A PHASE III, RANDOMISED CONTROLLED TRIAL ASSESSING THE VALUE OF INDOCYANINE GREEN IN THE LEAKAGE RATE OF COLORECTAL ANASTOMOSES

Published: 11-11-2019
Last updated: 19-03-2025

Primary Objective: To compare the difference in clinically relevant AL after 90 days between perfusion assessment with ICG and standard surgery in colorectal anastomoses.Secondary Objective(s): 1. Change in surgical plan will be assessed within each...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON52391

Source
ToetsingOnline

Brief title
AVOID

Condition

- Gastrointestinal therapeutic procedures

Synonym
Anastomotic leakage, intestinal connection leakage

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,Olympus

Intervention

Keyword: Anastomotic leakage, Fluorescence guided surgery, Indocyanine Green

Outcome measures

Primary outcome

The main endpoint is the clinically relevant anastomosis leakage rate at 90 days. AL will be defined according to the proposal of the International Study Group of Rectal Cancer; as a communication between the intra- and extraluminal compartments owing to a defect in of the integrity of the intestinal wall at the level of the anastomosis. According to our study clinical relevance depends on whether or not treatment is started.

Secondary outcome

1. Alteration of surgery

2. Difference in 30 day clinically relevant leakage rate

3. Difference in overall 30 and 90 day complication rate

4. Difference in 30 and 90 day mortality

5. Difference in 30 and 90 day reintervention rate

6. Difference in surgical time

7. Duration of in hospital treatment

Other study parameters

Important baseline criteria will be documented. This includes age, gender, weight, height, BMI, general history, concomitant medication and substance abuse. Surgical information like type of surgery (hemicolectomy left/right,

sigmoid resection, low anterior resection etc.), indication (malignancy,

inflammatory bowel disease, diverticulitis etc. and distance of anastomosis

from anal verge will be collected

Study description

Background summary

AL is still one of the major complications after gastrointestinal surgery accounting for considerable morbidity and mortality. The incidence of AL in colorectal surgery ranges from 2.4 to 11% with the highest reports up to 23.3% in rectal cancer surgery . Besides tumour location and level of anastomosis, risk factors for AL include male gender, high ASA score, comorbidities, smoking, obesity and (neoadjuvant) radiotherapy. Surprisingly, in most reports higher age is not a risk factor for AL and only correlated with the risk of death after AL.

Most risk factors can no longer be changed at the time of the initial surgical diagnosis. Therefore, it is especially important to optimize those few factors that can be influenced. It has been reported that compromised tissue perfusion at the site of the anastomosis significantly increases the risk of AL.
ICG combined with fluorescent near infrared imaging has proven to be a feasible and reproducible application for real-time intraoperative quantification of the tissue perfusion. Moreover, larger cohort studies have shown reduced leakage rates and hospital stay. On the other hand, Kin et al. have shown no benefit of the use of ICG peroperatively in preventing AL.

ICG was introduced by Fox et al in 1957 and is currently used for a variety of diagnostic implications. ICG is invisible for the naked eye and will break up in an aqueous solution, resulting in a reduction of fluorescence intensity of 50% in 2 hours. Very favourable characteristics such as the intravascular intake, the binding with plasma proteins, the rapid and almost exclusive clearance by the liver in bile and the very low toxicity quickly resulted in acceptance and registration of ICG for different diagnostic indications.

Despite these promising results, more evidence is needed. Previous studies were mostly not randomized and did not use clinical relevant leakage as the primary endpoint. Therefore, we propose a randomized controlled trial to identify the real value of ICG for AL rate of colorectal anastomoses.

Study objective

Primary Objective:
To compare the difference in clinically relevant AL after 90 days between perfusion assessment with ICG and standard surgery in colorectal anastomoses.

Secondary Objective(s):
1. Change in surgical plan will be assessed within each patient by comparing ICG surgery with standard of care surgery and assessing if ICG allowed to change the anastomosis level;
2. To compare the difference in clinically relevant AL after 30 days between perfusion assessment with ICG and standard surgery in colorectal anastomoses
3. To compare the difference in complication rates after 30 and 90 days between ICG and standard of care surgery in colorectal surgery;
4. To compare the difference in 30 and 90-day mortality rates between ICG and standard of care surgery in colorectal surgery;
5. To compare the difference in 30 and 90-day reinterventions between ICG and standard of care surgery;
6. To compare the difference in surgical time between ICG and standard of care surgery in colorectal surgery;
7. To compare the difference in duration of inpatient hospital treatment between ICG and standard of care surgery in colorectal surgery.

Study design

This is a prospective, national, multicenter, randomised controlled trial comparing the use of intraoperative ICG, a fluorochrome, with standard surgical care in perfusion assessment of colorectal anastomoses. Patients will be allocated to two groups; Image Guided Bowel Anastomosis group (IGBA) or the Conventional Bowel Anastomosis group (CBA).

A well perfused section will show a higher fluorescent signal then compromised tissue. The surgeon will determine the degree of tissue perfusion and desirably, in case of compromised perfusion, change the level of the anastomosis.

The aim of this trial is to assess the rates of clinically significant anastomotic leaks in the experimental group (using ICG to assess anastomosis perfusion) and the control group, consisting of patients undergoing standard of care surgery. The surgeon has the possibility to switch the fluorescence camera on and off before, during and after the resection.

In previous studies doses 2 to 15 milligram have been used. It has been shown that intravenous administration of ICG is safe and provides successful imaging of the vascularization. In this study a repeated dose of 5 milligram is chosen, with a maximum of 10 milligram per patient.
A patient is considered to have completed the study if she/he has completed all phases of the study including the last scheduled visit shown in the schedule of activities (SOA), i.e. the last visit performed 90 days after surgery.

In the past, different reports used various definitions of AL (ranging from clinical or radiologic evidence with or without the need for a reoperation). Therefore, the International Study Group of Rectal Cancer proposed a uniform definition in which grade A requires no active therapeutic intervention; grade B requires therapeutic intervention, but manageable without re-laparotomy; and grade C can only be handled with a re-laparotomy.

A clinically relevant leak is therefore, in this study, defined as an abscess or fluid collection close to the anastomosis or any leak that requires medical intervention. This includes reoperations, radiological interventions by means of drains and / or administration of antibiotics.

The planned duration of the study is 2 years with a total of 489 patients per arm (978 in the study). The expected start date is March 2019.

Intervention

Patients will be allocated to two groups; Image Guided Bowel Anastomosis group (IGBA) or the Conventional Bowel Anastomosis group (CBA). Patients in the IGBA group will receive a repeated dose of 5 milligram ICG, with a maximum of 15 milligram per patient. Imaging of the anastomosis will take place right after bowel resection and after finalization of the anastomosis. Based on the surgeon*s evaluation he or she may change the level of the anastomosis.
The CBA group will receive no study related intervention. The decision of the level of anastomosis in this group is made according to the current standard of care.
In both groups the anastomosis is created by the surgeon*s preference.

Study burden and risks

The burden for patients is low. No extra visits are necessary for this study. Moreover no extra blood samples, physical examinations, questionnaires or other tests will take place.
The investigational product (ICG) is safely used for over 60 years for different indications (including the one in this study). Only mild allergic reactions have been seen. Patients with known a known allergic reaction to ICG or a substance related to ICG are excluded.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2

Leiden 2333ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Scheduled for laparoscopic or robotic-assisted colorectal resection with primary anastomosis;
2. Patients aged over 18 years old;
3. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions;
4. Signed informed consent prior to any study-mandated procedure;

Exclusion criteria

1. Known allergy or history of adverse reaction to ICG, iodine or iodine dyes;
2. Severe liver and kidney insufficiency;
3. Hyperthyroidism or a benign thyroid tumour;
4. Pregnant or breastfeeding women;
5. Scheduled for palliative surgery or terminal ill
6. Any condition that the investigator considers to be potentially jeopardizing the patients well-being or the study objectives (following a detailed medical history and physical examination;
7. Subject taking phenobarbital, phenylbutazone, primidone, phenytoin, haloperidol, nitrofurantoin, probenecid;

8. Emergency surgery

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-07-2020
Enrollment:	978
Type:	Actual

Ethics review

Approved WMO Date:	11-11-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	31-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28098
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL68858.058.19
Other	NL7502
OMON	NL-OMON28098