Immune protective anesthesia during endoscopic colon surgery to improve long-term survival

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Main objective: 1. Is there a 24hr-postoperative difference in immunological response between conventional and immune protective anesthesia?Secondary objectives:Is there a difference between patients with conventional and immune protective...

Ethical review	Approved WMO
Status	Pending
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46294

Source
ToetsingOnline

Brief title
Immune protective strategy for oncological endoscopic colon surgery (IPSEC)

Condition

- Immune disorders NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
immune system, narcosis

Research involving
Human

Sponsors and support

Primary sponsor: Anesthesiologie
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anesthesia, immune-response, metastases, oncology

Outcome measures

Primary outcome

Primary study parameters:

immunological response 24hr-postoperative

Secondary outcome

Secundary study parameters:

1. Is there a 48hr-postoperative difference in immunological response between conventional and immune protective anesthesia?

2. Postoperative complications according to the Clavien Dindo classification

3. Postoperative VAS (Visual Analogue Scale) score

4. Hospital stay

5. Anesthetic variables

Exploratory endpoint:

1. Cancer free survival of colon surgery (follow up to 5 years postoperative)

During anesthesia: blood pressure, heart rate, respiratory rate, carbon dioxide concentration, saturation, and BIS values will be documented prior before anesthesia and every 10 minutes thereafter. Data will be collected

prospectively.

Patient*s characteristics: age, BMI, smoking habits, medical history, ASA classification, tumor characteristics (histology, stage, TNM classification, localization).

Study description

Background summary

Multimodal treatment of colon surgery has been improved dramatically in the last decades due to a better selection of appropriate candidates, introduction of minimal invasive surgery and optimized (neo)adjuvant treatment strategies. Although these improvements led to a better short- and long-term survival, still up to 40% of the patients with a stage II or III disease will develop recurrence disease and/or distant metastases after curative intended colon surgery. Further enhancements in survival might be achieved by a specific anesthetic regime with respect to physical defense mechanism for micro-metastases.

The majority of to date*s anesthetic literature is focused on the influence of anesthesia on short-term outcome. However, influences of anesthesia on long-term outcome should not be underestimated. During oncologic surgery, immunological defense mechanisms are extremely important to eliminate micro-metastases. Moreover, the risk for micro-metastases during oncologic surgery is significant due to manipulation of a solid tumor causing the release of tumor cells in the vascular and lymphatic system. Positive perioperative circulating tumor cells are an independent risk factor for long-term outcome. The primary defense against these micro-metastases includes natural killer (NK) cells, cytotoxic T cells, mononuclear cells, and dendritic cells4. Other cytokines involved in tumor progression and NK cell activation are IL 2, IL 6 and INF gamma. From several studies it has been suggested that frequently used anesthetics and analgesics techniques might have a positive or negative influence on immunological performance and consequently on long-term survival.

Epidural analgesia is one of the possible techniques that might contribute to a preserved NK cell activity. It attenuates the neuroendocrine stress response and reducing opioid requirements. Perioperative stress is responsible for the release of pro- and anti-inflammatory cytokines, which suppress the cell mediated immunity and NK cell activity in particular. The degree of surgical

trauma is proportional to the stress response and with the introduction of endoscopic surgery significant decreased. Furthermore, epidural analgesia is also known to reduce opioids requirements due to its analgesic properties. It has been suggested that opioids have immunomodulatory effects resulting in both cell-mediated and humeral decreased immunity. Opioids also stimulate angiogenesis, an essential process in tumor development. Next to these negative consequences, opioids have also some side effects like a decreased intestinal motility and postoperative nausea and vomiting (PONV). Dexamethasone is a glucocorticoid that is commonly used in anesthetic practice for prophylaxis against PONV. The effect of relatively low dose glucocorticoids on the immune response in cancer patients is not clear yet. In a randomized control trial, dexamethasone was associated with a higher rate of distant recurrence in patients undergoing colectomy for colon cancer. But opioids do have also some positive effects, in particular in patients with inadequately controlled pain which induce a significant stress response.

In an attempt to minimize perioperative stress and to tolerate intubation without the need of supplement opioids, Dexmedetomidine (DEX) will be given by continuous infusion. DEX is a potent α2-adrenerge agonist with sedative and sympatholytic properties and hence its effect might be used as adjuvant in anesthesia as stress response blocker, sedative and analgesic. From several studies DEX is known to reduce levels of pro-inflammatory cytokines, cortisol, perioperative opioid use and postoperative pain score.

Maintenance of anesthesia is divided in total intravenous anesthesia (TIVA) or volatile anesthesia. From experimental research in rats, it has been suggested that the use of older volatile anesthetics leads to an inverse relationship with NK cell activity. Sevoflurane, a frequently used volatile anesthetic, binds lymphocyte antigens which interfere with their activity. Propofol is the most frequently used TIVA and is associated with a significantly decreased production of prostaglandin E2. Moreover, propofol is not associated with a suppressed NK cell cytotoxicity and is recently in a large retrospective study associated with significant improved long-term outcome. Other intravenous anesthetics like ketamine or thiopental are associated with tumor metastasis and should therefore be avoided in cancer patients.

Although cancer surgery is one of the most commonly performed surgeries in daily practice, there is not a specialized anesthetic regime for this specific category of patients. Dosage and anesthetic techniques might be differing substantial between anesthesiologists. Anesthesia in cancer patients should be focused on long-term survival without compromising patient*s safety or comfort in the perioperative phase. We hypothesis that an especially designed strategy of anesthesia for cancer patients preserves immune response during endoscopic colon surgery which will also improve long-term survival.

Study objective

Main objective:
1. Is there a 24hr-postoperative difference in immunological response between conventional and immune protective anesthesia?

Secondary objectives:
Is there a difference between patients with conventional and immune protective anesthesia regarding:

1. Is there a 48hr-postoperative difference in immunological response between conventional and immune protective anesthesia?
2. Postoperative complications according to the Clavien Dindo classification
3. Postoperative VAS (Visual Analogue Scale) score
4. Hospital stay
5. Anesthetic variables

Exploratory endpoint:
1. Cancer free survival of colon surgery (follow up to 5 years postoperative)

Study design

Study design: multicenter randomized controlled trial (MRCT)
Duration: maximum of 4 years
Total number of patients: 300
Setting: laparoscopic colon surgery

Patients will be randomized in two groups:

1. Conventional anesthesia

2. Immune protective regime:

Escape medication
In the event of severe postoperative pain (Visual Analogue Scale (VAS) >= 4) and in spite of the use of Paracetamol and a bolus of local anesthetics (dosage according to the judgment of the anesthesiologist) trough a correct placed epidural, escape medication with Dipidolor or Morphine will be given (scored as: *treatment failure*). Dosage of Dipidolor or Morphine according to the judgment of the anesthesiologist or to local protocols.

Immunological parameter concentrations will be measured by FACS and ELISA and will be taken prior to surgery (T0), 24 hours (+/- 4 hours) after surgery (T1), and 48 hours (+/- 4 hours) after surgery (T2).

Intervention

Patients will be randomized in two groups:

1. Conventional anesthesia:
- Preopartive Paracetamol
- Intravenous analgesia with opioids and postoperative pain management with Dipidolor or morphine according to local protocols.
- Anesthesia only with Sevoflurane; dosage according to the bispectral index scale (BIS) with target values between 40 and 60.
- Ketamine, Clonidine and Dexamethason according to the judgment of the anesthesiologist.
- No Dexmedetomidine, epidurale analgesia, continueous lidocaine or COX-2 inhibitor.

2. Immune protective regime:
- Single dose of preoperative Paracetamol and Midazolam (dosage according to anesthesiologist)
- Analgesia perioperative: epidural (only with local anesthetic), Paracetamol, Dexmedetomidine (between 0.2 and 1.0 ug/kg/hr without any bolus) starting before epidural
- Analgesia postoperative: epidurale analgesia according to local protocols (only with local anesthetic) and Paracetamol
- Anesthesia only with Propofol; dosage according to the bispectral index scale (BIS) with target values between 40 and 60.
- Without peri- or postoperative use of opiates, Ketamine, Clonidine or Dexamethason
- Hypotension should preferably be treated with phenylephrine

Study burden and risks

Since we aimed that this especially designed anesthesia strategy for cancer patient*s preserves immune response during colon surgery, we expect a beneficial effect in concentrations of NK cell activity and stress mediated cytokines (lymphocytes and IL 6 concentrations). An intact immune response might be related to a better tumor free survival.

Based on data from literature and our own experience in the UMCG, the anesthetic department considers the use of the interventional anesthesia strategy as safe and comfortable. All medications are frequently used and are registered for use in the operating theatre (except for Dexmedetomidine). Dexmedetomidine (α2-adrenerge agonist) is in the Netherlands registered for use on the Intensive Care Unit (ICU) as a sedative agent. Dexmedetomidine may have some effects on patient*s hemodynamic response (hypotension and/or brady-arrhythmia). Under hemodynamic monitoring, Dexmedetomidine is considered

to be a safe drug with comparable mechanism of action as Clonidine, a frequently used α2-adrenerge agonist.

Although epidural analgesia during endoscopic surgery is standard care in some centers, patients diveded in the intervention group will always get epidural analgesia. This technique is associated with some common (like decreased blood pressure, loss of bladder control, itchy skin) and uncommon (severe headaches, infection, epidural haematoma, nerve damage) effects/complications. The risk for these effects/complications are not different from other patient categories and epidural analgesia is performed on a daily routine. Unforeseen complications or insufficient pain relief with the use of the interventional anesthesia strategy will come clear during this study.

As hematological testing is performed on a frequent basis, burden and risks are neglectable. Frequent vena punction carries limited risks and is usually well tolerated. In addition, blood samples will be combined as much as possible.

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

- All patients approved by the anesthesiologist for elective endoscopic colon surgery for cancer.
- > 18 year with written informed consent

Exclusion criteria

- neoadjuvant chemo and/or radiotherapy
- Perioperatieve conversion to an open surgical approach
- Insufficient pain relief in the intervention group (Visual Analogue Scale (VAS) >= 4)
- Absolute contra-indications for the use of a any of the listed medications in the intervention group
- Synchronous metastasis (stage IV/ M1 patients)
- Patients who are mentally disabled or incapable to give informed consent
- patients on chronic opioid use

Study design

Design

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

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2017
Enrollment:	366
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	dexdor
Generic name:	dexmedetomidine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-04-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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: 23133
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-000867-34-NL
CCMO	NL58206.056.17

Register	ID
OMON	NL-OMON23133