Surgical Management of Intestinal Failure: Initial Experiences from an Intestinal Failure, Rehabilitation and Transplant Unit in Iran

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Abstract

Background: Intestinal failure (IF) is a life-threatening medical condition. The management of IF in low- and middle-income countries without home parenteral nutrition (HPN) remains unclear. We recently established an intestinal rehabilitation unit (IRU) and aimed to provide our experience on the current management and outcomes of IF in Iran.

Methods: In this cross-sectional case series, data were collected from an established database on IF in the Shiraz Transplant Center in Abu Ali Sina hospital, affiliated to Shiraz University of Medical Sciences, Iran from January 2018 to October 2018.

Results: Overall, 30 patients with a mean age of 44.13 ± 10.32 years, which included 25 males, were recruited. Short bowel syndrome (SBS) (60%) and enterocutaneous fistulae (27%), as complication of previous surgeries, were the main causes of IF. The most common type of IF was type 3 (62.5%). Mesenteric ischemia was the leading mechanism of IF (47%). Fifteen patients (50%) received autologous gastrointestinal reconstructive surgery (AGIRS), and two (7%) patients had serial transverse enteroplasty (STEP). At the end of follow-up, 15 patients recovered from IF (50%). The overall survival rate was 83.3%.

Conclusion: This series introduced the results of a multidisciplinary program for the treatment of IF in a middle-income country that lacks facilities for HPN. Our protocol of care, understanding the need for development of HPN, showed promising clinical outcomes.

Keywords: Home Parenteral Nutrition, Intestinal Failure, Intestinal Transplant, Iran, Middle East


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Introduction

Intestinal failure (IF) is a complex condition, which is defined as reduction in gut flow in which absorption of nutrients is disrupted to a degree that necessitates intravenous supplementation in order to maintain health and growth.1 Difficulties in accessing health services, severity of the disease at presentation and the absence of adequate guidelines for early, mid-term and long-term management of this condition add to the complexities when facing patients with IF.2,3

Middle-income countries (MICs) are a very diverse group with regard to age distribution, population size and income, and include small nations to some of the largest countries in the world. Iran is considered to be an upper-middle income country according to the definition by the World Bank classification4. Low- and middle-income countries mainly lack facilities for home parenteral nutrition (HPN), considered the gold standard treatment for IF, which complicates treatment of the condition in these countries.5

Intestinal rehabilitation refers to a multidisciplinary process aimed at improving intestinal function so that patients will not require parenteral nutrition (PN) and will minimize future need for intestinal transplantation.6 This comprehensive approach in IF uses nutrition, pharmacology, and in some cases, non-transplant surgical reconstructions to achieve this objective.

We have recently established an intestinal rehabilitation unit (IRU) in Abu Ali Sina hospital, affiliated to Shiraz University of Medical Sciences, Iran. In this center, we provide specific IF rehabilitation and transplant programs which aim to provide state-of-the-art care for adult patients with different degrees of intestinal insufficiency and IF. Here, we report our first experience on the management of IF in our IRU in Iran.

Materials and Methods

Study Settings and Patient Selection

In this cross-sectional case series study, data were collected from an established database on IF in the Shiraz...
Transplant Center in Abu Ali Sina hospital, affiliated to Shiraz University of Medical Sciences, Iran. All patients diagnosed with IF from January 2018 to October 2018 were included.

Data on patients’ characteristics, diagnosis and type of IF, cause of IF, number of surgeries received before referral, type of operation performed for intestinal rehabilitation, and postsurgical complications based on the Clavien-Dindo classification of surgical complications were collected for each patient. The total number of patients who were weaned off PN, who were discharged and the number of patients achieving intestinal adaptation and survival at the end of follow-up were also recorded.

**Pre-operative Care**
After clinical and metabolic conditions were stabilized in patients, preoperative hospital PN management in patients with type II IF included the following steps:
1. Avoiding hydro-electrolytic imbalance and dehydration by use of anti-secretory and anti-motility drugs to decrease ostomy losses,
2. Improving nutritional conditions,
3. Completing an antifungal and antibiotic therapy course when needed,
4. Improving the abdominal wall condition,
5. Physical, motor and psychosocial rehabilitation,

**Antologous Gastronintestinal Reconstruction Surgery (AGIRS)**
AGIRS was always performed three to six months after the last surgery a patient had. If patients were not candidates for surgical or medical rehabilitation and/or developed serious complications related to the nutritional support, they would become candidates for intestinal transplantation.

AGIRS was done with the aim of resecting intestinal fistulae complexes, closing ostomies, and restoring intestinal continuity in order to preserve or increase the intestinal length. When possible, the ileocecal valve was preserved to favor intestinal adaptation. Sometimes, more than one procedure was needed to achieve a complete gastrointestinal reconstruction. AGIRS has several benefits including restoration of intestinal continuity, reducing dysfunctional bowel segments, reducing bacterial overgrowth, and improving motility.4,9

Serial transverse enteroplasty (STEP), a procedure described by Kim et al in 2003, requires having a dilated intestinal segment of more than 5 cm in order to performed subtotal transection of the intestine perpendicular to the main longitudinal axis, using multiple linear laparoscopic triple line staplers alternately placed at 2 cm intervals, depending on the length of the intestine requiring enteroplasty.9,10

**Post-operative Care**
All patients were admitted to the intensive care unit for immediate post-operative care. Once hemodynamic instability was treated, PN was started using pre-operative formulation. On the 5th post-operative day, a small bowel follow-through with water-soluble contrast and methylene blue or an abdominal CT scan with intravenous and oral contrast was performed. This was done to verify the indemnity of the intestinal anastomosis in order to initiate oral or gastrointestinal intake, as well as to rule out the presence of any residual intra-abdominal fluid collection. If oral intake of clear fluids was tolerated for 24 hours, diet was progressed to a low residue diet. Patients received anti-secretory (ranitidine/omeprazole) and anti-motility agents (loperamide) or cholestyramine when indicated. Once the oral and/or enteral intake reached 60% of the patient’s nutritional requirements, the volume and caloric intake of PN formulation were decreased. When the oral/ enteral intake covered 75% of the requirements, PN was suspended. It was considered that the patient recovered intestinal sufficiency when he was capable of maintaining weight and hydration for six months without any form of PN support.

**Follow-up**
For the first year after surgery, patients were visited every month. After the first year of surgery, patients were given annual follow-ups. In cases when patients did not refer for their follow-up, they were contacted and in cases of no answer, their first of kin was contacted and information regarding the patient’s condition (death, hospitalization etc) was acquired and another visit was appointed. In case of development of complications, patients were advised to refer to the transplantation center even without prior appointed visitations.

**Statistical Analysis**
The statistical analyses were carried out using the Statistical Package for Social Sciences software (IBM SPSS Inc. version 20, Chicago, IL, USA). Quantitative data with normal distribution are presented as means and standard deviation (SD) and those without normal distribution are presented as median and interquartile range (IQR). Qualitative data are presented as frequency and percentage. All values have been rounded. For means, values have been rounded to one decimal place and for percentages, values have been rounded to include no decimals.

**Results**
Thirty patients with a mean age of 44.13 ± 10.32 years were included in the study. Five patients were women (17%) and 25 (83%) were men.

Short bowel syndrome (SBS) was the main diagnosis for IF (60%) followed by enterocutaneous fistulae (27%). One patient (3%) presented with chronic intestinal
pseudo-obstruction; furthermore, one patient (3%) was admitted with prolonged ileus and two patients (7%) were hospitalized with IF post distal pancreatectomy with normal intestinal length.

Regarding the primary etiology of IF, the most common mechanism was mesenteric ischemia (47%), followed by post-surgical (more commonly after colon cancer) (33%). The most common types of IF were type III and type II, which were seen in 67% and 27% of patients, respectively.

Regarding the conditions for transplantation, the majority of patients were not candidates for any type of transplantation (70%). Moreover, 4 patients (13%) were candidates for isolated intestinal transplantation, two patients (7%) for multi-visceral transplantation, and two patients (7%) were candidates for isolated pancreas transplantation.

The median (IQR) length of hospital stay was 59 (35, 84) days (range 20-240 days). The median (IQR) number of operations done for patients was 3 (1.75, 4).

All the included patients received PN as standard therapy. Fifteen patients (50%) had AGIRS (Figure 1). The STEP procedure was performed in two patients (7%). Regarding complications, according to the Clavien-Dindo classification index, 8 patients (27%) had type 1, 13 patients (43%) had type 2, 2 patients (7%) had type 3, 2 patients (7%) had type 4, and 5 patients (17%) developed type 5 complications. The most common in-hospital complications included catheter infections (47%), sepsis (20%), and renal failure (10%).

At the end of the follow-up, 16 patients (53%) had recovered from IF and were discharged from the hospital (Figure 2). Moreover, four patients (13%) were candidates for re-reconstruction, five patients (17%) were candidates for transplantation, including two (7%) for pancreas transplantations and three (10%) for intestinal transplantations. Overall, five (17%) patients died during the study period. Table 1 shows the patients’ baseline and

| Table 1. Characteristic of Patients with Intestinal Failure* |
|-------------------------------------------|-----------------|-----------------|
| Variables | Statistics |
| Age, Mean ± SD | 44.1 ± 10.3 |
| Sex, No. (%) | Male, 25 (83) | Female, 15 (17) |
| Secondary etiology of IF, No. (%) | Short bowel syndrome, 18 (60) | Enterocutaneous fistula, 8 (27) | Chronic intestinal pseudo-obstruction, 1 (3) | Prolonged ileus, 2 (7) | Unknown, 2 (7) |
| Primary etiology of IF, No. (%) | Mesenteric ischemia, 14 (47) | Post-surgery, 10 (33) | Liver transplantation/portal vein thrombosis, 2 (7) | Colon cancer, 3 (10) |

| Table 1. Continues |
|------------------|-----------------|-----------------|
| Variables | Statistics |
| Gastric cancer | 1 (3) |
| Sleeve gastrectomy | 1 (3) |
| Fistula/appendectomy | 1 (3) |
| Total pancreatectomy | 2 (7) |
| Volvulus | 1 (3) |
| Chronic intestinal pseudo-obstruction | 1 (3) |
| Trauma | 1 (3) |
| Multiple resections | 1 (3) |
| Familial adenomatous polyposis | 1 (3) |
| Perforated duodenal ulcer | 1 (3) |
| Type of intestinal failure, No. (%) | 1, 2 (7) | 2, 8 (27) | 3, 20 (67) |
| Hospital stay, days | Mean ± SD, 69.0 ± 48.3 | Median (IQR), 59 (35, 84) | Number of operations, Median (IQR), 3.00 (1.75, 4) |
| Catheter infection, No. (%) | Yes, 14 (47) | No, 16 (53) |
| Sepsis, No. (%) | Yes, 6 (20) | No, 24 (80) |
| Liver failure, No. (%) | Yes, 1 (3) | No, 29 (97) |
| Diabetes mellitus, No. (%) | Yes, 2 (7) | No, 28 (93) |
| Pneumonia, No. (%) | Yes, 1 (3) | No, 29 (97) |
| Renal failure, No. (%) | Yes, 3 (10) | No, 27 (90) |
| Type of operation, No. (%) | Autologous gastrointestinal reconstruction, 15 (50) | Serial transverse enteroplasty, 2 (7) | Resection and anastomosis, 13 (43) |
| Follow-up outcomes, No. (%) | Discharged and recovered IF, 16 (53) | Candidate for re-reconstruction, 4 (13) | Transplantation candidate, 5 (17) | Bowed transplantation, 3 (10) | Pancreas transplantation, 2 (7) | Died, 5 (17) |
| Mortality, No. (%) | Yes, 5 (17) | No, 25 (83) |

*All values have been rounded. For means, values have been rounded to one decimal place and for percentages values have been rounded to include no decimals.
clinical characteristics in our study.

Discussion
In this study, we described our experience with 30 patients with IF. To the best of the authors’ knowledge, this is the first report from the Middle East on the outcomes and management of patients with IF in an IRU without facilities for HPN. Data published regarding the development of intestinal rehabilitation programs are scarce in Asia.

The first form of PN was established in Shiraz and was entitled the “hyperalimentation unit” in Sadi hospital affiliated to Shiraz University of Medical Sciences in 1972. Considering the high costs of intestinal transplantations and the non-existence of facilities for HPN, we established the first IRU in our region.

According to the European Society for Parenteral and Enteral Nutrition (ESPEN), the acute form of IF is categorized into two forms of functional and pathophysiological.

IF is “pathophysiologically” classified into five groups: short bowel (SB) with reduced absorptive mucosal surface; intestinal fistula caused by massive bypass of absorptive mucosal surface; intestinal dysmotility that is restricted oral/enteral nutrition or total fasting from intolerance due to feeding-related exacerbation of digestive symptoms or due to episodes of non-mechanical intestinal obstruction; mechanical obstruction; extensive SB mucosal disease, which is referred to as inefficient absorption and/or nutrient loss of mucosal surface. Patients with type 1 and most patients with type 2 IF recover fully over time. Type 3 IF is mainly observed in SBS cases which requires long-term PN.

In the case of SBs, EC fistula, or extensive SB disease, malabsorption can be considered the primary mechanism. In the case of intestinal dysmotility or intestinal mechanical obstruction, IF can be mainly attributed to oral/enteral nutrition blockade or total oral fasting.

SBS is the main reason for type 3 CIF, which involves about 75% of adults and 50% of children on HPN in Europe. There is a high risk for development of IF in...
adults with SB<35 cm with a jejunoleal anastomosis with an intact colon, <60 cm with a jejunorectal anastomosis or <115 cm with an end-jejunostomy. HPN can be weaned off in 50% of adult patients following medical and surgical treatments. Complete HPN wean-off is almost unlikely (<1%) in patients with SBS and almost always relapses after 2-3 years due to intestinal obstruction.17-19

Enterox fistulas are classified as internal (leak to the gastrointestinal tract or other organs such as the bladder and vagina) and external (leak to skin). The physiologic classification of enterocutaneous fistulas are as follows: low-output fistulas (<200 mL/d drainage); moderate-output fistulas (200-500 mL/d drainage); high-output fistulas (>500 mL/d drainage). Although various etiologies can lead to enterox fistula formation, the most common etiologies include distal obstruction, radiation, foreign body, inflammation or infection, neoplasia, and epithelialization. Approximately one third of all EC fistula cases are comorbidities associated with Crohn's disease.20,21

One of the main causes of type 2 IF in adults is EC fistulas (Figure 3). PN, which may cause metabolic instability, plays a vital role in the initiation of treatment in these patients.22 Spontaneous closure rates vary depending on the cause and volume of the fistula.23 About 33% of EC fistula cases improve spontaneously within five to six weeks with conservative measures.24-26 Generally, low-output, long-track, and proximal SB are most likely to heal with conservative measures. Patients with enterocutaneous fistulae who have failed 5 to 6 weeks of non-operative management will likely need surgery.27

The incidence of IF varies amongst European and South American countries. Prasad and Pollard28 reported the annual incidence rate of the condition to be 2.6 patients for the UK, 13.9 for Denmark, and 80-200 for the United States per one million individuals. Moreover, the incidence rate was reported to be 1.1-12.7 per million adults in Europe. According to a recent report from the Dutch registry for Intestinal Failure and Intestinal Transplantation in 2013, the prevalence of IF showed a remarkable rise during the past decades.29-31

All the 42 Latin American and Caribbean countries have patients diagnosed with IF, but few (6 out of 42, 16.66%) are currently capable of providing sustained and complete care for IF including HPN and intestinal transplantation.3 All postsurgical complications followed by mesenteric ischemia are the main causes of IF for adults in Latin America and the Caribbean region. The main etiology for IF in high-income countries are Crohn's disease followed by mesenteric ischemia, and postsurgical complications.3

The most common indication for PN in Asian adults is SBS secondary to mesenteric ischemia, postsurgical complications, followed by cancer. Inflammatory bowel diseases are an unusual cause of PN in Asia compared to the United States and Europe.32

With regard to our results, the most common indication for PN in Iranian adults was SBS secondary to mesenteric ischemia followed by postsurgical complications.

AGIRS and STEP were the most common surgical procedures performed among adults and children with IF, respectively (Figure 4). The first multidisciplinary IF rehabilitation and transplantation program was established in Latin America in 2006 in Argentina and Colombia. One report from Buenos Aires, Argentina showed that a total of 74.1% of patients with intestinal remnants of more than 50 cm after AGIRS were able to accomplish intestinal autonomy within 5 years after the operation.3

Although not precise, as no national registration program exists, the rate of SB transplantation is somewhat higher in Iran compared to other Asian countries.3 This can be due to two differences between Iran and other Asian countries: first is that unlike Iran, most South Eastern Asian countries are capable of providing HPN for their patients, and the second is due to the popularity of organ donation in Iran and better access to an organ pool of deceased donors as a result of social and cultural factors, which has caused patients in Iran to shift towards SB transplantation.

It is difficult to find reports on the existence of HPN in countries in Asia and few reports of successful HPN exist in Taiwan, Japan and China.35-37

This study was not without limitations. As we do not have a national registration system, we do not have information regarding the exact number of patients with IF in our country. We have established a multidisciplinary team that applies our treatment protocol which includes intestinal transplantation if needed; other centers with
limited resources may not be able to completely apply our protocol, although most of our patients were spared from transplantation using reconstructive surgeries. Considering that we have just recently established our IRU, the follow-up of our patients was limited by nature and longer follow-ups will better show the long-term complications and outcomes.

In conclusion, by establishing the first IRU in our center and practicing AGIR, we have been able to achieve intestinal autonomy in patients suffering from IF; reduce the number of candidates for intestinal transplantation, and reduce mortality rates. Our report shows a successful experience with management of patients with IF by establishing an IF, rehabilitation and transplant unit in a country that lacks facilities for HPN.

Clinical Relevancy Statement
We have recently established an IRU in Abu Ali Sina Hospital affiliated to Shiraz University of Medical Sciences, Iran. In this center, we provide specific IF, rehabilitation and transplant programs which aim to provide state-of-the-art care for adult patients with different degrees of intestinal insufficiency and IF. To the best of our knowledge, this is the first report on IF patients, their management and outcomes in Iran, a country that lacks facilities for HPN which is considered to be the gold standard treatment of this disease.

Authors’ Contribution
HN, AS, MS, GEG, and SN aided in study conceptionalization. HN, HE, AMM, MYK, and SN aided in study design and data gathering. PA aided in statistical analysis. HN, MS, AS and PA aided in interpretation of results. HN, MYK, PA and MS aided in preparation of manuscript draft. All authors aided in critical revision of final manuscript and approved the final format.

Conflict of Interest Disclosures
There is no conflict of interest to be declared regarding the manuscript.

Ethical Statement
The study protocol was approved by the Institutional Review Board of Shiraz University of Medical Sciences, Shiraz, Iran. All study protocols followed guidelines stated in the Declaration of Helsinki and the declaration of Istanbul.

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