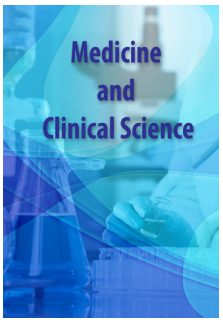
Medicine & Clinical Science

Original Article



Fast-track surgery in the treatment of Hirschsprung's disease: A prospective multicenter randomized controlled trial

Honglin Li[1], Jun Xiao[1], Yingjian Chen[1], Yongjun Chen[2], Zuxuan Wu[1], Hongyao Yuan[3], Xiaofeng Xiong[4] and Zhi Li[1*]

[1]*Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China*
[2]*Department of Biliary and Pancreatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China*
[3]*Department of Pediatric Surgery, Guangzhou Children's Hospital, Guangzhou, China*
[4]*Department of Pediatric Surgery, Wuhan Children's Hospital, Wuhan, China*

Correspondence

Zhi Li

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Tel. 86-13387664883

E-mail: lizhimdphd@163.com

- Received Date: 26 Aug 2019;
- Accepted Date: 03 Sep 2019;
- Publication Date: 12 Sep 2019.

Keywords:

Hirschsprung's disease; fast-track surgery; prospective multicenter randomized controlled trial

Abstract

Background: Fast-track surgery (FTS) is a novel, promising and comprehensive for surgical patients and is beneficial for recovery. Prospective multicenter randomized controlled trials on fast-track surgery in the treatment of Hirschsprung's disease (HD) are lacking. Objective: Our study aimed to evaluate the safety and efficacy of FTS in the treatment of HD and explore the underlying immunologic mechanism of FTS. Methods: A prospective multicenter randomized controlled trial was conducted from January 2010 to January 2015. The patients were randomly assigned into two groups and traditional managements group. The postoperative intestinal function recovery time, hospital stay, hospital expense were compared and analyzed. Blood samples were taken preoperatively (baseline), and 24, 72 hours after surgery. C-reactive protein, interleukin-6 and tumor necrosis factor-α as perioperative immunity parameters were evaluated. Results: Compared with the conventional group, fast-track surgery had significantly faster recovery of bowel movement ($P<0.05$) and significantly less hospital stay and hospital expense ($P<0.05$). Furthermore, FTS group effectively inhibited the release of post-operative inflammatory factors and yielded beneficial protection via cell immunity. Inflammatory reactions, based on C-reactive protein, interleukin-6, and tumor necrosis factor-α, were less intense following FTS group. Conclusions: Fast-track surgery in the treatment of HD was safe and effective. FTS could improve the bowel movement recovery, shorten hospital stay and reduce hospital expense. Moreover, FTS could attenuate postoperative stress reactions and accelerate rehabilitation for patients with HD.
(Registered with ClinicalTrials.Gov, NCT02350088)

Introduction

PFast-track surgery (FTS) combines various techniques used in the care of patients undergoing operations. The methods include preoperative carbohydrate treatment, epidural or regional anesthesia, minimally invasive surgery, optimal pain control, and positive postoperative rehabilitation, including early peroral enteral nutrition and ambulation [1]. The combination of these approaches not only reduces the stress response and organ dysfunction but also improve postoperative immune function and therefore greatly accelerates full recovery [2].

Fast-track surgery has been applied for specific procedures in children, such as appendectomy [3-5], nephrectomy, pyelolithotomy, and pyeloplasty [6-7]. Furthermore, fast- track concepts have been introduced by pediatric cardiac surgeons and anesthesiologists [8-10]. Nevertheless, to date, no randomized controlled trials (RCT) on the feasibility, safety, and efficacy of fast-track surgery in the treatment of Hirschsprung's disease (HD) have been reported.

In light of that, we conducted a prospective multicenter RCT to evaluate the safety and efficacy of fast track surgery in the treatment of HD. Furthermore, to explore the underlying immunologic mechanism of FTS. C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) as perioperative immunity parameters were evaluated.

The fast track recovery program comprises a multidisciplinary approach aiming to reduce surgical stress response, enhance immune function, and thereby reduce organ dysfunction and allow for a faster recovery after surgery [11]. Levels of CRP and cytokines are closely related with the inflammatory response and the extent of the inflamed tissue involved, and with the activity of the immune reaction [12]. Interleukin-6 levels are associated with postoperative complication rates and are a predictor of morbidity after surgical intervention [13]. Tumor necrosis factor-α also acts as the marker for the severity of the surgical stress response [14,15].

To date, there is little evidence for a better-preserved immune status, which is in line with the observed lower morbidity and faster recovery in the treatment

Citation: Li H, Xiao J, Chen Y, et al. Fast-track surgery in the treatment of Hirschsprung's disease: A prospective multicenter randomized controlled trial. Med Clin Sci. 2019;1(1):1-5.

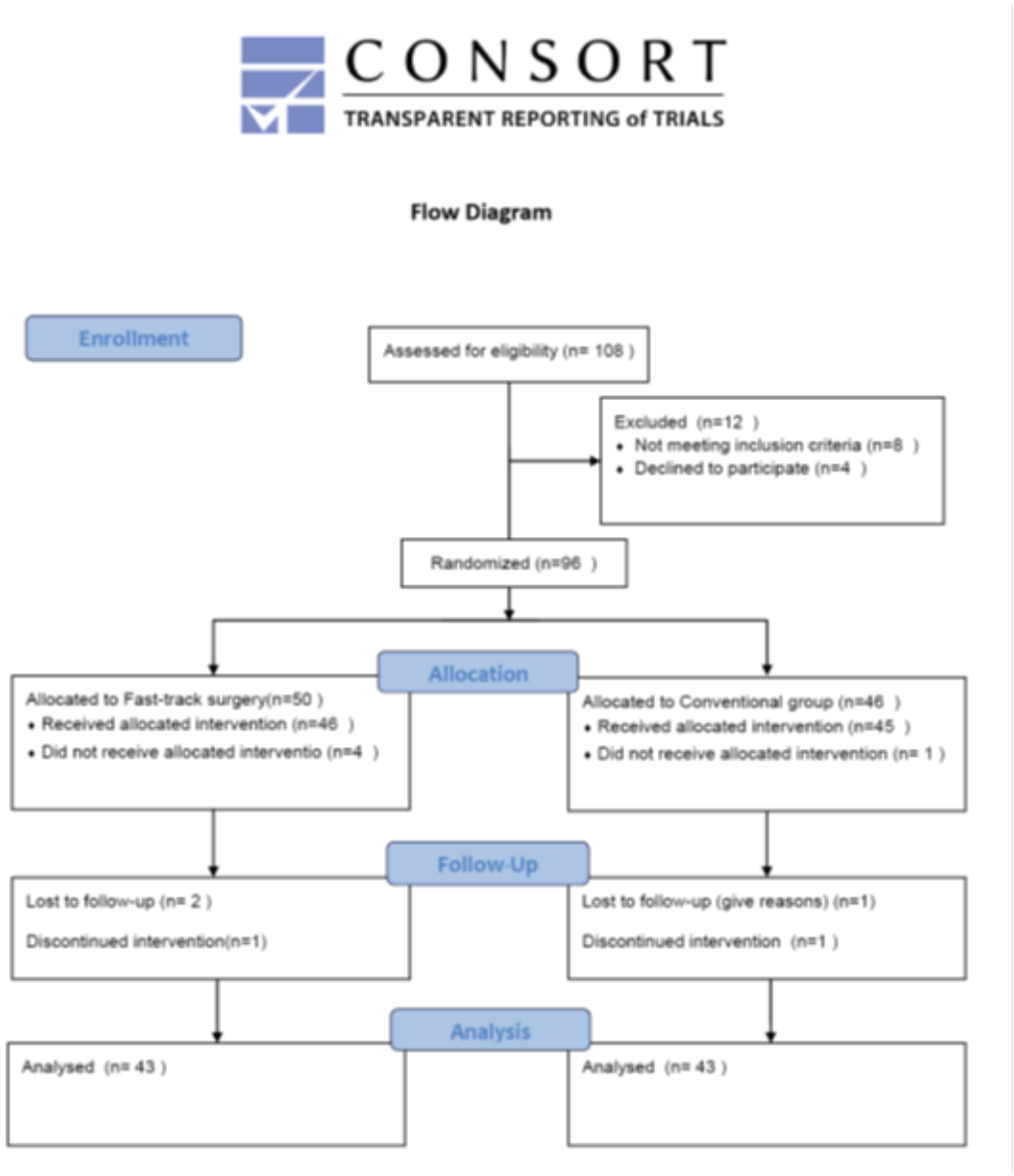


Figure 1. RCT flow diagram

of HD. In addition, no previous studies have investigated immune status and stress response after fast track recovery programs. The aim of this study was to evaluate the safety and efficacy of FTS and uncover the underlying immunologic mechanism.

Material and Methods

Patients Eligibility

Inclusion criteria

1. All patients suffering from HD at an age of less than 18 years old;
2. Hirschsprung's disease was confirmed by barium enema, anorectal manometry, and postoperative pathology;
3. All patients underwent primary surgery.

Exclusion criteria

1. Age>18 years;
2. Reoperation for HD;
3. With the conservative treatment for HD;
4. Patients who are complicated with mental and neurological disorders;
5. Patients who are complicated with other congenital gastrointestinal malformations;
6. Patients who are complicated with liver, kidney dysfunction, blood disorders, immune deficiency diseases, and significant ECG abnormalities.

Ethics

This study was carried out according to the rules of the Declaration of Helsinki and the CONSORT statement. The independent medical ethics committee of the participating hospital approved the study protocol, with the approval number: 2010008. The study was registered with ClinicalTrials.gov: NCT02350088

Study Design

Patient assignment

According to inclusion and exclusion criteria, 96 patients with HD from three medical centers: Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology; Guangzhou Children's Hospital; Wuhan Children's Hospital were randomly assigned into conventional and FTS group (Figure 1 and Table 1).

	Fast-track Surgery Group	Conventional Group
Day before surgery	A small amount of carbohydrate drink until 4 hours before surgery	No carbohydrate drink on the day of surgery
	Bowel preparation for 3 days	Bowel preparation for 1 week
	No nasogastric tube	Nasogastric tube
Day of Surgery	Sacral canal anesthesia	Tracheal intubation
	General anesthesia	General anesthesia
	Transanal pull-through/Laparo-scopic assisted Soave	Open surgery
Postoperative days	No nasogastric tube drainage on the first postoperative day	Nasogastric tube drainage for 3 days
	Patients had oral glucose on the second postoperative day	
	"Patients had oral milk catheter for only one day "	"Patients had oral milk catheter for 5 days "

Table1. Fast-Track Surgery Group and Conventional Group Protocol

Clinical Measurements

Hospital stay

The hospital stay is defined as time spent in the hospital from the day of admission to the day of discharge.

Postoperative bowel function recovery time

The postoperative bowel function recovery time is defined as the first postoperative anal exhaust time.

Hospitalization expense

The hospitalization expense is defined as the total expense in the hospital from the day of admission to the day of discharge.

Immunogical Measurements

C-Reactive protein

Plasma CRP levels were measured by immunoturbidimetric method, using the BM/Hitachi 705 (Boehringer, Mannheim, Germany).

Interleukin-6

Interleukin-6 concentrations in serum were measured using commercially available enzyme-linked immunosorbent assay kits (Pelikine compact human ELISA kits; Sanquin, Amsterdam, The Netherlands).

Tumor necrosis factor-α

Tumor necrosis factor-α were measured using an enzyme-linked immunosassay kit (Life Company, Boston, USA) according to manufacturer's instructions.

Statistical Analysis

Numerical variables are expressed as mean ± standard deviation or median (quartile range) [M (Q)]. Categorical variables were expressed by a constituent ratio or rate. Differences between the two groups were tested using a two-tailed Student's t test for normally distributed data and a Mann–Whitney U test for non-continuous variables. The chi-square test and Fisher's exact test were used to compare discrete variables. The level of significance was set at $P<0.05$. Data analysis was undertaken with SPSS® version 22.0 (SPSS, Chicago, IL, USA).

Results

Baseline Demographics and Clinical Characteristics

Table 2 shows the clinical characteristics of enrolled patients. There were no significant differences in age, sex, height, weight and BMI between the two groups ($P>0.05$).

Clinical Outcomes

Recovery of bowel movement

The recovery of bowel movement was faster in the fast-track surgery group (30±9 h) than the control group (48±8h); ($P<0.05$).

Hospital stay

The hospital stay of fast-track group (10±2 d) was significantly less than traditional group (14±3d); ($P<0.05$).

Hospital expense

The hospital expense of fast-track group (31028±2365 RMB) was significantly less than traditional group (45637±3126 RMB); ($P<0.01$).

Immunogical outcomes

Levels of serum TNF-α, IL-6, and CRP were closely associated with the surgical stress response and were used as parameters for extent of inflamed and damaged tissues. In the 24 and 72 hours after surgery, the mean serum levels of TNF-α, IL-6, and CRP in the FTS group were significantly lower than those in the conventional surgery group (all $P<0.01$; Table 3).

	Fast-track	Conventional	P value
Age (months)	12.6±9.6	11.6±8.8	0.46
Gender (M/F)	22/21	19/24	0.34
Height (cm)	86.2±6.3	80.8±7.0	0.45
Weight (kg)	10.2±1.1	9.6±1.2	0.39
BMI (kg/m^2)	23.1±2.1	23.3±1.9	0.31

Table 2. Baseline demographics and clinical characteristics .

Variable	Fast-track Surgery	Conventional	p value
TNF-α (fmol/L)			
Preoperative	97.3±5.8	95.8±6.2	0.61
Postoperative 24 h	113.6±5.8	143.2±7.1	<0.01
Postoperative 72 h	132.5±7.6	171.9±10.4	<0.01
IL-6 (pg/mL)			
Preoperative	10.2±1.7	10.4±1.5	0.58
Postoperative 24 h	11.8±2.3	15.7±3.1	<0.01
Postoperative 72 h	12.7±2.8	19.6±3.6	<0.01
CRP (mg/L)			
Preoperative	2.1±0.3	2.2±0.4	0.48
Postoperative 24 h	36.1±3.9	61.5±4.7	<0.01
Postoperative 72 h	53.8±6.3	89.2±7.6	<0.01

Table 3. The comparison of Immunogical outcomes in the FTS and conventional group

Discussion

The aim of our study was to evaluate the safety and efficacy of FTS in the treatment of HD. We found FTS was feasible for the treatment of HD. Compared with the conventional group; FTS had significantly faster recovery of bowel movement and significantly shorter hospital stay. It was encouraging and promising that the medical cost in the FTS group was significantly less than that in the conventional surgery group.

Furthermore, to explore the underlying immunological mechanism of fast-track surgery, we found inflammatory reactions, based on CRP, IL-6, and TNF-α were less intense following FTS group.

In our study, we supported the viewpoint of early removal of the nasogastric tube. Surgeons conventionally leave the nasogastric tube in situ after surgery. However, there is no evidence supporting its use because it may be associated with increased complications as well as patient discomfort [16]. Recent studies have demonstrated that a gastric tube is not essential, and that it may induce pulmonary complications after colonic surgery [17-19]. We believe that early removal of the nasogastric tube will result in early feeding, which has multiple advantages. Early feeding has been confirmed to maintain absorptive integrity of the bowel, to increase collagen content in the anastomosis, to allow positive nitrogen balance with reduction of insulin resistance, to favor wound healing, and to reduce risk of sepsis [20].

Our results also indicated that FTS without routine surgical drainage in combination with removing urinary catheter as early as possible after surgery enabled patients to have better physical movement without an increase in the risk of postoperative complications compared with conventional surgery. Increasing evidence supports the viewpoint that surgical drainage does not reduce the prevalence of complications, but does increase intra-abdominal fluid collection, infection, and risk of fistulas, leading to a delay in discharge from the hospital [21,22].

During the days before surgery, preoperative nutrition is beneficial to increase surgery tolerance and energy reserve. Preoperative fasting does not confer any benefit or advantage for surgical patients. Oral intake shortly before surgery did not increase anesthesia risk [23]. In con¬trast, consumption of an appropriate volume of water, minerals and carbohydrates offers beneficial effects against surgical trauma in terms of metabolic status, cardiac function and psychosomatic status.

Fast-track surgery evolved as a coordinated effort, combining modern concepts with advanced minimally invasive surgical techniques, and newer anaesthetic and analgesic methods .With the development of Hirschsprung's radical surgery, the transanal pull-through has become a milestone [24]. In our fast-track surgery group, we applied transanal pull-through as standard radical procedure. Meanwhile, sacral anesthesia was innovated in combination with transanal pull-through procedure.

In the FTS group, patients benefited from the use of epidural analgesia, postoperative analgesics, minimal invasive surgery, and early oral feeding which allowed patients to get out of bed faster after surgery. Ambulation is the key for accelerating the recovery period for patients because it induces a stimulant for return of normal gastrointestinal function [25]. Early ambulation is recognized as a critical step in FTS because it promotes patient recovery by improving the supply of oxygen to tissues, preserving muscle mass and function, as well as preventing problems with pulmonary function and embolic complications [26].

The correlation of clinical findings with the immune parameters indicates that the beneficial clinical data reported here are associated with better-preserved immunity. Several cytokines such as IL-6, TNF-α, and CRP have been demonstrated to be involved in the response to surgical stress and are therefore useful serum markers for evaluating the severity of surgery-induced stress [27-30]. The postoperative profile of IL-6, TNF-α and CRP in patients with HD supported the notion that FTS generated significantly less stress in patients. Compared with patients in the conventional surgery group, patients in the FTS group experienced milder stress, less damage to immune function, faster recovery and a better quality of life.

Conclusion

Fast-track surgery in the treatment of HD was safe and effective. FTS could improve the bowel movement recovery, shorten hospital stay and reduce hospital expense. Moreover, FTS could attenuate postoperative stress reactions and accelerate rehabilitation for patients with HD.

Acknowledgements

This study was funded by National Natural Science Foundation of China.

(PI:Zhi Li,No:81400579;PI:Yongjun Chen,No:81372239 and 81572783)

Author Contribution

Dr. Zhi Li designed and supervised this clinical trial. Zhi Li and Honglin Li wrote this manuscript. Honglin Li, Yongjun Chen, Zuxuan Wu, Hongyao Yuan, Xiaofeng Xiong, Xiaoyi Sun, Jiexiong Feng and Zhi Li coordinately conducted this clinical trial.

References

1. Wilmore DW, Kehlet H. Management of patients in fast track surgery. BMJ. 2001;322(7284):473-476.
2. Veenhof AA, Vlug MS, van der Pas MH, etal. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Ann Surg. 2012 ;255(2):216-221.
3. Grewal H, Sweat J, Vazquez WD. Laparoscopic appendectomy in children can be done as fast-track or same day surgery. JSLS. 2004;8:151-154.
4. Serour F, Witzling M, Gorenstein A. Is laparoscopic appendectomy in children associated with uncommon postoperative complication? Surg Endosc. 2005;19:919-922.
5. Vegunta RK, Ali A, Wallace LJ, et al. Laparoscopic appendectomy: technically feasible and safe in all stages of acute appendicitis. Am Surg.2004;70:198- 201.
6. Mohamed M, Hollins G, Eissa M. Experience in performing pyelolithotomy and pyeloplasty in children in day-surgery basis. Ped Urol. 2004;64:1220-1222.
7. Mulholland TL, Kropp BP, Wong C. Laparoscopic renal surgery in infants 10 kg or less. J Endourol. 2005;19:397- 400.
8. Ramesh IP, Verghese ST, Hannalah RS, et al. Fast-tracking children after ambulatory surgery. Anesth Analg.2001;92:122-918.
9. Vricella LA, Dearani JA, Gundry SR, et al. Ultra fast- track in elective congenital cardiac surgery. Ann Thorac Surg. 2000;69:865-871.
10. Kehlet H, Wilmore DW. Fast-track surgery. Br J Surg. 2005;92(1):3-4.
11. Kehlet H. Fast-track colorectal surgery. Lancet. 2008;371:791-793.
12. Fujita T. Interpreting postoperative CRP response and HLA-DR depression. Ann Surg. 2015;261(2):e39.
13. Donati M, Brancato G, Grosso G, et al. Immunological reaction and oxidative stress after light or heavy polypropylene mesh implantation in inguinal hernioplasty: A CONSORT-prospective, randomized, clinical trial. Medicine (Baltimore). 2016;95(24):e3791.
14. Melmed GY, Irving PM, Jones J, et al. Appropriateness of testing for anti-tumor necrosis factor agent and antibody concentrations, and interpretation of results. Clin Gastroenterol Hepatol. 2016; 14(9):1302-1309.
15. Ward-Kavanagh LK, Lin WW, Šedý JR, et al. The TNF receptor superfamily in co-stimulating and co-inhibitory responses. Immunity. 2016;44(5):1005-1019.
16. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev. 2005; (1):CD004929.
17. Carrere N, Seulin P, Julio CH, et al. Is nasogastric ornnasojejunal decompression necessary after gastrectomy? A prospective randomized trial. World J Surg 2007;31(1):122-127.
18. Yoo CH, Son BH, Han WK, et al. Nasogastric decompression is not necessary in operations for gastric cancer: prospective randomised trial. Eur J Surg 2002;168(7): 379-383.
19. Cheatham ML, Chapman WC, Key SP, et al. A metaanalysis of selective versus routine nasogastric decompression after elective laparotomy. Ann Surg 1995;221(5): 469-476.
20. Ng WQ, Neill J. Evidence for early oral feeding of patients after elective open colorectal surgery: a literature review. J Clin Nurs. 2006;15(6):696-709.
21. Petrowsky H, Demartines N, Rousson V, et al. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. Ann Surg 2004;240(6):1074-1084.
22. Conlon KC, Labow D, Leung D, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg. 2001;234(4): 487-493.
23. Kaska M, Grosmanová T, Havel E, et al. The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery--a randomized controlled trial. Wien Klin Wochenschr. 2010;122(1-2):23-30.
24. Oh C, Lee S, Lee SK, et al. Difference of postoperative stool frequency in hirschsprung disease according to anastomosis level in a single-stage, laparoscopy-assisted transanal endorectal pull-through procedure. Medicine (Baltimore). 2016;95(14):e3092
25. Vather R, Bissett I. Management of prolonged post-operative ileus: evidence-based recommendations. ANZ J Surg. 2013;83(5):319-324.
26. Hole J, Hirsch M, Ball E, et al. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. Lancet. 2015;386(10004):1659-1671.
27. Raeburn CD, Sheppard F, Barsness KA, et al. Cytokines for surgeons. Am J Surg 2002;183(3): 268-273.
28. Ananth AA, Tai LH, Lansdell C, et al. Surgical stress abrogates pre-existing protective T cell mediated anti-tumor immunity leading to postoperative cancer recurrence. PLoS One. 2016;11(5):e0155947.
29. Zhou L, Li Y, Li X, et al. Propranolol attenuates surgical stress-induced elevation of the regulatory T cell response in patients undergoing radical mastectomy. J Immunol. 2016;196(8):3460-3469.
30. Tohme S, Yazdani HO, Al-Khafaji AB, et al. Neutrophil Extracellular Traps Promote the Development and Progression of Liver Metastases after Surgical Stress. Cancer Res. 2016;76(6):1367-1380.