increase in the number of PN free days post surgery (as part of PN weaning to reach enteral autonomy). This hypothesis appears credible and seems likely to contribute to the witnessed effect; investigators have reported that CVC sepsis originates largely from direct contamination of the catheter hub (e.g. during access) and subsequent growth within a luminal biofilm [12]. However, other mechanisms such as a reduction in bacterial translocation need to be considered and will be discussed below. Given that AGIR has been shown to improve intestinal adaptation and hence expedite the development of enteral autonomy [13], even if the principal mechanism behind the observed effect is a reduction in direct catheter contamination, the reduction in CRBSI may in part be due to AGIR allowing a more rapid weaning of PN and catheter access frequency.

Bacterial translocation is considered by many to be an important factor in CRBSI development, particularly in infants and children with intestinal failure and dilated bowel [14-16]. A further explanation for the decrease in CRBSI may therefore relate to the nature of the reconstructive surgery: the techniques of AGIR used in this study were tapering enteroplasty, the Longitudinal Intestinal Lengthening and Tailoring (LILT) procedure devised by Bianchi [7] and the Serial Transverse Enteroplasty (STEP) devised by Kim [9]. All of these procedures aim to improve bowel dynamics by reducing calibre of the pathologically dilated bowel and therefore also reducing stasis and bacterial overgrowth: if this is the case, then the risk of microorganism translocation to the blood should also be lowered [17-19]. Further experimental support for this hypothesis is learnt from: (i) findings that relate bacterial translocation to dilated, dysmotile bowel; and (ii) the STEP procedure reducing bacterial overgrowth in an animal model [5,6,11].

The LILT and STEP procedures also lengthen the dilated bowel at the expense of a reduction in its circumference. Given that: (i) small bowel length has been shown to inversely relate to CRBSI frequency [4]; and (ii) a reduction in bowel volume will reduce potential space for fluid stagnation and hence bacterial overgrowth, it seems plausible that changes to bowel length and volume from AGIR may also contribute to the witnessed decrease in CRBSI, in addition to the reduction in calibre discussed above. Interestingly, this combination of: (i) experimental evidence (discussed above); (ii) promising clinical observations such as those reported here; and (iii) a strong mechanical theory behind calibre reducing surgery also reducing stasis, has led other authors to propose that AGIR be used for the treatment of recurrent bacterial overgrowth in children with short bowel syndrome [17,19].

A significant strength of this study is the homogeneity of the patient group and the availability of follow-up data for 'completed episodes' managed with AGIR: all patients included had undergone surgery, subsequently gained enteral autonomy and had their CVC removed. Data on CRBSI incidence therefore incorporated each patient's entire duration of PN treatment. Other strengths of the study design relate to the fact that all patients were treated at a single centre and had similar packages of care e.g. PN; it is therefore expected that each episode of CVC sepsis would be captured by the study. The patients treated in this study did not receive any prophylactic agents' central venous catheters lock.

Although there is significant support in the literature for intestinal lengthening surgery reducing bacterial overgrowth and translocation, this is largely based on observations of case series: a lack of controlled studies means that the evidence base is limited by potential influence of factors such as selection and performance biases, along with the inherent problems of retrospective studies, such as inaccuracies of clinical data [20,21]. Our study is similarly limited however, a randomised controlled trial would be challenging in such a small, potentially heterogeneous group of patients. A further limitation of this study relates to the absence of more detailed microbiological data such as paired peripheral and central blood cultures, quantitative cultures and time to culture positivity [22]: episodes of bacteraemia identified here could potentially be unrelated to CVC sepsis. However, we believe the likelihood of this significantly influencing the study is low.

In conclusion, CRBSI frequency in PN dependent patients with dilated bowel reduces after AGIR. We propose two disparate

mechanisms to explain this observation, but it is unclear what the relative influence of each of these is. Given the clinical importance of CVC sepsis in children dependent on parenteral nutrition, these novel findings warrant further exploration in larger, preferably controlled studies.

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