RECOVER study: the effect of low- versus normal pressure pneumoperitoneum during laparoscopic colorectal surgery on the early quality of recovery with perioperative care according to the enhanced recovery principles. Substudy: the effectiveness of low pressure pneumoperitoneum during laparoscopic colorectal surgery in preserving innate immune homeostasis by reducing peritoneal mesothelial cell injury.

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Main study: to establish the relationship between the use of low pressure pneumoperitoneum with deep neuromuscular blockade and the early quality of recovery after laparoscopic colorectal surgery with perioperative care according to the enhanced...

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

Summary

ID

NL-OMON48793

Source
ToetsingOnline

Brief title
RECOVER-study

Condition

- Gastrointestinal therapeutic procedures

Synonym
keyhole surgery of the large intestine, Laparoscopic colorectal surgery

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Merck Sharp & Dohme BV

Intervention

Keyword: Deep neuromuscular blockade, Laparoscopy, Low pressure pneumoperitoneum, Postoperative recovery

Outcome measures

Primary outcome

Main study: Quality of recovery score (QoR-40) 24 hours after surgery.

Substudy: leucocyte responsiveness ex-vivo as reflected by IL-6 and IL-10

release upon LPS stimulation.

Secondary outcome

Main study

Questionnaires

* Quality of recovery-40 score on day 3 and 7 after surgery (appendix 1).

* McGill Pain questionnaire (Dutch version) on admission and 3 months after

surgery.

* RAND-36 general health questionnaire on admission and 3 months after surgery

Pain scores

* Pain at rest and pain on movement (NRS 0-10) at 1, 8, 24 and 72 hours after surgery

* Is pain acceptable or unacceptable at 1, 8, 24 and 72 hours after surgery

* Referred shoulder pain yes/no at 1, 8, 24 and 72 hours after surgery

Post-operative nausea and vomiting

* PONV (NRS 0-10) at 1, 8, 24 and 72 hours after surgery

Medication use

* Cumulative opiate use

* Cumulative use of other analgesics and anti-emetics

Clinical parameters

* Length of hospital stay

* Post-operative complications (e.g. pulmonary complications)

* Surgical conditions; the Surgical Rating Scale is used to quantify the quality of the surgical field during the pneumoperitoneum phase

* Time to reach discharge criteria

Substudy:

Immune function

* Peritoneal mesothelial hypoxia as reflected by peritoneal HIF1* mRNA

expression.

* Histological peritoneal mesothelial cell injury and plasma levels of DAMPs

and cytokines.

Study description

Background summary

The laparoscopic approach reduced trauma as compared to open surgery, however, the pressure used to create a PNP with sufficient surgical workspace still leads to significant tissue injury. Prior studies show that the use of low-pressure pneumoperitoneum (PNP) during laparoscopic surgery reduced postoperative pain scores, cumulative opioid consumption and improved bowel function recovery. Deep neuromuscular blockade (NMB) as compared to moderate NMB decreases the amount of intra-abdominal pressure required to achieve similar surgical conditions and enables the use of low-pressure PNP without compromising the quality of the surgical field and patient safety. Therefore, the use of deep NMB with low-pressure PNP could be a significant addition to the conventional Enhanced Recovery After Surgery (ERAS) protocols.
Increased intra-abdominal pressure can cause peritoneal mesothelial cell injury either directly or by compression of the capillary vessels, causing a variable degree of ischemia reperfusion injury. The immune system can identify damage to host cells by recognising Danger-Associated Molecular Patterns (DAMPs) that are released upon cell death in an uncontrolled fashion, such as during surgical trauma. DAMPs elicit an immune response similar to the response to invading pathogens and induce an anti-inflammatory immune response strongly related to postoperative recovery, infectious complications and mortality. Low pressure PNP is associated with lower levels of serum pro- and anti-inflammatory cytokines and better preservation of innate immune function.

Study objective

Main study: to establish the relationship between the use of low pressure pneumoperitoneum with deep neuromuscular blockade and the early quality of recovery after laparoscopic colorectal surgery with perioperative care according to the enhanced recovery principles.

Substudy: To establish the relationship between the use of low pressure pneumoperitoneum with deep neuromuscular blockade and innate immune function

after laparoscopic colorectal surgery.

Study design

A multi-center, blinded, randomized controlled clinical trial.

Intervention

Participants will be randomly assigned in a 1:1 fashion to:
Group A: low pressure PNP (8 mmHg) with deep NMB (PTC 1-2)
Group B (standard treatment, control group): normal pressure PNP (12 mmHg) with moderate NMB (TOF 1-2)

Study burden and risks

Recent studies show that the use of a deep NMB enables safe use of low-pressure PNP(1-3). If visibility is compromised at low pressure, pressure will be increased to ensure no additional risks related to the surgery. A deep NMB is achieved by higher doses of rocuronium that are within normal therapeutical range used in clinical practice, and can safely be used (4). Depth of NMB will be monitored throughout the whole surgery. At the end of surgery, the effects of rocuronium are antagonized by suggamadex to ensure no extended effects. Randomized controlled trails have shown sugammadex can be safely administered (5). Regarding the substudy, peritoneal tissue is directly visible and easily accessible during laparoscopic colorectal surgery. Biopsies are obtained in a standardized manner previously used in other studies (6,7) who report no complications. After biopsy, hemostasis will be established under direct vision and therefore no additional complications are to be expected. Therefore, risks of participating in the study are minimal. Previous studies have shown low-pressure PNP is associated with reduced postoperative pain scores, reduced opioid consumption and improved bowel function (2,3,8,9). This may lead to enhanced recovery. Blood samples will be combined with routine laboratory assessment as much as possible. Assessment of pain, nausea, complications and discharge criteria are part of the normal treatment. The burden for participants is mainly related to the evaluation of the endpoints during the early postoperative phase. Questionnaires will take approximately 10-15 minutes per time-point.

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(3) Kim MH1, Lee KY, Lee KY, Min BS, Yoo YC. Maintaining Optimal Surgical Conditions With Low Insufflation Pressures is Possible With Deep Neuromuscular Blockade During Laparoscopic Colorectal Surgery: A Prospective, Randomized, Double-Blind, Parallel-Group Clinical Trial. Medicine (Baltimore). 2016 Mar;95(9):e2920.
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(5) https://www.medicines.org.uk/emc/medicine/21299/SPC/Bridion+100+mg+ml+solution+for+injection/
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(8) Özdemir-van Brunschot DM, van Laarhoven KC, Scheffer GJ, Wever KE, Warlé MC. What is the evidence for the use of low-pressure pneumoperitoneum? A systematic review. Surg Endosc. 2016 May;30(5):2049-65.
(9) Madsen MV, Istre O, Staehr-Rye AK, Springborg HH, Rosenberg J, Lund J, Gätke MR. Postoperative shoulder pain after laparoscopic hysterectomy with deep neuromuscular blockade and low-pressure pneumoperitoneum: A randomised controlled trial. Eur J Anaesthesiol. 2016 May;33(5):341-7.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Scheduled for laparoscopic colorectal surgery with a primary anastomosis
- Age * 18 years
- Obtained informed consent

Exclusion criteria

- Insufficient control of the Dutch language to read the patient information and to fill out the questionnaires
- Primary colostomy
- Neo-adjuvant chemotherapy (substudy)
- Chronic use of analgesics or psychotropic drugs
- Use of NSAIDs shorter than 5 days before surgery
- Known or suspected allergy to rocuronium of sugammadex
- Neuromuscular disease
- Indication for rapid sequence induction
- Severe liver- or renal disease (creatinine clearance <30ml/min)
- BMI >35 kg/m²
- Deficiency of vitamin K dependent clotting factors or coagulopathy

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-10-2018
Enrollment:	204
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rocuroniumbromide
Generic name:	Esmeron
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sugammadex
Generic name:	Bridion
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-05-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-06-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-07-2019
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001485-42-NL
CCMO	NL65290.091.18

Study results

Date completed:	03-06-2021
Actual enrolment:	185