RESEARCH

Impact of perioperative enteral synbiotics in hepatic and pancreatic surgery: design and rationale of a single blind placebo controlled prospective randomised control trial

Ashwin Rammohan, Jeswanth Sathyanesan, Kamalakannan Rajendran, Anbalagan Pitchaimuthu, Senthil Kumar Perumal, U P Srinivasan, Ravi Ramasamy, Ravichandran Palaniappan, Manoharan Govindan

Institute of Surgical Gastroenterology & Liver Transplantation, Centre for GI Bleed, Division of HPB diseases, Government Stanley Medical College Hospital, Chennai, India

Correspondence to

Dr Ashwin Rammohan, Institute of Surgical Gastroenterology & Liver Transplantation, Centre for GI Bleed, Division of HPB diseases, Government Stanley Medical College Hospital, Old Jail Road, Chennai 600001, India; ashwinrammohan@gmail.com

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ABSTRACT

Background Prebiotics and probiotics influence all pathogenic mechanisms of bacterial translocation. Used in combination, they are called synbiotics. Postoperative infective complications in patients undergoing hepatic and pancreatic surgery lead to a significant prolongation of hospital stay and increased costs. While synbiotics are considered to have beneficial effects on human health, their clinical value in surgical patients, especially in South Asia remains unclear given a paucity of applicable clinical studies. In this study we aim to assess their clinical usefulness in patients who undergo hepatic and pancreatic surgery.

Methods A prospective monocentric randomised single blind controlled trial is being conducted in patients undergoing major pancreatic resections (Whipple procedure, distal pancreatectomy, Frey procedure) and hepatic resections. Group A received a specific synbiotic composition, 5 days prior and 10 days after the surgery. Group B received a placebo. Primary study end point was the occurrence of postoperative infection during the first 30 days. Secondary outcome measures were mortality, first bowel movement, days in intensive care unit, length of hospital stay, and duration of antibiotic therapy. Side effects of probiotics were evaluated. From previous studies we assumed that perioperative synbiotics reduce the proportion of patients with infectious complications from 50% to 12%, with α of 0.05 and power 80%, the calculated sample size was 35 patients for each group with a dropout rate of 10%.

Conclusions This study is intended at determining the impact of perioperative synbiotic therapy on postoperative infectious complications, morbidity and mortality in patients undergoing major pancreatic and hepatic surgery.

Clinical trial The Clinical Trials Registry of India (CTRI/2013/06/003737).

INTRODUCTION

Postoperative infections occur despite the improvements in surgical techniques, refinements in perioperative care, use of aggressive perioperative antibiotic prophylaxis, potent antibiotics and application of total parenteral nutrition in approximately 30% of patients after abdominal surgery, leading to significant prolongation of hospital stay and increased costs.^{1 2}

The majority of the observed infections are caused by bacteria from the gut, especially *Enterococci* and *Escherichia coli*, which translocate into mesenteric lymph nodes or into the blood. Several conditions before, during or after major pancreatic and hepatic resection facilitate bacterial translocation. These include decreased postoperative intestinal motility, jaundice, use of antibiotics resulting in small bowel bacterial overgrowth, loss of mucosal barrier function caused by malnutrition, manipulation of the bowel, parenteral nutrition, suppression of the immune system caused by blood products and operative trauma.^{3–6}

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Probiotics (living bacteria) are able to influence all pathogenic mechanisms of bacterial translocation: they increase intestinal motility, stabilise the intestinal barrier (feeding of enterocytes, production of ω -3 fatty acids, stimulation of mucus secretion) and enhance the innate immune system (induction of interleukin 10, inhibition of T helper-1 cell generation by dendritic cells, activation of macrophages, stimulation of secretory IgA and neutrophils with reduction of inflammatory cytokines).³ Prebiotics are non-digestible food constituents that selectively alter growth or activity of one or a limited number of bacterial species in the colon in a manner that potentially improves the health of the host. Prebiotics reach the colon untouched and serve as colonic food that will be fermented by probiotics to ω -3 fatty acids and other important nutrients.^{3 6 8} Therefore, prebiotics and probiotics are potentially useful in prevention of bacterial infections. Used in combination, probiotics and prebiotics are called synbiotics. While synbiotic combinations are considered to have beneficial effects on human health, their clinical value in surgical patients remains unclear given a paucity of applicable clinical studies. In this study we assess the clinical usefulness of synbiotics in patients who undergo hepatic and pancreatic resections.

AIM

The objective of the present investigation is to determine the impact of perioperative synbiotic therapy on postoperative infectious complications, mortality, first bowel movement, days in intensive care unit, length of hospital stay and duration of antibiotic therapy in patients after major pancreatic and hepatic surgery.

STUDY DESIGN AND SETTING

It is a two-arm, single blind prospective placebo controlled randomised clinical trial to be conducted at the Institute of Surgical Gastroenterology and Liver Transplantation, Government Stanley Medical College, Chennai, India. The randomisation is stratified according to the primary organ operated (pancreas or liver) with block randomisation for the type of surgery (pancreaticoduodenectomy, distal pancreatectomy, Frey procedure and major liver resection). Randomisation is computer generated using an onsite computer system, with the participant being blinded. The study design is presented in figure 1.

Patients

All patients scheduled for major hepatic and pancreatic surgery are included in the prospective monocentric single-blind randomised control study.

Inclusion criteria

- ▶ Adults between 18 years and 75 years of age in good general status (Karnofsky performance score >80)
- ▶ All major pancreatic resection surgeries (Whipple procedure, distal pancreatectomy, Frey procedure)
- ▶ All hepatic resections

Exclusion criteria

- ▶ Renal insufficiency (creatinine >1.1 mg/dL)
- ▶ Intestinal obstruction
- ▶ Emergency surgery
- ▶ Cerebral disorders with danger of aspiration
- ▶ Contraindications for enteral nutrition.

Figure 1 Study design.

Primary study end point

Primary study end point is the occurrence of post-operative infection during the first 30 days after surgery. The diagnosis of bacterial infection was based on fever ($\geq 38^{\circ}\text{C}$), elevation of C reactive protein, specific clinical symptoms of infection and a positive bacterial culture. Sources/sites of infection included wound infections defined as detection of pus in the wound along with a positive bacterial culture; pneumonia defined as fever, cough, dyspnoea, reduced arterial oxygen, typical pulmonary infiltrate on chest X-ray and a positive culture from sputum or broncho-alveolar lavage; peritonitis/intra-abdominal abscess defined as fever, intra-abdominal pus, positive bacterial cultures from intra-abdominal smears; sepsis defined as fever, low arterial blood pressure, systemic inflammatory response and positive bacterial blood cultures; urinary tract infection defined as dysuria, leukocyturia and a positive urine culture with 10^5 colony forming units/mL.

Secondary study end points

Secondary outcome measures are mortality, first bowel movement, days in intensive care unit, length of hospital stay and duration of antibiotic therapy.

Ethics, informed consent and safety

This study is conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. Approval from the institutional ethics committee has been obtained and all patients give a written informed consent before inclusion in the trial. All the synbiotics used in this study have a long history of use in the pharmaceutical industry. During administration of the study product the patient and the nursing staff are asked to register any potential side effect or adverse event. Criteria to stop the study are withdrawal of patient consent and occurrence of serious adverse events.

Statistical analysis

Statistical analysis will be performed with the SPSS V20.0. To compare specific variables, the extended χ^2 test will be used. For non-parametric analysis of continuous distributed variables, the Mann-Whitney U test and the Kruskal-Wallis test will be used. $p < 0.05$ is considered statistically significant with a power of 80%. The statistical analysis is performed at the Department of Biostatistics and from previous studies and our own data we assume that perioperative synbiotics reduce the incidence of infectious complications from 50% to 12%, with α of 0.05 and power 80%, the calculated sample size was 35 patients for each group with a dropout rate of 10%.

Treatment program

Patients' complete medical history and clinical examination, analysis of laboratory parameters and disease-

specific further examinations are evaluated. Serum albumin and body mass index are measured and calculated to evaluate the nutritional status. All patients are stratified using the classification of the American Society of Anesthesiologists. Patients are then individually randomised using randomisation software to one of the two study groups.

Surgical procedure

All major pancreatic resections (Whipple procedure, distal pancreatectomy, Frey procedure) and hepatic resections are included in the study.

STUDY GROUPS

Group A

Specific synbiotic composition of prebiotics and probiotics (*Streptococcus faecalis* T-110–60 million, *Clostridium butyricum* TO-A–4 million, *Bacillus mesentericus* TO-A–2 million, *Lactobacillus sporogenes*–100 million, Fructo-oligosaccharides) administered three times daily via the feeding tube or orally. The treatment is started 5 days preoperatively and continued during the first 10 days after surgery.

Group B

Identical treatment as group A, with the only difference being that the patients receive only placebo, the contents look identical in both groups. The smell and taste of the study substances are identical too. The persons who know the type of treatment are the nurse and the investigating clinician. The patients are completely blinded to the study randomisation.

REGIMEN OF ANTIBIOTICS AND CATHETERS

All patients receive a single-shot intravenous prophylaxis with Cefazolin (2 g) at induction, following which antibiotics are repeated if the procedure lasts more than 6 h. Antibiotics are then administered only in cases of bacterial infection. If infections occur, patients are initially treated empirically and then following resistance testing of the isolated bacteria. Proton pump inhibitors (Pantoprazole 40 mg) are routinely given daily during the whole study period. During the operation, all patients receive a central line, an intra-abdominal drainage and a urinary catheter. These catheters are removed as soon as possible except in the case of serious complications.

ANALYSED PARAMETERS

Primary study end point is the occurrence of post-operative bacterial infection during the first 30 post-operative days. Therefore, incidence, type of infections and type of isolated bacteria are specifically recorded. Secondary outcome measures are mortality, first bowel movement, length of hospital stay, days in intensive care unit and duration of antibiotic therapy. In addition, side effects of the synbiotics are evaluated. The duration of antibiotic therapy is determined

by counting the number of days on which the patients received antibiotic therapy. The single-shot antibiotic prophylaxis is excluded. Total length of hospital stay is defined as the period between day of operation and discharge. To rule out differences in intraoperative and postoperative risk factors for infections and to avoid a bias, we analyse relevant accompanying diseases, alcohol and nicotine abuse, antibiotic therapy 1 month prior to operation, operating time, and number of transfused units of blood and fresh frozen plasma intraoperatively and postoperatively. Also evaluated are the lengths of stay in the intensive care unit, the first day of bowel movement, and the type and amount of antibiotic treatment. Diarrhoea, constipation, vomiting, abdominal cramps, or distention and other side effects of enteral or parenteral nutrition are monitored daily until discharge. Complications are monitored daily. Samples are taken preoperatively and on postoperative days 1, 5 and 10. The following parameters are studied: complete blood count, renal function tests, electrolytes, liver functions tests and C reactive protein. Body temperature is recorded serially. Bacterial cultures from urine, blood, wound, and intra-abdominal drainages are done in case of suspected infection. The respective specimens are cultivated on agar plates for aerobic and anaerobic bacteria. Differentiation of bacteria is performed by using routine clinical methods. Results of the cultures are reported, but only patients with clinical signs of infection plus positive cultures are treated with antibiotics.

DISCUSSION

Patients undergoing pancreatic resection have multiple risk factors for bacterial translocation and infection leading to bacterial infection rates of up to 61%.^{1 2} Nomura *et al*⁸ showed that probiotics led to significant reductions in infectious complications (23% vs 53%) and median length of hospital stay (19 days vs 24 days) following pancreatic surgery. A double blind randomised study in patients undergoing pylorus-preserving pancreaticoduodenectomy from Berlin concluded that the incidence of nosocomial bacterial infections was significantly lower (12.5% vs 40%), and only mild wound and urinary tract infections occurred in those who were administered perioperative probiotics.⁵ The PROPARTRIA trial conducted in patients with severe pancreatitis showed serious adverse events of synbiotics.⁹ The rate of infectious complications was comparable in both groups (30% vs 28%), but the mortality rate was higher in the synbiotic group (16% vs %). Studies from Japan investigating the impact of synbiotics on the clinical course of extended liver resection have shown a significant reduction in bacterial infections (19% vs 52%).¹⁰ Studies from Europe conducted on patients undergoing colorectal and abdominal surgery have shown equivocal results.^{11–13} Current evidence suggests that synbiotic treatment is promising in

maintaining and repairing the gut microbiota and gut environment, it also significantly reduces septic complications in patients with severe systemic inflammatory response syndrome.⁷ Finally, despite the promising clinical results with the use of these therapies, the mechanisms of action in the gastrointestinal tract remain undefined. Further clinical research is necessary to clarify the effectiveness of such therapies and define the appropriate conditions for use, before widespread application of synbiotics in the perioperative setting.

With its environmental, social, cultural and dietary distinctiveness, it might not be entirely appropriate to extrapolate western data onto the South Asian subset of the population. Furthermore, there are no clinical trials from South-East Asia, and the effectiveness of synbiotics in this population remains to be assessed.^{14 15}

CONCLUSION

In our study, we attempt to bridge a lacuna in literature by determining the impact of perioperative synbiotic therapy on postoperative infectious complications, morbidity and mortality in patients undergoing major pancreatic and hepatic surgery.

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Competing interests None.

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Patient consent Obtained.

Ethics approval Institutional Review Board—Government Stanley Medical College Hospital, Chennai, India.

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Transparency declaration The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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