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ORIGINAL ARTICLE

A meta-analysis of clinical outcome of intestinal transplantation in patients with total intestinal aganglionosis

Hiroki Nakamura[1] · Davina Henderson[2] · Prem Puri[1,3]

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Abstract
Aim of the study Total intestinal aganglionosis (TIA) occurs in less than 1% of patients with Hirschsprung disease (HD), and TIA is the most severe form of HD. Survival has improved with the advent of parenteral nutrition and intestinal transplantation (ITx). The field of ITx has rapidly progressed in the last two decades and has now become an established treatment for patients with intestinal failure. The purpose of this meta-analysis was to determine the clinical outcome of ITx in patients with TIA.
Methods A systematic literature search for relevant articles was performed in four databases using the combinations of the following terms: "total intestinal aganglionosis", "intestinal transplantation", and "Hirschsprung disease/Hirschsprung's disease" for studies published between 2003 and 2016. The relevant cohorts of ITx in patients with TIA were systematically searched for clinical outcomes.
Main results Thirteen studies met defined inclusion criteria, reporting a total of 63 patients who underwent ITx for TIA. Majority of patients were males (71.0%), and median age of ITx was 4.3 (range 0.25–17.6) years. Isolated ITx was performed in 37% patients and multivisceral ITx in 63%. Mean follow-up period was 40 months (range 1–154). Overall survival rate was 66%; the longest survivor was 12.8-year-old after ITx.
Conclusion ITx appears promising in the management of TIA. ITx can be considered a feasible treatment option for patients with TIA who suffer from life-threatening complications of intestinal failure.

Keywords Intestinal transplantation · Total intestinal aganglionosis

Introduction

Total intestinal aganglionosis (TIA) occurs in less than 1% of patients with Hirschsprung disease (HD), and TIA is the most severe form of HD [1–7]. Survival has improved with the advent of total parenteral nutrition (TPN) and intestinal transplantation (ITx) [8–11]. TPN and central catheter placement has made it possible to maintain children with TIA in a stable nutrition state for many years [12]. However, the long-term use of TPN is associated with serious complications such as recurrent episodes of central venous catheter sepsis and end-stage liver disease [13–16].

Various surgical procedures have been proposed for the treatment of TIA, but these procedures have not provided a sufficient improvement to allow patients to be weaned from TPN [17–21]. In 1987, extended myectomy–myotomy procedure was described for the management of TIA [22]. However, there are a few long-term survivors reported in TIA following myectomy–myotomy procedure and therefore most surgeons have abandoned this procedure for the better option of ITx.

The field of ITx has rapidly progressed in the last two decades and has now become an established treatment for patients with intestinal failure [8–11]. The purpose of this

✉ Hiroki Nakamura
hinakamu@juntendo.ac.jp

[1] National Children's Research Centre, Our Lady's Children's Hospital, Dublin, Ireland

[2] Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin 2, Ireland

[3] School of Medicine and Medical Science, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland

meta-analysis was to determine the clinical outcome of ITx in patients with TIA.

Materials and methods

A systematic review and meta-analysis were conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of the literature was performed in the PubMed, Embase, Medline and Cochrane Library electronic database for the keywords "total intestinal aganglionosis", "intestinal transplantation", and "Hirschsprung disease/Hirschsprung's disease" for studies published between 2003 and 2016. There was no restriction regarding the language of the publications. Reference lists of relevant articles were manually searched for further cohorts. Duplicates were deleted. Resulting publications were reviewed in detail for epidemiology, operative treatment, morbidity, and clinical outcome. The relevant articles were reviewed by title, keywords, and abstract by the authors (H.N. and P.P.), and a full-text assessment of selected articles was performed.

Results

The initial search yielded a total of 332 publications, of which 318 were identified by electronic database searching and 14 from cross-referencing (Fig. 1). After removal of 190 duplicate listed articles, 142 titles, keywords, and abstracts were screened. Of these, 62 nonrelevant studies were excluded. The remaining 80 publications were assessed in full-text for eligibility, and 67 articles were excluded because they did not address any of the selection criteria. In total, data from 13 studies [8, 23–33] (published between 2003 and 2016) met defined inclusion criteria and were included in the cumulative analysis.

Sixty-three patients who underwent ITx for TIA were included in this study. Table 1 summarizes the characteristics of the included studies. Majority of patients were males (71.0%), and median age of ITx was 4.3 (range 0.25–17.6) years. Isolated ITx was performed in 37% patients and multivisceral ITx in 63%. Mean follow-up period was 40 months (range 1–154). Overall survival rate was 66%; the longest survivor was 12.8-year-old after ITx.

The main complications were infectious (bacterial, CMV, EBV, HSV, mucormycosis, fungal), immunological (cellular ± humoral rejection, autoimmune hemolytic anemia), tumoral (EBV-related lymphoproliferative disorders), toxic (hypertension, impairment of renal function), dermatologic (severe generalized dermatosis, probably multifactorial: GVH, HSV6, medication toxicity), and encephalopathy.

Some authors prescribed anti-infective prophylaxis. Sauvat et al. used 1 month of total gut decontamination and acyclovir or ganciclovir during the first three postoperative months. Pakarinen et al. used rotating enteral antimicrobial therapy for bacterial overgrowth, including different combinations of metronidazole, ciprofloxacin, amoxicillin, and fluconazole.

Four studies reported immunosuppressive medication. IL-2 antibody, thymoglobulin, steroids, tacrolimus, sirolimus, daclizumab, basiliximab, and a combination of basiliximab and rabbit antithymocyte globulin or alemtuzumab were used.

Discussion

The total intestinal aganglionosis (TIA) with an absence of ganglion cells from the duodenum or upper jejunum to the rectum is the most rarest form of HD and is associated with high morbidity and mortality [34]. Various surgical procedures such as myectomy–myotomy have proved fruitless in achieving stable enteral autonomy. Permanent dependency on parenteral nutrition was the only available therapy for patients with TIA until intestinal transplantation (ITx) became an acceptable form of replacement therapy for intestinal failure. During the last two decades, ITx has rapidly progressed and has now become an established treatment for patients with intestinal failure. Our meta-analysis revealed 63 patients with TIA who underwent ITx.

Difficulty to arrive at a definite diagnosis was a common finding in all the cases of TIA. There were no absolute clinical criteria for TIA that were reproducible except the presence of nonspecific signs of intestinal obstruction [17]. In a previous report [34], in only 5.9% cases, meconium passage within the first 2 days was documented. Most of the patients presented with abdominal distention and bile-stained vomiting shortly after birth. Diarrhea, fever, and abdominal distention in HD are always symptoms of enterocolitis, and this remains the most serious complication of TIA [35]. Plain abdominal radiographs showing dilated or normal caliber intestinal loops are not always helpful. The findings on the barium enema are uncertain, and a delayed film at 24 h may confirm the diagnosis by demonstrating the retained barium. The only positive means of identifying the extent of aganglionosis was by rectal biopsy or operative biopsy. However, the extent of aganglionosis was often not accomplished at an initial laparotomy and most cases required multiple laparotomies to confirm the extent of aganglionosis. TIA most often lead to the placement of an end-jejunostomy, short bowel syndrome, and associated parenteral nutrition dependence,

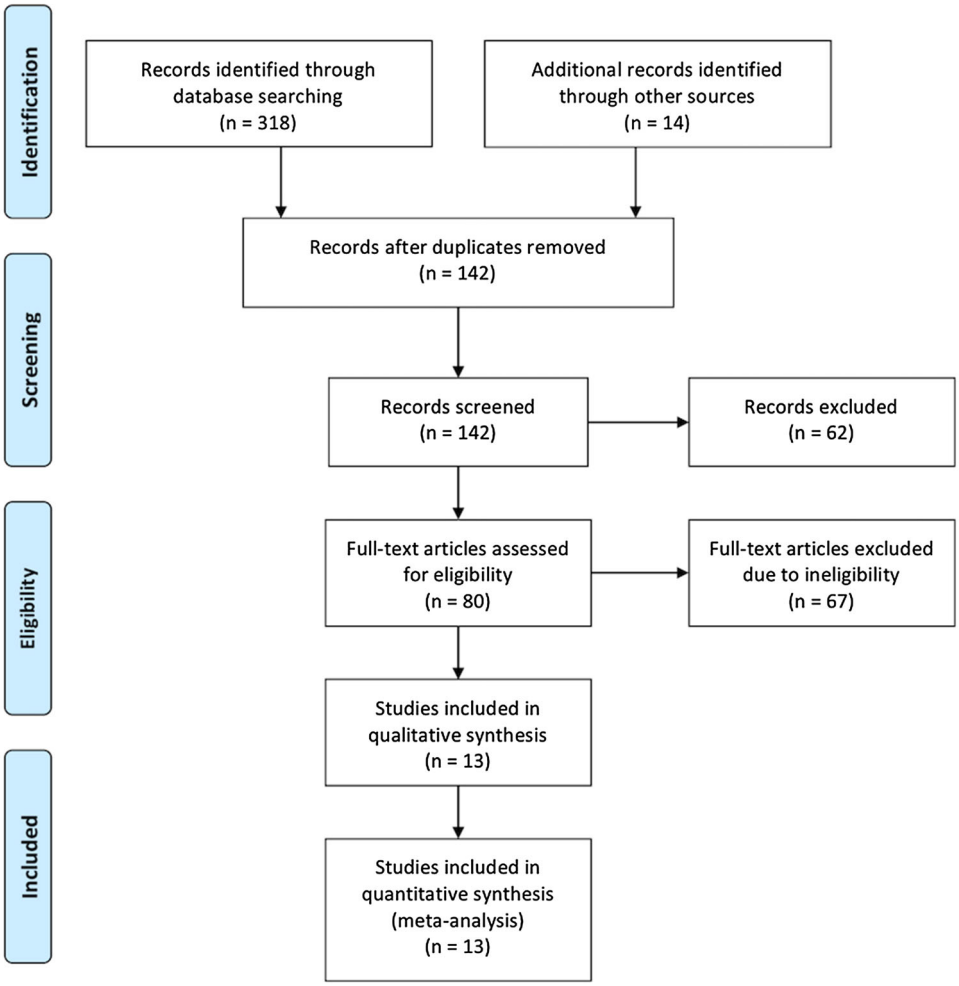

Fig. 1 This is an information flow diagram, demonstrating the process of selection and exclusion of articles from the literature search for the purposes of systematic review

Table 1 Study characteristics

Study	Country	Number of ITx
Ramisch et al.	Argentina	7
Chang et al.	Korea	2
Varkey et al.	Finland	2
Neuvonen et al.	Finland	1
Hukkinen et al.	Finland	1
Ganousse-Mazeron et al.	France	18
Pakarinen et al.	Finland	1
Chardot et al.	France	2
Nwoye et al.	USA	16
Mannan et al.	USA	1
Sharif et al.	England	2
Tovar et al.	Spine	2
Sauvat et al.	France	8

ITx intestinal transplantation

which predisposes patients to further complications [12, 34]. Development of intestinal failure-associated liver failure, loss of venous access sites, or frequent septic catheter infections were indications for ITx in the majority of patients [8, 36]. Intestinal failure-associated liver failure is the most life-threatening complication [37, 38]. Recent data have confirmed the role of small intestinal bacterial overgrowth in the onset of intestinal failure-associated liver failure especially in the patients with short bowel syndrome [39–41].

The main complications of ITx were infectious, immunological, toxic, dermatologic, and encephalopathy. Nearly 80% of the immune cells of the human body reside in the gut. After the ITx, the graft is repopulated with recipient cells; this is the main reason for the complexity of the immunological management of the intestinal graft compared to other organs. The immunotherapy must be targeted to each patient [42–44].

Data from the International Transplant Registry have proved the importance of using induction therapies that include monoclonal or polyclonal antibodies against leukocytes [45, 46]. Not only has the use of tacrolimus allowed better survival, but also the implementation of different immunosuppressive agents, such as sirolimus, has

had a positive impact on survival [45, 47]. The improvements in immunosuppressive regimens and graft monitoring have increased the 5-year survival to greater than 55%, and 10-year survival to greater than 30% [45]. A previous review [34] showed that overall survival rate was 34% after ITx; however, in the present review, the overall survival rate was 66%; the longest survivor was 12.8-year-old after ITx.

In conclusion, these results suggest that ITx has become the standard of care for patients with irreversible intestinal failure due to markedly improve outcomes. ITx can be considered a definitive treatment option for patients with TIA who are suffering from life-threatening complications of intestinal failure.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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