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Study protocol for the nutritional route in oesophageal resection trial: a single-arm feasibility trial (NUTRIENT trial)

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ABSTRACT

Introduction: The best route of feeding for patients undergoing an oesophagectomy is unclear. Concerns exist that early oral intake would increase the incidence and severity of pneumonia and anastomotic leakage. However, in studies including patients after many other types of gastrointestinal surgery and in animal experiments, early oral intake has been shown to be beneficial and enhance recovery. Therefore, we aim to determine the feasibility of early oral intake after oesophagectomy.

Methods and analysis: This study is a feasibility trial in which 50 consecutive patients will start oral intake directly following oesophagectomy. Primary outcomes will be the frequency and severity of anastomotic leakage and (aspiration) pneumonia. Clinical parameters will be registered prospectively and nutritional requirements and intake will be assessed by a dietician. Surgical complications will be registered.

Ethics and dissemination: Approval for this study has been obtained from the Medical Ethical Committee of the Catharina Hospital Eindhoven and the study has been registered at the Dutch Trial Register, NTR4136. Results will be published and presented at international congresses.

Discussion: We hypothesise that the oral route of feeding is safe and feasible following oesophagectomy, as has been shown previously for other types of gastrointestinal surgery. It is expected that early oral nutrition will result in enhanced recovery. Furthermore, complications related to artificial feeding, such as jejunostomy tube feeding, are believed to be reduced. However, (aspiration) pneumonia and anastomotic leakage are potential risks that are carefully monitored.

Trial registration number: NTR4136.

Strengths and limitations of this study

A strength of this study is the careful monitoring of safety regarding the relevant clinical outcomes pneumonia and anastomotic leakage, for safety of early oral intake after oesophagectomy is a major concern for many surgeons. A limitation is its descriptive single arm design. However, owing to the lack of data, we consider a safety and feasibility trial more appropriate before the start of a randomised controlled trial in which standard of care is compared with early oral nutrition.

BACKGROUND

For many types of gastrointestinal surgery, early oral intake has been shown to be beneficial and to enhance recovery.[1–3] However, for patients undergoing an oesophagectomy, it is unclear what the best route of feeding is.[4] There is concern that early oral intake following oesophagectomy would result in vomiting with subsequent aspiration pneumonia. Furthermore, the sequelae of anastomotic leakage are thought to be more severe if the leaked fluids contain food besides saliva. Although these arguments are widely accepted, there is no clear scientific evidence to support this hypothesis.

On the other hand, early oral intake has been demonstrated to be feasible and can result in faster recovery of bowel function and a shorter hospitalisation after partial or total gastrectomy.[2] Furthermore, a randomised controlled trial in patients after major upper abdominal surgery, including oesophagectomy, demonstrated that early oral intake directly after surgery does not increase morbidity compared to a nil-by-mouth regimen with jejunostomy feeding for the first five postoperative days. However, only few patients undergoing oesophagectomy were included in this trial.[3] Additionally, experimental evidence shows that early enteral feeding above the anastomosis improves anastomotic healing after upper abdominal surgery in rats.[5 6]

Owing to the paucity of evidence on this topic, we designed a feasibility trial to

investigate whether starting oral intake early after oesophagectomy is feasible and safe.

METHODS

Design

This is an exploratory single-arm multicentre trial to determine the feasibility and safety of early oral intake from the first day after oesophagectomy. The trial is approved by the independent ethical committee of the Catharina Hospital in Eindhoven, The Netherlands.

Population

All patients older than 18 years who undergo a minimally invasive oesophagectomy and intrathoracic anastomosis (Ivor Lewis) are eligible for inclusion. Patients are excluded in case of >15% weight loss at the time of surgery, a swallowing disorder, mental retardation or an inability for oral intake. Weight loss >15% at the time of surgery is regarded as an exclusion criterion because it is not expected that these patients will achieve sufficient intake to compensate for their weight loss. Furthermore, patients undergoing conventional open surgery and cervical anastomosis are excluded in order to improve homogeneity. Owing to the paucity of evidence, we designed a descriptive study; therefore, no power calculation has been performed. In this study, 50 patients will be included.

Study outline

The early oral intake regimen will start with clear liquid fluids directly following surgery. On the first postoperative day, a liquid diet is started under the supervision of a dietician. Supplementary nutrition, such as Nutridrink, is given to ensure adequate caloric intake. Adequate caloric intake is defined as >50% of energy needs on the fifth postoperative day. The dietician will calculate the energy needs for each patient using the Harris-Benedict formula with a surplus of 30% for energy expenditure in the postoperative phase. For male patients, the Harris-Benedict formula is 88.362 + (13.397 ´ weight in kg)+(4.799 × height in cm) − (5.677×age in years), and for female patients 447.593+(9.247 × weight in kg) + (3.098 × height in cm)−(4.330×age in years).

After 1 week, if the clinical condition is good and inflammatory mediators decrease, the patient may progress to a solid diet. A good clinical condition is defined as a decreasing C-reactive protein, good mobilisation, being independent of supplementary intravenous fluids and pain being adequately controlled with oral medication.

Oral feeding will be terminated immediately if there is suspicion of anastomotic leakage. Artificial feeding will be started in case of anastomotic leakage, the ileus requiring nasogastric decompression, complications for which the patient requires treatment at the intensive care unit (ICU), or when the caloric intake is <50% of the energy needs on day 5 postoperative.

In case of an indication for artificial feeding, enteral nutrition is preferred. The surgeon is free to surgically place a jejunostomy during the procedure. However, the jejunostomy will be sealed directly after surgery and not be used until the patient meets the criteria for artificial nutrition as mentioned above. In cases where no jejunostomy tube has been placed during surgery, a nasojejunal tube will be inserted via endoscopy by a gastroenterologist. Total parenteral nutrition will be started only in case of chylothorax or other conditions prohibiting enteral nutrition.

Surgical procedures

All patients will undergo a minimally invasive Ivor Lewis oesophagectomy by surgeons experienced in minimally invasive surgery. In all centres, more than 30 oesophagectomies yearly have been performed by two dedicated surgeons over the past 3 years.

The operation is started with a laparoscopic phase, and followed by the thoracoscopic phase in the prone position, as described previously.[7] At the end of the laparoscopic phase, a gastric conduit is created intracorporally with endostaplers. The intrathoracic anastomosis is made at the level of the carina, depending on the height of the tumour. The anastomosis is created with staplers or V-lock sutures in an E-t-S way or S-t-S way. The remaining opening is closed with V-Lock sutures. In all patients, an omental wrap is draped around the anastomosis.

Outcomes

Primary outcomes are the incidence and severity (according to the modified Clavien Dindo classification for surgical complications) of pneumonia and anastomotic leakage.[8] Pneumonia is defined according to the definition of the Utrecht Pneumonia Scoring System.[9] In this system, points are assigned based on temperature, leucocyte count and radiography. Pneumonia is defined as a score of 2 points or more, with at least 1 point assigned based on radiography. Aspiration pneumonia is defined as pneumonia following a clear history of aspiration of material (solid or liquid, vomit, saliva). Cases of silent aspiration leading to pneumonia might be missed. However, by recording the overall pneumonia rate with grading of the severity, we will detect if early oral intake increases the incidence and/or severity of pneumonia in general. In this case, major or minor aspiration might be a cause. Anastomotic leakage is defined as clinical signs of leakage from a drain or radiological signs of anastomotic leakage (contrast leakage, or fluid/air levels surrounding the anastomosis) or signs of anastomotic leakage during endoscopy, re-operation or postmortal investigation. When anastomotic leakage is clinically suspected, a CT scan will be performed. Based on the individual clinical situation, an endoscopic, radiological or surgical intervention will be performed in case anastomotic leakage is present. Adequate drainage is the primary goal.

Secondary outcomes are caloric intake during the postoperative admission; need and amount of artificial nutrition (nasojejunal tube feeding/parenteral nutrition); occurrence of vomiting; placement of a nasogastric tube; length of hospital stay; hospital readmissions within 30 days of discharge; complications classified according to the Clavien–Dindo classification[8]; need for ICU admission and total length of ICU stay; 30-day and 90-day mortalities.

All clinical data will be prospectively registered in an electronic surgical database.

Data and safety monitoring board

An independent data and safety monitoring board (DSMB) will evaluate the progress of the trial and will examine safety variables. Every five patients, individualised patient data will be provided to the DSMB. The members of the DSMB will discuss the consequences of the data presented separately, and the outcome of this meeting will be discussed with the project group. If the DSMB suspects harm, there will be a meeting between the DSMB, the study group and an independent statistician. During this meeting, any potential causal relation between early start of postoperative oral nutrition and harm and necessity for stopping the trial will be discussed.

Statistical analysis

The data analysis will consist of simple descriptive analyses. All analyses will be according to the intention-to-treat approach, incorporating all included patients, regardless of adherence to the study protocol.

Categorical data will be summarised as frequencies. Normally distributed continuous data will be summarised as means with corresponding SDs. Not-normally distributed continuous data will be summarised as medians with the corresponding range.

Dissemination

The results will be presented at relevant national and international congresses, and published in article format. The results will be relevant for current guidelines on postoperative care for patients undergoing oesophagectomy and made known to the developers of these guidelines. However, owing to the explorative nature of this study, it will primarily assess the safety and feasibility of early oral intake and provide directions for further research.

DISCUSSION

The NUTRIENT trial investigates the feasibility of early oral intake after oesophagectomy. The rationale for this trial emerges from fast-track programmes in other types of gastrointestinal surgery showing that there is no clear advantage to withholding enteral nutrition in the direct postoperative phase and that early (oral) feeding may even be beneficial compared with the traditionally applied nil-by-mouth strategy.[1 10 11]

Also, for patients undergoing other upper gastrointestinal surgery, it has been shown that early oral nutrition is just as safe as traditional care, consisting of a delayed oral intake.[3] Although these findings are promising, the patient group was very heterogeneous and included only a few patients undergoing an oesophagectomy. There is one other randomised controlled trial, of which the definitive results are still awaited, that among others included patients undergoing oesophagectomy.[12] Next to these studies, one conference abstract has been published in 2008 on a small prospective study in which patients undergoing oesophagectomy with three-field lymph node dissection started an oral liquid diet on day 2 postoperative.[13] Altogether, this illustrates that data on early oral intake are still scarce and more research is needed.

A general concern regarding the early start of oral intake following an oesophagectomy is safety, especially regarding the sequelae of anastomotic leakage and incidence of pulmonary complications such as aspiration pneumonia.[4] However, there are no data to support these arguments. Studies supporting a delayed oral intake following oesophagectomy are scarce and retrospectively performed. In one study, it was shown that anastomotic leakage rates are lower when a radiographic contrast swallow was omitted postoperatively and patients were fed over a jejunostomy and kept nil-by-mouth for 4 weeks.[14] A more recent study investigated a 'planned delay of oral intake'.[15] However, owing to the retrospective nature of both studies, differences in definitions, selection and timing of oral intake, the results are difficult to interpret.

On the other hand, existing evidence in other types of upper gastrointestinal surgery and animal studies points towards beneficial effects of early oral nutrition.[3 5 6] Since enteral nutrition is preferred postoperatively, a jejunostomy is often placed during surgery to bridge the delayed oral intake.[16] However, a jejunostomy is associated with specific complications, sometimes leading to re-laparotomy and even death.[17]

Another cause for concern is an insufficient caloric intake postoperatively. While this can be expected for some patients, for example, those who will develop anastomotic leakage, adequate caloric intake can be secured by endoscopic placement of a nasojejunal tube in these patients.[18]

CONCLUSION

This trial investigates whether early oral intake after minimally invasive oesophagectomy is safe and possible. Owing to the paucity of evidence, this will be a feasibility trial in 50 patients using anastomotic leakage and pulmonary complications as primary endpoints.

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Competing interests None.

Ethics approval Medical Ethical Commitee of the Catharina Hospital Eindhoven.

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