SANICS II trial

Stimulation of the autonomic nervous system in colorectal surgery by perioperative nutrition

A multicenter prospective double blinded controlled randomized controlled trial

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1. SUMMARY

Rationale: Postoperative ileus and anastomotic leakage are complications associated with short-term morbidity and mortality following colorectal surgery. Based on experimental studies, we hypothesize that enriched enteral nutrition shortly before, during and early after colorectal surgery reduces inflammation by stimulation of the autonomic nervous system and thereby postoperative ileus (POI) and anastomotic leakage.

Objective: The main objective is to investigate the effects of perioperative nutrition on postoperative ileus and anastomotic leakage in patients undergoing colorectal surgery.

Study design: A prospective randomized double blinded controlled trial

Study population: Patients undergoing segmental colon/ rectum resection with a primary anastomosis for colorectal cancer >18 years.

Intervention: Perioperative nutrition via a nasojejunal tube.

Main study parameters: Main clinical outcome parameters are postoperative ileus and anastomotic leakage. Risk of aspiration pneumonia is closely monitored. Before intubation, gastric volumes are measured and the stomach is emptied. The inflammatory response will be quantified by standard assays including Enzyme Linked Immunosorbent Assay (ELISA) and Polymerase Chain Reaction (PCR). Mediators important in the pathogenesis of POI will also be measured in peritoneal lavage fluid. Clinical parameters are prospectively registered in a database and complications are classified using the Clavien-Dindo classification of surgical complications. Other parameters include intestinal barrier integrity and local inflammation in the intestine (measured by PCR and immunohistochemistry). Long-term outcome parameters such as local recurrence, overall and cancer-specific survival will also be registered.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

All patients will receive a selfmigrating nasojejunal tube (Flocare Bengmark) one day before surgery. The position of the tube is checked via X-ray the same day. Via a specially designed blinded setup (produced by ECM bv, Gemert) patients in the intervention group receive enriched enteral nutrition in low amounts before, during and directly after surgery until oral intake is started. Patients in the control group do not receive nutrition and get a standard preoperative fast until standard oral intake is commenced.

Blood samples will be collected at several predefined moments in relation to the moment of incision. Furthermore, gastric emptying will be assessed via ultrasound before and following a standard meal at day 2 postoperatively. This intervention may benefit the patient by reducing postoperative complications and enhancement of recovery.

Peritoneal lavage is performed at the start of surgery and at the end of surgery. Also gastric content is measured during surgery. It is expected that these procedures will be no burden for the patient.

1. INTRODUCTION AND RATIONALE

Postoperative ileus and anastomotic leakage are important clinical determinants of short-term morbidity and mortality following colorectal surgery. Importantly, anastomotic leakage is also a risk factor for local recurrence of colorectal cancer and has a significant impact on disease-free and overall survival.[1] It is therefore believed that improving postoperative outcome following colorectal surgery will also improve long-term oncological outcomes regarding overall survival and tumour recurrence.[2, 3]

Postoperative ileus (POI) is a common complication after colorectal surgery that causes discomfort for the patient but also leads to a prolonged hospital length of stay and increasing health care costs. Although the underlying mechanism has been studied extensively in animal experiments, targeted therapeutical strategies are lacking in a clinical setting and only supportive arrangements are taken to optimize the patient's condition. For POI it is believed that formation of an inflammatory infiltrate in the muscular layers of the intestine following bowel manipulation during surgery leads to a decreased gastrointestinal motility.[5] In recent years our group has demonstrated in experimental models that administration of enteral nutrition modulates the inflammatory response via the autonomic nervous system by release of cholecystokinin (CCK).[7-9] Composition of the enteral nutrition and timing of administration are both essential for the magnitude of effect.[10] For the most optimal effect, nutrition is given with a higher fraction of lipids and protein and is administered just before, during and directly after the inciting event. In this way, the inflammatory response is optimally dampened via release of CCK. In an experimental study has been shown that such a lipid-enriched enteral nutrition reduces systemic inflammation and postoperative ileus in a CCK-dependent manner when given just before and directly after bowel manipulation.[11]

Next, we performed a study in healthy volunteers in which the effect of continuous low volume enteral nutrition was investigated on inflammatory parameters in a human endotoxemia model.[12] In this study was shown that lipid enriched nutrition reduced the inflammatory response upon endotoxemia in man.

Also in a clinical setting we have shown that enteral nutrition reduces inflammation and POI. In a randomized controlled trial our group has shown that enteral nutrition early after colorectal surgery reduced POI. Furthermore, in a model of sham-feeding using chewing gum was shown that inflammation and POI were reduced following colorectal surgery (vd Heijkant et al, accepted in The British Journal of Surgery).

Interestingly, both clinical studies with sham feeding and early enteral nutrition revealed a yet unaccountable effect on anastomotic leakage. Evidence on the relation between POI and anastomotic leakage is scarce but has great impact. Early inhibition of the inflammatory response may play a role since release of proinflammatory cytokines such as TNF-α modulates intestinal epithelial function and is an inhibitory factor in the wound healing process of intestinal anastomoses.[6] Therefore, it seems that an early intervention with enteral nutrition shortly before, during and early after colorectal surgery may reduce inflammation and reduce important determinants in postoperative morbidity as POI and anastomotic leakage. In the current study we plan to investigate the effectiveness of perioperative nutrition compared with standard of care (nil-per-mouth) in a large-scale trial in patients undergoing colorectal surgery.

2. OBJECTIVE

2.1 Primary objective

To investigate the effect of perioperative nutrition on postoperative ileus and anastomotic leakage in patients undergoing colorectal surgery with primary anastomosis compared with standard care.

2.2 Secondary objectives

To investigate the effect of preoperative nutrition in colorectal surgery on:

- Aspiration pneumonia
- Gastric volumes preoperatively
- Length of functional recovery
- The pro- and anti-inflammatory response both locally, systemically and in peritoneal lavage fluid
- Damage to the intestinal barrier (I-FABP)
- Need for additional surgical, radiological or endoscopic interventions
- Other complications requiring treatment (i.e. urinary tract infection)
- Need for ICU admission and total length of ICU stay
- Cost-effectiveness ratios

3. STUDY DESIGN

A prospective randomized double blinded controlled trial performed at the Catharina Hospital Eindhoven. We start the trial in one centre, and continue the trial in multicentre setting. Participating centres can be found in Appendix B. It is expected that patients will be included over a period of 3 years. At our hospital it was shown in previous studies that at least 75-100

patients undergoing colorectal surgery each year can be included. Most included patients will have colorectal cancer. Due to the nationwide screening program for colon cancer, it is expected that the amount of colorectal operations will further increase. In the experimental group patients receive enriched enteral nutrition. In the control group patients receive standard of care (enhanced recovery after surgery protocol).

4. STUDY POPULATION

4.1 population (base)

Patients undergoing segmental colon resection with primary anastomosis.

4.2 inclusion criteria

- patients that undergo elective surgical resection with primary anastomosis.
- written informed consent
- age >18 years

4.3 exclusion criteria

- use of medication that disrupts acetylcholine metabolism
- steroid use
- previous gastric or oesophageal resection
- peritoneal metastases found during surgery
- pre-existent or creation of an ileostomy

4.4 Definitions

Anastomotic leakage is defined as clinical and radiological signs of anastomotic leakage, or confirmed by re-operation or occurrence of an enterocutaneous fistula. Postoperative ileus will be assessed as time to first flatus and defaecation and by measurements of gastrointestinal transit times via ultrasonography (using antrum measurements). Aspiration pneumonia is defined as inflammation in the lungs following aspiration of material (solid or liquid, vomit, saliva).

4.5 Sample size calculation

Patients will be recruited at the outpatient clinic of the Catharina Hospital Eindhoven. Reduction of anastomotic leakage and postoperative ileus are primary outcome parameters for the sample size calculation. Anastomotic leakage is the most detrimental complication

following colorectal surgery associated with high hospital costs and also with effects on long-term general and cancer-specific outcome. We have performed two clinical studies in colorectal surgery patients that can be used as basis for the power calculation. In one study in which we compared very early enteral nutrition with very early parenteral nutrition, we observed a reduction of anastomotic leakage from 12.9% in the parenteral group to 1.6% in the enteral group. However, this effect may be confounded by the potential detrimental effect of parenteral nutrition. Early postoperative ileus reduced in this study from 35% in the parenteral group to 16% in the enterally fed patients.

In a second study, the effect of sham-feeding via chewing gum on postoperative ileus was compared with controls. In this study postoperative ileus was reduced from 47% in the controls to 27% in the intervention group. The effect on anastomotic leakage was also apparent and leak-rates reduced from 13% in the placebo group to 3% in the intervention group

Based on these previous results a power calculation can be performed. For postoperative ileus a sample size of at least 91 patients per group is needed based on a power of 0.8 and an alpha of 0.05. For anastomotic leakage a reduction of anastomotic leakage of at least 75% was observed in the previous clinical studies. Using a power of 0.8 and a drop-out percentage of 5% a total of 140 patients are needed per group. Since perioperative nutrition is a new concept, an interim analysis is performed after inclusion of 40 patients in which feasibility and safety of preoperative nutrition are assessed. All analyses will be done according to the intention-to-treat approach in which all randomised patients are included, regardless of adherence to study protocol. Occurrences of the primary and secondary endpoints are compared between the treatment groups. Results are presented as risk ratios with corresponding 95% confidence intervals. A two-tailed $P < 0.05$ is considered statistically significant.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The composition of the nutrition we will use is based on previous experimental findings and has already been tested in a human volunteer study (NCT00468507) showing that this nutrition is well-tolerated in healthy individuals. The lipid- and protein-rich nutrition contains 44 energy percent (en%) fat, 25en% protein, and 31en% carbohydrates. The protein fraction consists of intact casein, whey protein, and soy protein hydrolysate. The lipid fraction of the

feeding contains less than 5 weight percent omega-3 fatty acids. The nutrition provides 1 kcal/ml. The specific constituents of the feeding compositions are provided as Supplement.

6. METHODS

6.1 Primary endpoint

- Postoperative ileus

6.2 Secondary endpoints

- Anastomotic leakage
- Aspiration pneumonia
- Gastric volumes preoperatively
- Length of functional recovery
- The local and systemic inflammatory response
- Surgical complications
- Length of stay
- Intestinal barrier function and local inflammation in the gut
- Need for additional surgical, radiological or endoscopic interventions
- Need for ICU admission and total length of ICU stay
- Quality of life (EQ-5D-5L and EORTC-QLQ-C30 at baseline, after 3 and 6 months)
- Cost-effectiveness ratios (iMCQ and iPCQ at baseline, after 3 and 6 months)
- Composition of faecal microbiome

6.3 Randomisation, blinding and treatment allocation

After obtaining written informed consent patients will be randomly assigned to one of two groups by randomization software (TENALEA Clinical Trial Data Management System). The randomization list was generated by this computerized program using random blocks with maximum block size 6, stratified by operation location (colon or rectum) and operation type (laparoscopic or open). Blinded, study-specific enteral feeding systems are prepared and coded according to this list. A corresponding randomization website will be used that generates the sequential randomization number corresponding to the stratified randomization list upon randomization of a patient. All patients will receive a selfmigrating nasojejunal tube (Flocare Bengmark) one day before surgery. The position of the nasojejunal tube is controlled by abdominal X-ray at the day before surgery. Enriched enteral nutrition (Danone research™) is lead through a programmed Flocare enteral feeding pump. The pump is connected to an opaque branched enteral feeding system (produced by ECM bv, Gemert, the Netherlands) that is connected both to the nasojejunal tube and to a sealed container.

Three hours before surgery the pump is started to administer nutrition in standardized amounts.
Patients are either allocated to the experimental group, in which the blinded branched enteral feeding system leads the enteral nutrition via the nasojenunal tube to the patient. Via this route, the patients in the experimental group will receive the enteral nutrition just before, during and directly after surgery.
In patients allocated to the control group, the blinded branched enteral feeding system leads the enteral nutrition to the container. Consequently, when the feeding pump starts just before surgery, patients in the control group do not receive the nutrition. In both groups, the pump with enteral nutrition is stopped 6 hours after surgery and normal intake is resumed. The used enteral feeding systems are stored by an independent person, to create a checkpoint whether allocation to intervention and control group happened correctly.

The study is blinded for the patient, the surgeon and nursing staff. A protocol explaining the study design and blinding is attached (Appendix A)

6.4 Study procedures

Blood samples will be collected at several predefined moments in relation to the moment of incision. Based on previous clinical trials in which we have measured the inflammatory response, these time points will be at 4h, 24h and 48h after surgery. Tissue samples from the resected colorectal segment are collected during the surgical procedure for immunohistochemistry, Western Blot and PCR analysis. When collected, all samples are stored at -80ºC until further analysis. The inflammatory response is measured by analysing the blood plasma and tissue samples for inflammatory mediators (amongst which TNF-alpha and interleukins such as IL-6 and IL-8). This will be done for a large part using commercially available enzyme linked immune assays (ELISA) and by PCR. Also, the inflammatory response and tissue damage parameters will be monitored in peritoneal lavage fluid. For this, 500cc saline will be installed just after opening of the abdomen and at the end of surgery.
Intestinal tissue damage is measured by analysis of several markers for intestinal damage in blood and tissue samples such as Intestinal Fatty acid Binding Protein (I-FABP). Patient characteristics and clinical parameters are registered in an electronic database. All surgical complications are classified using the Clavien-Dindo classification.[14]
Postoperative ileus will be measured clinically in a patient diary (Supplement) based on parameters such as time to first flatus and first defecation, which are the most suitable according to the available literature. Furthermore, gastric motility will be assessed by ultrasound of the gastric antrum just before and following a standardized meal after 15 minutes and 90 minutes as previously performed (trial M11-1102, CCMO NL25588.096.08).

Previous studies have shown that antrum measurements are representative for determining gastric emptying and thereby gastric motility.[15] This ultrasound measurement will be performed by a specifically trained M.D.

All results of these measurements are registered in an electronic database. Patients are discharged according to known criteria as in ERAS/ fast-track surgery.

Quality of life is measured via a checklist (EQ-5D-5L and EORTC QLQ C-30) for cancer patients pre- and postoperatively. Long-term outcome parameters such as local recurrence, overall and cancer-specific survival will be registered in a database. Healthcare costs, costs to patients and family are measured at the individual level using data from registration systems of the hospitals and patient questionnaires (including adapted version of the iMTA Medical Consumption Questionnaire (iMCQ) and the iMTA Productivity Cost Questionnaire (iPCQ)).

Preoperatively and on the fourth postoperative day, a total of two fecal samples will be collected. Using the E-Nose, composition of the luminal microbiome will be determined.

6.5 Withdrawal of individual subjects

Subject can leave the study at any time for any reason if the wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7. NUTRITION

7.1 Perioperative enteral nutrition

Perioperative administration of enteral nutrition is a new concept. Restriction of food and fluid intake prior to general anaesthesia has long been applied as a method to reduce the risk of regurgitation of gastric contents. Increasing evidence has been build over the last years that this insight may be out of date and not evidence-based. A Cochrane review showed that it was safe to apply a shortened fluid fast (of 2 hours before surgery) and that such a regimen did not results in an increased risk of aspiration, regurgitation or related morbidity compared with the standard 'nil by mouth from midnight' fasting policy.[16] Permitting patients to drink water preoperatively even resulted in significantly lower gastric volumes. Since perioperative nutrition is a new concept the risk of aspiration pneumonia needs to be monitored closely. For aspiration pneumonia gastric volume and acidity are important. Emergency patients with larger initial gastric volumes are more susceptible for pneumonia. [17]

In this trial nutrition will be administered postpylorically thereby reducing gastric volumes. All patients will receive a selfmigrating nasojejunal tube (Flocare Bengmark) one day before

surgery at the ward. The position of the nasojejunal tube will be controlled by X-ray at the night before surgery. Enteral nutrition will be administered postpylorically in low amounts.
The lipid rich nutrition provides 1 kcal/ml. The rate of infusion will be determined according to the re-evaluated Harris and Benedict equation of Roza and Shizgal[18]. In this way a rate of 1,5 ml/ minute is generally infused.
The nutrition is administered during a timeframe of 3 hours before, until 6 hours after surgery. Preoperatively, patients receive standard of care with a fast for solid (oral) food of 6 hours and a (oral) fluid fast for 2 hours before administration of the nutrition by the nasojejunal tube. To minimize the risk of aspiration pneumonia the stomach will be emptied by a gastric tube before start of surgery. In a human volunteer study the nutrition was well tolerated and did not lead to unwanted side-effects[12]. Gastric volumes will be measured when the stomach is emptied, before start of surgery at the operating room. Based on the above, the risk of administering perioperative nutrition is minimized by given the nutrition postpylorically, in a low volume and assuring an empty stomach before intubation.

8. PATIENT SAFETY, DATA MONITORING

This prospective randomized clinical trial will be conducted according to the rules of Good Clinical Practice (GCP). An independent data safety monitoring board will be appointed by the investigators that will evaluate all complications and monitor patient safety. Specifically, the aspect of safety of perioperative administration of enteral nutrition will be closely monitored. The clinical trial will be conducted at the Catharina Hospital in Eindhoven.

8.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon

appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Infectious complications and serious complications as a result of the operation that lead to prolongation of the patients' stay in the hospital will be registered as a SAE

The investigator will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

8.3 Annual safety report

The sponsor/investigator will submit a safety report to the METC once a year. This report consists of a list of all suspected serious adverse reactions and a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.5 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. SAE's need to be reported to the principal investigator within 24 hours, some SAE's will be specified such as: re-intervention, respiratory failure, aspiration pneumonia, myocardial infarction, transfer to the ICU for any reason. Per 10 patients, individualized patient data will be presented to the DSMB. After full explanation of the data presented, the members of the DSMB discuss the consequences of the data presented separately. Besides the assessment of SAE's and AE's a safety analysis will be made after inclusion of 40 patients. In this analysis there is a special focus on gastric

volumes which will be compared as well as incidence of aspiration pneumonia. Adverse events will be listed and discussed with the DSMB. The outcome of the meeting of the DSMB will be discussed with the research group. The outcome will also be sent to the Medical Ethics Committee. All possible adverse events will be reported to the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek (CCMO)) and the IRB using the online module https://toetsingonline.ccmo.nl.

The DSMB includes:

1. Prof P. Soeters, Emeritus Professor Clinical Nutrition
2. Dr. E. Schoon, Gastroenterologist
3. Dr. A. Roos, Intensive Care Medicine
4. Dr. S. Houterman, Epidemiologist.

8.6 Premature termination of the study

In addition to safeguarding the safety of the patients in the study, the DSMB will check for early proof of efficacy during an interim-analysis for benefit which will be performed halfway the study. If the DSMB suspects harm there will be a meeting between the DSMB, the study group and an independent statistician. During this meeting there should be a discussion about any potential causal relation between early start of postoperative oral nutrition and harm.

9. STATISTICAL ANALYSIS

All analyses will be done according to the intention-to-treat approach in which all randomized patients are included, regardless of adherence to study protocol. Occurrences of the primary and secondary endpoints are compared between the treatment groups. Results are presented as risk ratios with corresponding 95% confidence intervals. A two-tailed $P < 0.05$ is considered statistically significant. To compare the groups the data will be tested for normal distribution and an unpaired T-test will be performed when appropriate, otherwise the Mann-Whitney U or Chi-square tests.

10 ETHICAL CONSIDERATIONS

10.1 Regulation statement

Participation in the current study is on a volunteer basis and will only be possible when informed consent is obtained. Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. The study will be performed in accordance with

the declaration of Helsinki and the Dutch “Wet Medisch-wetenschappelijk Onderzoek met Mensen, WMO” (Medical Research Involving Human Subjects Act).
Patients can withdraw from this research at any time, without reason. Furthermore, patients can stop the study at any time, without consequences for the quality of treatment.

10.2 Recruitment and consent

All patients that meet the inclusion criteria and do not have exclusion criteria will be asked to participate in the study. After full explanation of the study protocol informed consent will be obtained. Informed consent will be obtained from each participating patient in oral and written form prior to randomization. Informed consent will be obtained by a member of the research group.

10.3 Compensation for injury

An insurance policy is signed with an insurance company for all patients in the study. They will be insured for injury or death due to participation in this study during the study period and for four years after termination of this study. A more detailed overview is given in appendix I.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

After obtaining written informed consent patients will be randomly assigned to one of two groups by randomization software (TENALEA Clinical Trial Data Management System). The randomization list was generated by this computerized program using random blocks with maximum block size 6, stratified by operation location (colon or rectum) and operation type (laparoscopic or open). Blinded, study-specific enteral feeding systems are prepared and coded according to this list. A corresponding randomization website will be used that generates the sequential randomization number corresponding to the stratified randomization list upon randomization of a patient.
The obtained results will be handled confidentially and will be accessible and viewed by study personnel, the Ethical commission, the Data Safety monitoring Board, the Health Inspection (Inspectie voor de Gezondheidszorg) and Danone/ Nutricia Research. Data will be coded so anonymity is preserved, also when data are published. The data and/or human material will be kept for 15 years in storage in the Catharina Ziekenhuis

11.2 Monitoring and Quality Assurance

A Data Safety Monitoring board is installed. More information can be found in appendix II (DSMB)

The DSMB includes:

1. Prof P. Soeters, Emeritus Professor Clinical Nutrition
2. Dr. E. Schoon, Gastroenterologist
3. Dr. A. Roos, Intensive Care medicine
4. Dr. S. Houterman, Epidemiologist.

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments (for example typing errors or administrative changes) will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Publication of results

Results will be analyzed and presented in scientific journals. The CCMO Statement Publication policy will be followed.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

The enriched enteral nutrition that is used, has been investigated before in healthy volunteers during endotoxemia.[12] In this study there were no adverse or serious adverse events. Enclosed is the diet composition.

a. Level of knowledge about mechanism of action: The mechanism has been extensively shown in experimental models. A (pre) clinical study in healthy volunteers and a prospective randomized controlled trial in patients undergoing colorectal surgery showed results in line with the found hypothesis.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism. As mentioned before, the enteral nutrition that is used, has been investigated before in healthy volunteers during endotoxemia. [12]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material? Yes

d. Selectivity of the mechanism to target tissue in animals and/or human beings. The found effects in previous studies is specifically targeting the inflammatory response and has shown to affect both anastomotic leakage and postoperative ileus, the two primary outcome parameters.

e. Analysis of potential effect. The nutrition itself is not considered to be harmful. Administration of enteral nutrition during surgery is a new concept. For this reason a data safety monitoring board is installed. There have been no described effects at all. A potential complication is aspiration pneumonia.

f. Pharmacokinetic considerations: *not applicable*

g. Study population. Patients undergoing colorectal surgery with primary anastomosis.

h. Interaction with other products: *not applicable*

i. Predictability of effect. The found effects in animal experiments were on both the inflammatory response and clinical parameters. The effects were consistent in various experimental models and in the clinical studies.

j. Can effects be managed? During surgery, gastric volumes are measured and gastric content is aspirated to minimize risk of aspiration pneumonia.

12.2 Synthesis

The potential risk of this intervention is aspiration pneumonia. Several measures are taken to prevent this potentially increased risk.

1. Gastric content is aspirated; the volume of gastric content has been shown to be related to risk of aspiration pneumonia.
2. Nutrition is given postpylorically
3. A Data Safety Monitoring Board is installed.

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APPENDIX I: INSURANCE

Voor de deelnemers aan dit onderzoek is een verzekering afgesloten. Deze verzekering dekt schade door dood of letsel die het gevolg is van deelname aan het onderzoek, en die zich gedurende de deelname aan het onderzoek openbaart, of binnen vier jaar na beëindiging van de deelname aan het onderzoek. De schade wordt geacht zich te hebben geopenbaard wanneer deze bij de verzekeraar is gemeld.
(In geval van schade kunt u zich direct wenden tot de verzekeraar.)

Centramed:
Onderlinge Waarborgmaatschappij Centramed B.A.
Appelgaarde 4
2272 TK Voorburg

Telefoon 070-301 70 70 – Fax 070-301 70 71

De verzekeraar kan dan vragen naar aanvullende schriftelijke informatie.

De verzekering biedt een maximum dekking van € 450.000 per proefpersoon en € 3.500.000 voor het gehele onderzoek, en € 5.000.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever. De dekking van specifieke schades en kosten is verder tot bepaalde bedragen beperkt. Dit is opgenomen in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Informatie hierover kunt u vinden op de website van de Centrale Commissie Mensgebonden Onderzoek: www.ccmo.nl.

Voor deze verzekering gelden een aantal uitsluitingen. De verzekering dekt niet:
- schade waarvan op grond van de aard van het onderzoek zeker of nagenoeg zeker was dat deze zich zou voordoen;
- schade aan de gezondheid die ook zou zijn ontstaan indien u niet aan het onderzoek had deelgenomen;
- schade die het gevolg is van het niet of niet volledig nakomen van aanwijzingen of instructies;
- schade aan nakomelingen, als gevolg van een nadelige inwerking van het onderzoek op u of uw nakomeling;
- bij onderzoek naar bestaande behandelmethoden: schade die het gevolg is van één van deze behandelmethoden;
- bij onderzoek naar de behandeling van specifieke gezondheidsproblemen: schade die het gevolg is van het niet verbeteren of van het verslechteren van deze gezondheidsproblemen.

Naast de directe schadeverzekering blijven de wettelijke regels omtrent reguliere, medische- en (product) aansprakelijkheid van toepassing.

In geval van schade kunt u ook contact opnemen met Bureau Patiëntenbelangen van het Catharina-ziekenhuis te Eindhoven, bereikbaar via telefoonnummer 040-2398410.

APPENDIX II: DATA AND SAFETY MONITORING BOARD

Roles and responsibilities

The Data Safety and Monitoring Board (DSMB) is an independent group of experts that advises the participating investigators and the Institutional Review Board.
The members of the DSMB serve in an individual way and provide their expertise and recommendations. The primary responsibilities include:

1. Periodically review and evaluate the accumulated study data for participant's safety, the study conduct and progress
2. Make a recommendation to the investigators concerning continuation, modification or termination of the trial.

* The DSMB considers study-specific data as well as relevant background knowledge about the disease or patient population under study.
* The DSMB is responsible to define the processes, including the event triggers that would call for an unscheduled review, stopping guidelines and voting procedures prior to the first data review.
* The DSMB is responsible for maintaining the confidentiality of its internal discussions and activities.
* The DSMB should review each protocol for any major concern prior to implementation.

During the trial, the DSMB should review cumulative study data to evaluate the safety, the study conduct and the scientific validity and integrity of the trial.
It is the responsibility of the DSMB to provide a written report after each review with a recommendation to continue or terminate the study.

Documentation

Each member of the DSMB will receive all documents as provided to the Medical Ethics Committee, including study protocol, ABR-form and patient information.

Membership

The DSMB will consist of at least three members with relevant clinical expertise, clinical trial methodology and biostatistics. Members will be completely independent. Written documentation specifying the absence of any conflict of interest will be obtained. A chairperson will be appointed who will act as the spokesperson

Review and recommendation process

It is the responsibility of the DSMB to:

- review the research protocol for data safety and monitoring
- evaluate the progress of the trial, including periodic assessments of data quality and timelines, participant recruitment, accrual and retention, participant risk versus benefit and other factors that can affect the study outcome.
- Consider factors external tot the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or on the ethical conduct of the trial.
- Protect the safety of the study participants.
- Report on the safety and progress of the trial.
- Make a recommendation to the investigators concerning continuation, modification or termination of the trial.
- Ensure the confidentiality of the trial data and the results of the monitoring.

Meetings and reports

The first meeting of the DSMB will be a face-to-face meeting before initiation of the trial to discuss the protocol and to establish the guidelines to monitor the study. During the course of the trial the DSMB will meet after inclusion of every 20 patients. These meetings may be convened as conference calls, as well as in person. An emergency meeting of the DSMB may be called at any time by the chairperson, the investigators or any other party involved in the trial. Meetings must be attended by all members and the DSMB may invite other parties involved in the trial, when necessary. The investigators will provide the DSMB with an overview / listing of the occurred events.

A formal report from the DSMB chair will be prepared and sent to all members of the DSMB within two weeks after the meeting. Once approved by all members of the DSMB, the report including a written statement (no safety concern/ safety concern) will be sent to the investigators and the Medical Ethics Committee.

Registration of events

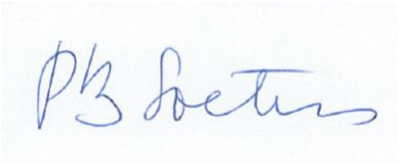
All Adverse Events (AE's) and Serious Adverse Events (SAE's) as mentioned in the protocol will be registered. Any SAE must be reported within 24 hours of knowledge by the investigator. All serious irreversible events will be reported to the DSMB on receipt. All reversible serious adverse events will be reported during the regular meetings.

In case the number of events is unacceptably high, the trial will be suspended and potentially prematurely terminated.

Members

Name *Signature*

P.B. Soeters, MD, PhD (Chair)
Emeritus Professor of Surgery
Maastricht University Medical Center
Maastricht, the Netherlands



A. Roos, MD PhD
Intensive care,
Catharina Hospital Eindhoven, The Netherlands .....

E.J. Schoon, MD PhD
Gastroenterologist,
Catharina Hospital Eindhoven, The Netherlands .....

S. Houterrman, PhD
Epidemiologist
Catharina Hospital Eindhoven, The Netherlands .....

CASE REPORT FORM

Patiënt identificatie nummer: ☐☐☐☐☐☐☐
Randomisatienummer: ☐☐☐☐

Patiëntgegevens

Geb datum: ___ / ___/ 19__
Geslacht: M / V
Lengte: _____ cm Gewicht _____ kg
ASA klasse: 1 / 2 / 3 / 4 / 5
SNAQ score:
MUST score:
Roken: ☐ Nee ☐ Ja
Alcohol: ☐ Nee ☐ Ja
dagelijks / wekelijks / maandelijks
Abdominale chirurgie in de voorgeschiedenis:
☐ Nee ☐ Ja:_____
Bestaand colostoma
☐ Nee ☐ Ja:_____

Huidige situatie

Diabetes ☐ Nee ☐ Ja
insuline ☐ Nee ☐ Ja
Gebruik van psychofarmaca:
☐ Nee ☐ Ja:_____
Dosering:_____
Gebruik van statine:☐ Nee ☐ Ja:_____
Dosering:_____
Gebruik van PPI: ☐ Nee ☐ Ja:_____
Dosering:_____
Gebruik van aspirine:
☐ Nee ☐ Ja:_____
Dosering:_____

Maligniteit: ☐ Nee ☐ Ja
Afstand tumor tot de anus: _____ cm
Neoadjuvante beh: ☐ Nee ☐ Ja
chemo / RT / CRT _____

Preop bloedtransfusie: ☐ Nee ☐ Ja _____
Preop NSAID: ☐ Nee ☐ Ja
Welke_____start ___ / ___/ 20__
Dosering:_____stop ___ / ___ / 20__

Dag van opname: ___ / ___ / 20____; Tijdstip ___:___ uur

Operatie

Datum operatie: ___ /___ /20_____ Operateur: _____
Starttijd operatie: ___:___ uur
Eindtijd operatie: ___:___ uur

Aspiratie bij intubatie/OK: ☐ Nee ☐ Ja

Procedure: ☐ Open ☐ Laparoscopisch
☐ conversie

Type OK: ☐ Hemicolectomie links
☐ Hemicolectomie rechts
☐ Low Anterior resectie
☐ Ileocoecaal resectie
☐ Sigmoidresectie
☐ Rectosigmoidresectie
☐ Transversum resectie
☐ Overig, namelijk _____

iORT ☐ Nee ☐ Ja

Stoma aangelegd: ☐ Nee ☐ Ja
Eindstanding / dubbelloops
Ileostoma / colostoma

Epiduraal: ☐ Nee ☐ Ja
Start hoeveelheid: _____
Tijdens OK hoeveelheid: _____

Noradrenaline: ☐ Nee ☐ Ja hoeveelheid: _____

Maagvolume preoperatief: _____ml

Intra-operatief bloedverlies: _____ml

Vocht toegediend tijdens OK: _____ml

Postoperatief Beloop

Epiduraal: ☐ Nee ☐ Ja
in datum ___ / ___ / 20____
uit datum ___ / ___ / 20____

Postop NSAID ☐ Nee ☐ Ja
Welke_____ start ___ / ___ / 20____
Dosering:_____stop ___ / ___ / 20____
Oraal / iv

Postop Opioid ☐ Nee ☐ Ja
1.Welke_____ start ___ / ___ / 20____
Dosering:_____stop ___ / ___ / 20____
Oraal / iv / im

2.Welke_____ start ___ / ___ / 20____
Dosering:_____stop ___ / ___ / 20____
Oraal / iv / im

Postop antibiotica ☐ Nee ☐ Ja
Welke_____ start ___ / ___ / 20____
Dosering:_____stop ___ / ___ / 20____
Oraal / iv

Maagsonde: ☐ Nee ☐ Ja
in datum ___ / ___ / 20____
uit datum ___ / ___ / 20____

Orale intake, 24 uur tolerantie: datum ___ / ___ / 20____ Tijdstip ___:___ uur
Eerste flatus datum ___ / ___ / 20____ Tijdstip ___:___ uur
Eerste defaecatie datum ___ / ___ / 20____ Tijdstip ___:___ uur

POI: ☐ Nee ☐ Ja
Interval from surgery until both the following criteria are met:
a. Passage of flatus OR stool
b. Tolerance of an oral diet
These events should occur before day four postoperatively.

Prolonged POI: ☐ Nee ☐ Ja
defined if two or more of the following five criteria are met on or after day four postoperatively without prior resolution of “POI” (as described above):
☐ Nausea or vomiting
☐ Inability to tolerate an oral diet over last 24 h
☐ Absence of flatus over last 24 h
☐ Abdominal distension
☐ Radiologic confirmation

Opname IC: ☐ Nee ☐ Ja
in datum ___ / ___ / 20____
uit datum ___ / ___ / 20____
reden IC opname:_____

Postoperatieve complicaties: ☐ Geen complicaties

Naadlekkage ☐ Nee ☐ Ja, datum vaststellen: ___ /___ / 20____
☐ Klinische tekenen AL
☐ Radiologische tekenen AL
☐ Bevestigd bij reoperatie
☐ enterocutane fisteling

Aspiratiepneumonie ☐ Nee ☐ Ja, datum vaststellen: ___ /___ / 20____

Overige postoperatieve complicaties:

	Clavien-Dindo graad:
	Clavien-Dindo graad:
	Clavien-Dindo graad:
	Clavien-Dindo graad:
	Clavien-Dindo graad:

Reoperatie: ☐ Nee ☐ Ja, datum ___ / ___ / 20_____
Reden: _____

Overplaatsing ander ziekenhuis: ☐ Nee ☐ Ja, datum ___ / ___ / 20_____

Functioneel hersteld: datum ___ / ___ / 20____
(ADL zelfstandig, eten, drinken etc)

Dag van ontslag: datum___ / ___ / 20_____ tijd: ____:____uur

Mortaliteit: ☐ Nee ☐ Ja, datum: ___ / ___ / 20_____

Opmerkingen:
_____
_____
_____

Clavien Dindo Classification	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anaesthesia
- IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	Multi-organ dysfunction
Grade V	Death of a patient