Protocol:

ANIMOX-study: **An**esthesia and **Im**munological and **Ox**idative Stress in relation to Abdominal Cancer Surgery

Protocol version: v6_23052019 (approved protocol will be submitted to clinicaltrials.org)

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Background and Purpose

Colorectal cancer is a frequent type of cancer accounting for 600,000 deaths annually. Surgical resection remains the best treatment for long-term survival. However, studies suggest that events in the perioperative period can induce metastasis formation and tumor growth[1,2,3]. Tumor cells are released into the blood stream during surgery and the surgical stress may create a favorable environment for dissemination of tumor cells into distant tissue[4,5,6,7,8]. This is done by a cascade of pro-cancerous catecholamines, prostaglandins and cytokines combined with an impaired anti-cancerous cell mediated immune response[9,10,11].

Until recently, focus on the anesthetic management of cancer patients has been limited. Relatively small alterations in the perioperative anesthetic management may play a tremendous role in tumor progression[9]. Optimizing anesthesia to reduce the surgical stress response could improve recurrence rates and long-term outcomes for cancer patients by inhibiting perioperative metastasis formation. Regional anesthesia and amide local anesthetics are suspected to calm the immunologic storm of prostaglandins, catecholamines and cytokines when used in the perioperative phase[12,13,14,15,16,17,]. Furthermore, volatile inhalational anesthesia is thought to modulate the immune system in a pro-cancerous way, while propofol may have opposite effects[18,19,20,21,22]. Many of these recent studies are statistically underpowered and susceptible to bias, and experts in cancer treatment and anesthesia have emphasized the need for further research within this specific field[5,23,24].

In this study we aim to characterize differences in the immunologic response to surgery between inhalational, total intravenous and epidural anesthesia. This will be done by analyzing blood samples obtained in the perioperative period in patients undergoing different modes of anesthesia. We will furthermore describe the quality of recovery for patients anesthetized with the different methods

Objectives

We hypothesize that the immunologic response to surgery and metastasis progression are influenced by the anesthetic technique.

Methods

The study is initiated by Center for Surgical Science, Department of Surgery, Zealand University Hospital. It will be included in the Ph.D. studies of Rune Hasselager at University of Copenhagen.

Design and approvals

This study, initiated by Center for Surgical Science, Zealand University Hospital, will be a prospective cohort study. Approval from Danish Data Protection Agency and the Regional Committee for Health Research and Ethics is required. The study will require informed consent from participants.

Permission to transfer data from the IMOX study will be obtained from the Danish Data Protection Agency. The trial protocol will be submitted to clinicaltrials.org before initiation of the trial. Manuscripts will be prepared according to the STROBE statement[25].

Study setting

The study will take place at Hvidovre Hospital. This is a Danish university hospital. It supports 500,000 people and is one of four main emergency hospitals in Copenhagen Denmark. About 300 laparoscopic colon resections are performed at this facility every year.

Intervention

Participants will undergo laparoscopic colon resection for cancer. They will be anaesthetized according to the standard operating procedure at Hvidovre Hospital (see appendix 1) with the exception that no dexamethasone is administered as it could modulate the immune response. This includes anesthesia induction and maintenance with intravenous propofol and remifentanil. Patients will receive 4 mg ondansetron at the end of anesthesia.

A thoracic epidural catheter will be installed preoperatively and kept for up to three days. After an initial bolus with bupivacaine, continuous infusion of bupivacaine and sufentanil will be used to maintain the epidural analgesic effect. Postoperatively the epidural will be paused or discontinued if it is displaced or if side effects occur. It will only be re-installed if there is still need of neuraxial analgesia.

Patients will follow a standard Enhanced Recovery After Surgery (ERAS) protocol used at the facility.

Blood samples will be obtained before surgery and at four time points postoperatively and patient files will be assessed for adverse events within 30 days from surgery.

Withdrawal criteria:

Patients can be withdrawn from the study for any of the following reasons:

- Failure to adhere to the anesthesia intervention described above- including failure to install effective continuous epidural anesthesia.
- Adverse events after surgery
    - Any complication over grade 2 in Clavien-Dindo[26] classification
    - Blood transfusion
    - Deep vein thrombosis or pulmonary embolism
    - Anastomotic leak
    - Acute renal failure
    - Infection (wound infection or systemic infection) during the observation period.
- After consultation patients can be withdrawn due to withdrawal of informed consent to participate in the study at the patients' own request at any time for any reason.

Population

Study group: The "Hvidovre population":

We will include patients undergoing laparoscopic hemicolectomy for cancer scheduled for anesthesia with total intravenous anesthesia combined with epidural anesthesia on Hvidovre Hospital according to the intervention described above.

Eligibility criteria:

Inclusion criteria:

1. Patients over 18 years
2. Patients diagnosed with colorectal cancer (UICC stadium I-III) and scheduled for laparoscopic hemicolectomy.
3. ASA class I-III (Classification of the American Society of Anesthesiology)

4. Patients scheduled for anesthesia with propofol, remifentanil and epidural anesthesia.
5. Signed informed consent

Exclusion criteria:

1. Known immune-defects
2. Patients undergoing neoadjuvant chemo or radiotherapy
3. History of previous cancer
4. Patients in immunomodulatory treatment within last 6 months
5. Daily oral or intravenous steroid-use
6. Patients that have undergone major surgery within one month before planned colon resection.

Control group: The "Zealand University Hospital population"

The immunological and oxidative stress in relation to abdominal surgery (IMOX) study is ongoing at Zealand University Hospital, Roskilde. It is a prospective explorative study cohort that consists of 60 patients undergoing laparoscopic colorectal cancer surgery. The aim of the study is to characterize the immunological and oxidative stress response to surgery. Outcomes similar to the primary and secondary outcomes of the ANIMOX-study are included in the IMOX-study. Patients are already included in the IMOX-study and blood samples are collected and kept in a bio bank.

We will retrieve data on our main outcomes from the IMOX study in our analysis. Only electronic data will be used and no biologic material will be transferred from the IMOX project to ANIMOX. The population will be stratified according to anesthetic technique, which, according to the standard operating procedure, is either total intravenous anesthesia with propofol and remifentanil or volatile anesthesia with sevoflurane combined with a fast acting opioid (remifentanil or sufentanil). Patients anaesthetized with other techniques including epidural or other regional blocks will be excluded from the analysis.

Biological samples

To characterize the immunological response to surgery we obtain blood samples for analysis on postoperative day -1, 1, 2, 3 and 10 (or at the visit on day 10-14 where pathology results are given).

Handling of blood samples

Blood samples will be drawn by a trained professional and analyzed immediately at the standard lab facilities at Hvidovre Hospital and destroyed immediately hereafter. The results will be accessible in Sundhedsplatformen.

Primary outcome:

The primary outcome will be changes in neutrophil to lymphocyte ratio from day 0 to day 1. Neutrophil to lymphocyte ratio has been linked to poor outcome after colorectal cancer surgery. The ratio will be estimated using absolute numbers from differential counts pre and postoperatively.

Blood samples

Standard blood samples will be obtained and analyzed immediately at each time point. These include Hgb, Leucocytes including a differential count, thrombocytes, ALAT, LDH, Alkaline phosphatase, bilirubin, INR, albumin, Na, K, Creatinine, CRP and Glucose.

Quality of Recovery – 15 questionnaire

At each time point (day -1, 1,2 and 10) the patients are asked to fill in the validated Quality of Recovery Questionnaire QoR-15[27]. The QoR-15 questionnaire results in a score of 0–150. These outcome measures will be correlated with changes in immunologic outcome measures in the perioperative period.

Guidelines for oral and written consent and participant timeline

The first contact with a potential participant will be either during a stable phase of the primary admission, during an out-patient visit or during an introduction meeting prior to surgery. Patients will receive both oral and written information about the study. Patients will be contacted and a meeting where the inclusion will take place will be planned. An appropriately trained investigator will give information about the study including potential risks, harms and inconveniences. Before this meeting, patients will be informed that:

1. The patients have 24 hours or more to consider their informed consent.
2. An observer at the meeting can accompany the patient.

The meeting will take place in a quiet and undisturbed room. Amended to the patient information will be a document from the Central Ethical Committee with the title of ”Your rights as a test subject in a biomedical research”, which the patient will be recommended to read before inclusion.
Patients will have blood samples taken at four time-points - before surgery, day 1, day 2, day 3 and at the out-patient visit 10-14 days after surgery, where pathology results are given. The patient timeline is outlined in figure 1.
Participation is voluntary and no financial compensation will be given to participants.

Sample size

Study size
Due to the exploratory nature of this study, it is not possible to perform a valid sample size estimation. However, based on a pilot study of 45 patients undergoing laparoscopic hemicolectomy we found that the neutrophil to lymphocyte ratio increased 5.33 neutrophils/lymphocyte from preoperatively to postoperative day 1 (SD 3.33). With a power of 0.8 and an alpha value of 0.05 we will be able to detect a 50% smaller increase in neutrophil to lymphocyte ratio with 25 participants. As this power calculation is associated with much uncertainty we will include 30 evaluable patients (patients completing the study without meeting withdrawal criteria) to avoid a type 2 error.
We estimate that 10-20% of included patients will meet withdrawal criteria before completing the study. Therefore we expect that we need to include 36 patients to complete the study.
They will be compared to the patients included in the IMOX-study at Zealand University Hospital.

Recruitment timeline
Patients scheduled for laparoscopic hemicolectomy at Hvidovre Hospital will be screened for eligibility. 300 laparoscopic colon resections for cancer are performed at this facility each year and most of these are scheduled for total intravenous anesthesia with epidural anesthesia. With an inclusion rate of 50% we expect to be able to

include 30 participants that completes the study and does not meet the withdrawal criteria within 26-52 weeks.
We expect to begin inclusion in January 2019 and to finish the trial by 31th December 2019.

Data collection and management

To screen for eligibility to be included in the study we will request and obtain data on tumor stage, age, known immune defects, ASA-score, type of surgery, planned anaesthesia type and use of steroids.
After informed consent and inclusion in the study, data on demographics (comorbitities, age, sex), disease stage (clinical and pathological tumor histology), perioperative management (anesthesia type, medication, surgical procedure) and adverse events up to 30 days postoperatively will be obtained from the patient file.
Nurses at the Surgical Ward will be trained to encourage participants to fill in the QoR-15 questionnaires. The questionnaires will be kept with the patient in a folder that will be returned at the time of discharge. The patient will bring one QoR-15 questionnaire home to fill in at day 10. This questionnaire will be returned at the pathology result visit at day 10-14.
Blood samples will be taken and handled by a trained health care professional and brought to the laboratory for preparation and analysis within one hour.
Patients who are discharged before blood samples are taken on day 1,2, and 3 will asked if they wish attend the blood sampling as out-patients at the same timepoints.
Patients who does not show up to, or does not have the final blood samples taken at the time of out-patient pathology results will be contacted and encouraged to have the final blood samples taken and return the last QoR-15 questionnaire.
Study data will be stored according to guidelines from the Danish Data Protection Agency and “databeskyttelsesforordningen” and “databeskyttelsesloven” will be adhered to.

Statistical analysis plan

Data will be analyzed using R, SAS institute or SPSS. All tests will be two-sided with $p<0.05$ considered to be significant.

Data analysis

Data from the Hvidovre population and the Zealand University Hospital population will be combined to evaluate the effects of inhalational anesthesia (sevoflurane and opioid), total intravenous anesthesia (propofol and remifentanil) and total intravenous anesthesia (propofol and remifentanil) combined with epidural anesthesia (bupivacaine with opioid). Only electronic data will be used from the IMOX project – no biologic material will be transferred.

Baseline and clinical characteristics for patients, stratified for anesthesia type will be presented as frequencies for nominal, dichotomous and ordinal variables and medians with IQR for continuous variables. Outcome variables will be presented and described with appropriate tests. Depending on whether data is normally distributed or not, differences between the groups will be assessed using parametric or non-parametric statistics, respectively.

Risks, harms and inconveniences

Patients will receive the standard care at the respective hospital. The study does not influence any treatment or intervention related to the hospitalization.

Peripheral blood samples

Blood will be drawn from puncture of the cubic vein. The needle can cause minor discomfort including hematoma, which will disappear within few days.

QoR-15 questionnaires

Filling in the QoR-15 questionnaire will require a short amount of time and effort at the four time points.

Ethical considerations

Research within this field is until now very limited, but optimization of the anesthetic technique used for cancer surgery can benefit millions of people undergoing surgery for cancer in the future.

Approval from the regional scientific ethical committee is mandatory. Important modifications in the protocol will be communicated to the committee and approved before implementation.
Written consent from all participants will be obtained before inclusion as described above. Participants can at any time withdraw their consent.
All personal information about enrolled patients will be collected and protected according to Danish Law to ensure confidentiality before, during and after the study. Data will only be assessed by participants of the study group according to the approval from the Danish Data Protection Agency.

Risk of random findings

We do not expect random findings that will affect participants, as the scope of this study is to explore mechanisms of the immune system in the short perioperative period. We will not perform genome or DNA analysis, which potentially could reveal unknown underlying genetic disease.

Publication of results

Results of the study will, regardless of the results, be submitted for publication in an international peer-reviewed medical journal. No personal data that can be directly linked to a participant will be published.

Economy

Budget

	DKK
Sample collection incl. test tubes	66,000
Presentation of results (travel and conference fees)	30,000
Publication fee	10,000
6 months salary for Ph.D. student Rune Hasselager	275,000
Total	**381,000**

Funding

The study is initiated and will be funded by Center for Surgical Science, Zealand University Hospital. On an ongoing basis we will apply for grants from private or public foundations. We have received a grant from Hesse's Mindefond of 66,000

DKK for lab assistance for this project. Financial transactions and bookkeeping will be administered by Department of Surgery, Zealand University Hospital.
Sources of economical support will be declared in manuscripts.

Insurance

Patients included in this study are covered by the insurance of Hvidovre Hospital. The project is included in "Patienterstatningsordningen".

Conflicts of interest

None of the investigators have any conflicts of interest in this study.

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Appendices

Appendix 1: Standard operating procedure for anesthesia to major abdominal laparotomy and laparoscopic surgery at Hvidovre Hospital

LOP nr. 102

Instruks vedrørende anæstesi til større abdominalkirurgisk laparoskopi og laparotomi

Område:

Denne LOP dækker anæstesi til:

- Colon og rectum resectioner både åbne og laparoskopiske
- Ventrikel og tyndtarmskirurgi ikke dækket i andre SOP
- Tilbagelægning af end-stomier
- Større ventralhernieopertioner (jvf LOP 104)
- Større abdominalkirugiske indgreb der ikke er dækket af andre LOP

Denne LOP dækker *IKKE* akut abdominalkirurgi og elektive indgreb på ventrikel og oesophagus, til hvilke der findes separate SOP.

Præmedicin:

Al vanlig medicin fraset marevan, clopidogrel, magnyl og antidiabetisk medicin.

Anæstesimetode:

Som standard anvendes generel anæstesi med intubation og epidural anæstesi anlagt præoperativt.

- Luftvejsvurdering og håndtering foretages jvf SOP 272: luftvejshåndtering af patienter i generel anæstesi
- Alle patienter skal have Bair-hugger på højeste indstilling.
- Ved laparoskopi: **Ventrikelsonde** efter intubationen
- Patient skal have mindst én arm tilgængelig for anæstesien. Hvis begge arme på helt særlig indikation lægges ind til siden, skal der etableres PVK eller CVK på hals.
- Mindst to iv adgange, hvor den sidste kan anlægges efter induktion.
- *Obs* risiko for tryk fra og på iv adgange, polstres evt med vaskeklude.
- Foreslå kirurg "normalt leje" x 1/time ved Trendelenburg

HUSK antibiotika efter skema

Anæstesimetode:

Epidural

Test: Lidokain 2% m.adr., 3 ml

Bolus: Marcain 0.5 %, 5+5 ml med fem minutters mellemrum.

Epi-morfin: 2 mg (< 70 år); 1 mg (>70 år)
Ved tidligere opkastning pga. morfin - ingen bolus

Øvre (ventrikel til colon transversum):
Epidural anlægges på T7-8 niveau

Nedre (venstre colon til rectum):,
Epidural anlægges T9-10 niveau

Ved epidural anlæggelse kan analgeseres med Remifentanil 0.1-0.2 mikrog/kg/min

Vedligeholdelse:
- Epiduralpumpe 4 ml/time "standardblanding".
- Marcain 0,25 %, 5 ml/2.time og ved kirurgiafslutning.
- Tidligere PONV pga. morfin, skift til Sufenta 1 mcg/ml i pumpen.

Generel

Induktion:
- Propofol 1.0-2.0 mg/kg
- Remifentanil 5-6 mikrog/kg
- Dexamethason 8 mg
- Start infusion

Vedligeholdelse:
- Propofol 3-5 mg/kg/time
- Remifentanil 0.5 mikrog/kg/min

10 minutter før kirurgiafslutning:
- Toradol 30 mg i.v.
  (ikke ved rectum anastomoser)
- Zofran 4 mg i.v.
- *Stop* Propofol

5 minutter før kirurgiafslutning:
Stop Remifentanil

Der intuberes normalt uden relaksans efter indgift af mindst 5 mikrog/kg remifentanil
Ved luftvejsproblemer eller akut induktion anvendes suxamethonium 1.0 mg/kg

Ved patienter > 70 reduceres propofol/remifentanil dosis med 25%

Alle patienter skal have mindst 10 cm PEEP under laparoskopi

Ved behov for relaksering suppleres med Cisatracurium 2-4 mg pn

Væske og inotropi:

- Der gives ialt 20-30 ml/kg Ringers acetat perioperativt
- Ved hypovolæmi gives Voluven 500 ml
  - Blod gives efter samråd med kirurg og ud fra H:S's retningslinier. Behandles med Efedrin 10 mg i.v. pn , hvis der ikke er tegn på hypovolæmi.
  - Vedvarende MAP < 65: infusion dopamin 1-4 mikrog/kg/min.
  - Alternativt infusion metaoxedrin ved HR > 100.
    (inotropi kan gives I velobserveret perifer vene)