RESEARCH PROTOCOL

(october 2016)

Study: Reduces intravenous lidocaine the need for alfentanyl during colonoscopy under Procedural Sedation and Analgesia?

Versie 4

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PROTOCOL TITLE '**Study: Reduce is the administration of lidocaine the need for alfentanyl during colonoscopy under procedural sedation and analgesia (PSA)?**

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Subsidising party	
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Pharmacy	***Radboudumc***

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PROTOCOL SIGNATURE SHEET

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Principal Inverstigator: Prof. Dr. G.J. Scheffer		6-6-2016
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IBD	**inflammatory bowel disease (IBD)**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MAP	**Mean Arterial Pressure**
PONV	**Postoperative nausea en vomiting**
PSA	**Procedural sedation and analgesia**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale:

Colonoscopy is a commonly performed procedure to diagnose or follow up an inflammatory bowel disease (IBD) like Crohn's disease and ulcerative colitis. For some of these patients, this can be a very painful procedure.
Propofol in combination with a short-acting opioid i.e. alfentanyl is commonly used for procedural sedation and analgesia (PSA).
However, alfentanyl can induce some serious adverse effects like hypotension, bradycardia, and respiratory depression.
Perioperative administration of lidocaine, has a proven beneficial effect in abdominal surgery: reduction of postoperative pain scores and peri-operative opioid dosage.
We hypothesize that intravenous lidocaine reduces the need of alfentanyl during colonoscopy.

Objective:
Primary Objective:
To evaluate whether continuous infusion of lidocaine reduces the need for alfentanyl in diagnostic colonoscopy in patients with Crohn's disease or ulcerative colitis.

Secondary Objective(s):
To evaluate the differences in side effects like respiratory depression, hypotension, postoperative nausea and vomiting (PONV) and post procedural pain between placebo and intravenous lidocaine.

Study design:

This study will be a single centre double-blinded randomized placebo-controlled trial.

Study population:

All patients with IBD, between 18 and 65 years, which are scheduled for a colonoscopy with PSA, will be screened for this study. Seventy-six evaluable patients will be enrolled in the trial.

Intervention:

The following intravenous lidocaine infusion regimen will be conducted: At the start of the PSA, patient will receive a bolus of 1.5 mg/kg followed by continuous infusion of 2 mg/kg/h lidocaine during the colonoscopy.

Main study parameters/endpoints:

Primary objective is to evaluate the efficacy of intravenous lidocaine in comparison with placebo in terms of alfentanyl dosage during diagnostic colonoscopy.

Secondary study parameters/endpoints

Does lidocaine influences the incidence of respiratory depression, hypotension, PONV and post procedural pain compared with placebo alone.

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

All measurement and handlings to the patients which participate in this study are part of standard care.
Patients will have little extra risks due to the known low and non-toxic plasma levels with this commonly used infusing regimen of lidocaine. Monitoring of patients will ensure that any potential side effect or adverse event are noticed and treated as quickly as possible.
The benefit for the patients can be that less alfentanyl needs to be given during colonoscopy, which can lead to less negative side effects like hypotension, respiratory depression and PONV.

1. INTRODUCTION AND RATIONALE

Colonoscopy is a commonly performed procedure to diagnose or follow up inflammatory bowel disease (IBD) like Crohn's disease and ulcerative colitis. However, especially in this patient category, this can be a very uncomfortable and painful procedure.[1] Patients with IBD are known for visceral afferent hypersensitivity caused by the chronic, recurrent, inflammatory characteristics and has a significantly higer prevalence of narcotic alalgesic use compared with the general population.[2, 3]

PSA is commonly used during colonoscopy to facilitate the procedure and relieve patient's discomfort.[4]
Propofol in combination with a short-acting opioid i.e. alfentanyl is commonly used for PSA.[5] This combination during colonoscopy is associated with greater patient satisfaction and less pain when compared with midazolam/fentanyl.[6]
Yet some serious adverse cardiorespiratory complications related to PSA can occur in up to 20% of the patients, i.e. hypotension, bradycardia, and respiratory depression.[7]
There is a continuous search to find alternatives, which can minimize the risk for these adverse side effects without quality loss of PSA.

Lidocaine can be a suitable alternative analgesic during colonoscopy in IBD patients. To our knowledge, no other studies have evaluated the administration of intravenous lidocaine during colonoscopy.
Intravenous lidocaine has a proven beneficial analgesic efficacy and reduces per- and postoperative use of opioids during abdominal surgery.[8]
It reduces ectopic discharges and hyperalgesia; it modulates the inflammatory response and has an inhibitory effect on the evoked and spontaneous activity of neurons, which are –activated by colorectal distension.[9, 10]
No major adverse events during lidocaine administration in the perioperative setting have been notified on the basis of 45 RCT's.[11]

For lidocaine the therapeutic range for pain treatment seems to be between 1 and 5 µg/ml. Lidocaine bolus of 1.5 mg/kg followed by continuous infusion of 2 mg/kg/h reaches plasma levels of 2-4 µg/ml.[10] The administration of a infusion dose of 2 mg/kg/hour is a commonly used dosage in perioperative setting.[11]

We hypothesize that intravenous lidocaine reduces the need for alfentanyl and subsequently can reduce the incidence of cardiorespiratory adverse events.

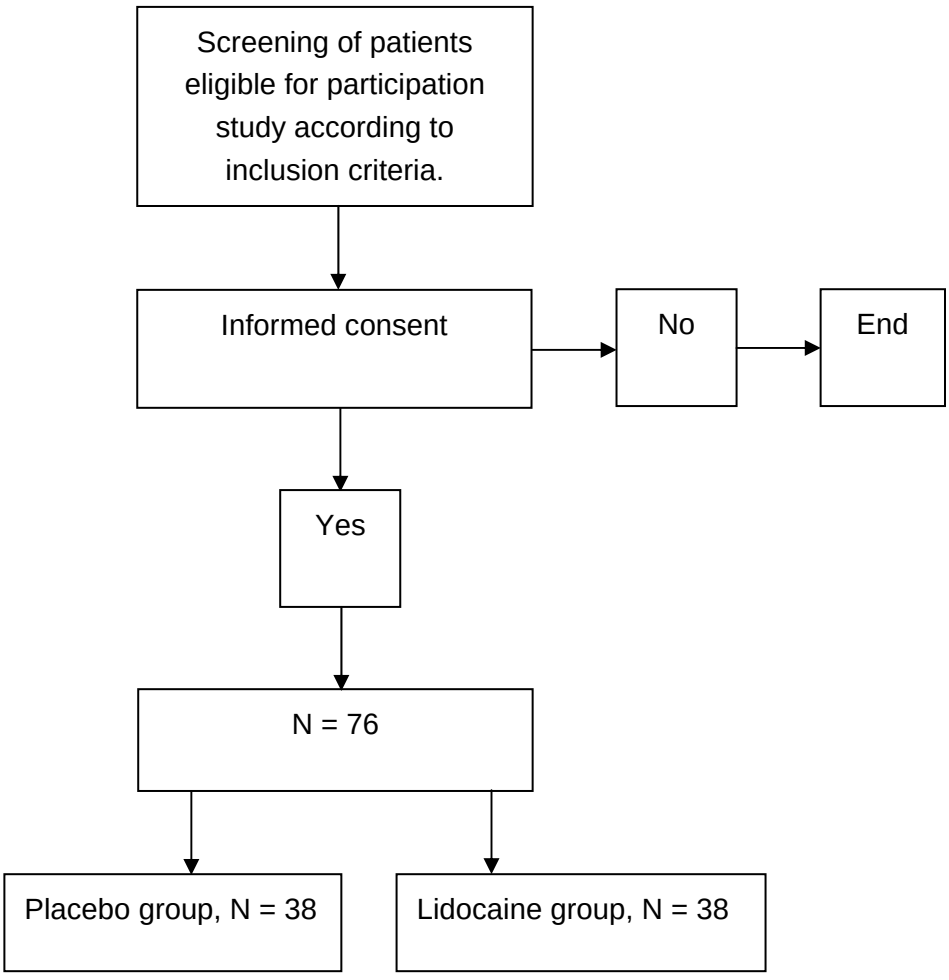
2. OBJECTIVES

Primary Objective:
The primary objective of this study is to evaluate whether lidocaine reduces the need for alfentanyl during colonoscopy in patients with IBD.

Secondary Objective(s):
The secondary objective of this study is to evaluate whether lidocaine reduces the incidence of respiratory depression, hypotension, PONV and postprocedural pain.

3. STUDY DESIGN

This study will be a single centre double-blinded randomized placebo-controlled trial, which will performed at the endoscopy centre of the Radboud University Medical Centre, Nijmegen, Netherland.
We will evaluate the effect of intravenous lidocaine during colonoscopy in patients with IBD.
All patients who meet the inclusion criteria are informed at the outpatient clinic of the department anesthesiology. After obtaining written informed consent the patient will be randomized to either intravenous lidocaine treatment or placebo.
The PSA to all patients in the study will perform by the same physician assistant anesthesiology to reduce bias.



Consequences for patients

PSA for colonoscopy is a commonly performed procedure. Patients will have a preprocedural screening according to our local protocol.
The same iv-line for administering sedatives, will be used to administer the study medication; so no extra venous access is needed.
Additionally, all other measurements during colonoscopy and postprocedural are part of standard care.

4. STUDY POPULATION

4.1 Population

All patients with IBD, between 18 and 65 years, which are scheduled for a colonoscopy with PSA, will be screened for this study. Seventy-six evaluable patients will be enrolled in the trial.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet the following criteria:

Colonoscopy performed under PSA
Age 18-65 years
Inflammatory bowel disease: Crohn's disease or ulcerative colitis
Informed consent
ASA classification 1 or 2

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

Pregnancy.
Emergency colonoscopy.
Known allergies for study medication
Known rhythm disorders i.e. first, second or third degree AV block
Known Brugada syndrome
Known cardiomyopathy
BMI >35
BMI <18
Obstructive sleep apnea syndrome
Uncontrolled hypertension

4.4 Sample size calculation

We expect a need for 0.5 – 0.75mg alfentanyl in the placebo group and 0.25mg alfentanyl in the intervention group. As standard deviation we postulate a value of 0.50mg. This leaves us with N = 38 per group, to achieve a 90% chance for the difference of 0.375 to be statistically significant with an alpha of 0.05. So 76 patients will be needed.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The following lidocaine infusion regimen will be conducted. At the start of PSA, patient will receive 1.5 mg/kg intravenous bolus in 5 minutes followed by a continuous infusion of 2 mg/kg/h lidocaine during the colonoscopy.

Lidocaine concentration used in the study will be lidocaine 1%. The therapeutic range for pain treatment seems to be between 1 and 5 µg/ml. Lidocaine bolus of 1.5 mg/kg followed by continuous infusion of 2 mg/kg/h reaches plasma levels of 2-4 µg/ml.[12]
Thus, with this infusion regimen lidocaine plasma levels, will stay below the toxic plasma level, which is above 5 µg/ml.[8]

Patients who are included in the placebo group of the study will receive saline in equivalent volumes and time.

5.2 Use of co-intervention

Not applicable

5.3 Escape medication

Additional 20 mg bolus of propofol will be given when the Ramsey Sedation Scale score is less than four.
Additional 0.25 mg bolus of alfentanyl will be given when a score of four or higher on the Facial Pain Rating Scale is observed.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Lidocaine hydrochloride 1%

6.2 Summary of findings from non-clinical studies

The summary is provided in the SPC for lidocaine supplied with this protocol.

6.3 Summary of findings from clinical studies

The summary is provided in the SPC for lidocaine supplied with this protocol.

6.4 Summary of known and potential risks and benefits

The summary is provided in the SPC for lidocaine supplied with this protocol.

6.5 Description and justification of route of administration and dosage

In previous clinical trials this method and dosage has led to safe plasma levels of lidocaine with no signs of toxicity of local anesthetic or lidocaine related side effects.[2,5,8,16]

6.6 Dosages, dosage modifications and method of administration

There will be no dosage modifications. Lidocaine 1% will be used. This will be administered intravenously.

6.7 Preparation and labelling of Investigational Medicinal Product

As there is very limited budget for this investigator-driven study and because the investigational medicinal product is made ready to administer in a 50 ml syringe from the lidocaine ampoules or normal saline by a qualified unblinded research team member immediately before administration, and because the product is only administered intramurally, we request to waive the necessity of GMP Annex 13 compliant labelling of the lidocaine and normal saline ampoules and bags. The hospital pharmacy will supply the required drugs (lidocaine or placebo) directly on a per patient basis to the unblinded research team member.
Medication is drawn up into a 50 ml syringe on the surgical department. The amount of studymedication depends on the weight of the patient.
Blinding, preparation and labelling of the study medication will be done by an unblinded team of the department of Anesthesiology, Pain and Palliative medicine, Radboud University Medical Centre according to the relevant GMP guidelines.

6.8 Drug accountability

After preparation the study medication will be delivered. After administration the syringes will be stored for evaluation of correct dosing.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary objective of this study is to evaluate whether intravenously lidocaine reduces the need for alfentanyl during colonoscopy in patients with IBD.

8.1.2 Secondary study parameters/endpoints

Incidence of hypotension (a mean arterial pressure (MAP < 60 mmHg), is recorded as an adverse event if an intervention is performed to improve the blood pressure.[12]
These interventions include administration of:

- IV Fluid challenge
- Medications

Incidence of oxygen desaturation (<92%), is recorded as an adverse event if an intervention is performed to improve the oxygen saturation.[13]
These interventions include the following:

- Vigorous tactile stimulation
- Airway repositioning
- Suctioning
- Increased oxygen delivery
- Oral or nasal airway placement
- Application of positive pressure or ventilation with bag mask

Incidence of unpleasant recall of the procedure.[14]
Postprocedural NRS
Incidence of PONV
Incidence of adverse effects of lidocaine:
light headedness, tinnitus, dizziness, blurred vision or double vision, metal taste.
Total propofol dose
Colonoscopy time

8.1.3 Other study parameters

Demographic data:
Age
Gender
Weight
BMI
ASA classification

8.2 Randomisation, blinding and treatment allocation

An unblinded research team of the anesthesiology department will do the randomization. Breaking of the randomization code will be done in case of any serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs). The person who is controlling the randomization list, will perform the

unblinding. This person is available 24/7, and there is always backup for this person, when he is unintentionally not available. Before inclusion of patients a randomization list will be prepared before start study. According to the randomization the study medication will blinded be administered.

8.3 Study procedures

Patients will be informed at the preoperative outpatient clinic of the anesthesiology department, where a physician or a physician assistant supervised by a physician will inform the patient and receive the informed consent. If the patient wishes to read the information at home they are allowed to do so. The patient sent their informed consent by mail.

Requesting the patients' medical history is part of standard care and will be performed on the preoperative outpatient clinic anesthesiology.
Patients admitted at the daycare unit of the endoscopy ward, will receive an intravenous line and are monitored with noninvasive systemic blood pressure, ECG, pulse oximetry and capnografy.
Supplemental oxygen (3 L/min) is standardly administered by a nasal cannula.
The noninvasive systemic blood pressure is placed on the other arm as the intravenous line.

According to a standardized PSA protocol both groups receive a bolus propofol of 1 mg/kg followed by a infusion of 4.5 mg/kg/hour ideal body weight intravenously.
The intervention group receives lidocaine 1.5 mg/kg in 5 minutes followed by a continuous infusion of 2 mg/kg/hour body weight intravenously. The placebo group will receive saline in equivalent volumes and time.

The Ramsey Sedation Scale scores will be maintained at 4-5 during colonoscopy and if needed, an additional 20 mg bolus of propofol is administered.
The pain score is measured with the Facial Pain Rating Scale (Wong baker face scale). An additional alfentanyl dose of 0.25 mg is given when a score of 4 or higher is observed.

Each 5 minutes the blood pressure will be measured. A MAP below 60 mmHg will be recorded as an adverse event and 5 mg ephedrine will be administered.

ECG is monitored continuously. The original rhythm will be recorded before the start of the study medication. Changes in the rhythm will be recorded.

Saturation is monitored continuously. An oxygen desaturation below 92% or interventions with the intention of improving the oxygen saturation will be recorded as an adverse event.[13]
These interventions include the following:

- Vigorous tactile stimulation
- Airway repositioning
- Suctioning
- Increased oxygen delivery
- Oral or nasal airway placement
- Application of positive pressure or ventilation with bag mask

At the end of the colonoscopy all sedation and study medication will be stopped. Patients will recover at the recovery room according to a standardized recovery protocol. Pain scores and incidence of PONV will be registered. The incidence of adverse effects of lidocaine will be registered. These include the following:

- Tinnitus
- Blurred vision or double vision
- Metal taste during procedure

According to the PSA protocol patients will be monitored until they reach an Aldrete recovery score of nine or higher and for at least 30 minutes.
Afterwards, patients will be discharged.

8.4 Withdrawal of individual subjects

Patients 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. Reason for withdrawal from the study will be recorded.

8.4.1 Specific criteria for withdrawal

Specific criteria for withdrawal during the study are rhythm changes and the occurrence of an epileptic seizure during the administration of the studymedication.

8.5 Replacement of individual subjects after withdrawal

If patients decide to withdraw before the diagnostic colonoscopy, they will be omitted from the data collection and will be replaced by a new study patient. If patients have received study medication, the will be included in the analysis.

8.6 Follow-up of subjects withdrawn from treatment

After withdrawal patients will receive standard care

8.7 Premature termination of the study

The data safety monitoring board will be informed in case of a serious adverse event. The study will be terminated prematurely if the investigators feel there is a risk to the patients enrolled. Patient safety will continue to be monitored by the investigator for the duration of the study.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 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 investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

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

- 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; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;

- 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.

9.4 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

9.5 Data Safety Monitoring Board (DSMB)

According to the NFU-classification this trail has a low risk. A Data Safety Monitoring Board will be established to perform ongoing safety surveillance and interim analyses on the safety data e.g. AEs, SAEs and SUSARs.
Because of the limited number of patients in this study is conducted an interim analysis after 38 patients.
All SAEs and SUSARs will reported to the DSMB for a review.
The DSMB will not conduct an interim efficacy analysis.

The DSMB will consist of:

Chairman:	Prof. dr. J. Bruhn, Department of anesthesiology, Pain and Palliative Medicine, Radboud University Medical Centre, Nijmegen.
Member:	Dr. G.J. van Geffen, Department of anesthesiology, Pain and Palliative Medicine, Radboud University Medical Centre, Nijmegen.
Member:	Dr. E.J.M. van Geenen, Department of gastroenterology and hepatology, Radboud University Medical Centre, Nijmegen.

None of these persons have a conflict of interest with Dhr. T.T.J. Aalbers.
The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the investigator will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10.STATISTICAL ANALYSIS

Statistical analysis will be performed using Statistical Package for te Social Sciences (SPSS), P-valeus < 0,05 will be considered significant.
Descriptive analysis will be carried out for baseline characteristics: Date of birth, gender, weight, BMI, ASA-classification.

10.1 Primary study parameter(s)

For the primary outcome, the mean number of applications of 0,25 mg alfentanyl during the colonoscopy will be compared between the both groups using a independent T-test

10.2 Secondary study parameter(s)

All secondary study parameters, except the last two (colonoscopy time and total propofol dose), concern the occurrence of adverse events. They will be registered and their frequencies will be reported using the classification as given in 8.1.2. The mean colonoscopy time and the total propofol dose will be compared between the groups using T-tests.

10.3 Other study parameters

Not applicable

10.4 Interim analysis

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki version 2013, and in accordance with the Medical Research Involving Human Subjects Act (WMO), WGBO, WBP and BIG

11.2 Recruitment and consent

Patients will be informed at the preoperative outpatient clinic of the anesthesiology department, where a physician or a physician assistant supervised by a physician will inform the patient and receive the informed consent. If the patient wishes to read the information at home they are allowed to do so. The patient sent their informed consent by mail..

Time between the preoperative visit and the colonoscopy is between 1 to 8 weeks. Which allows enough time for the informed consent procedure.

11.3 Objection by minors or incapacitated subjects

Not applicable

11.4 Benefits and risks assessment, group relatedness

Patients will have little extra risks due to the known low and non-toxic plasma levels with this infusion regimen of lidocaine. Monitoring of patients will ensure that any potential side effect or adverse event are noticed and treated as quickly as possible. The benefit for the patients can be that less alfentanyl needs to be given during colonoscopu, which can lead to less negative side effects like hypotension, respiratory depression and PONV.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be handled anonymously through coding. Patients will only be able to be linked to the coded investigation product through the source document which contains the linking between patient and investigation number. All subject data will be stored in locked offices. All electronic data will be password-protected on computers in locked offices. Access to subject information will be limited to trial personnel only and to the DSMB in case of any SAE. Any data, including photographs, videos, and interviews with the subject that may be published in abstracts, scientific journals, marketing material or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity without the express approval of the subject. Subjects will be asked for approval at the start of the trial as part of the IC. The research data will be saved for 15 years. When we want to use these data for another study patients will be asked for permission first.

12.2 Monitoring and Quality Assurance

According to the NFU criteria this study will be of low risk due to the administration of lidocaine intravenously at the endoscopy centre. Low dose lidocaine is considered safe for intravenous use and patients' vital functions will be monitored continuously. Physician assistants anesthesiology are trained to treat unexpected side effects like local anesthetic intoxication.
We will monitor according to the NFU criteria.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

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

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 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.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority 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 and the Competent Authority.

12.6 Public disclosure and publication policy

Data will be anonymous. Because the sponsor and investigator are the same, there are no arrangements. Plans are to publish the findings of this study in a prominent magazine in the work field of anesthesiology or gastroenterology.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

There is a high amount of knowledge of the effects of lidocaine in the body. There a no studies found who research the effect of intravenous lidocaine in diagnostic colonoscopy. There is no knowledge about the effect of intravenous lidocaine on the dosages of alfentanyl during diagnostic colonoscopy with PSA.
During the infusion regimen of intravenous lidocaine used in the study, no signs of toxicity of local anesthetic are observed in other studies.[8, 10]
Besides those studies we refer to the supplied SPC of lidocaine.
The patients will be monitored heamodynamiccally and respiratory during the diagnostic colonoscopy in order to reduce the risk of serious adverse events.

a. Level of knowledge about mechanism of action

Lidocaine caused a selective depression of pain transmission in the spinal cord and a reduction in tonic neural discharge of active peripheral nerve fibres. The peripheral A-delta and C-fibres appeared uniquely sensitive to the effects of lidocaine without signs of toxicity or disturbance in haemodynamics.[8]

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

There were no adverse events related to lidocaine infusion during abdominal surgery and the overall morphine consumption was clearly reduced in the lidocaine group.[15]

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

In rats lidocaine produced inhibition of neuronal and reflex responses to colorectal distension.[9]

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Lidocaine, a non-specific sodium channel blocker, reduces ectopic nerve discharges, relieves hyperalgesia and modulates the inflammatory response, because of an inhibitory effect on sodium-, calcium-, and potassium ion channels, G-protein coupled pathways, NMDA- receptors and the glycinergic system

e. Analysis of potential effect

The potential effect is that lidocaine reduces the need of alfentanyl during colonoscopy. The use of a short-acting opiod as alfentanyl is associated with some serious side effects like hypotension, bradycardia and respiratory depression.

f. Pharmacokinetic considerations

Lidocaine is mainly metabolized in the liver by CYP3A4 and has active metabolites mono-
ethylglycinexylidide (MEGX) and glycinexylidide (GX). Elimination: renal, < 10% unchanged. V_d = 1,3 l/kg. $T_{1/2el}$ = 90–120 min (lidocaïne); 2 hour (MEGX); 10 hour (GX). After a bolus injection or continuous administration for up to 12 h, the half-life of lidocaine shows linear pharmacokinetics.[16]

g. Study population

Patients in this study will have IBD and are screened for exclusion criteria before participation in this study.

h. Interaction with other products

Propofol is mainly metabolized in the liver by CYP2B6. CYP3A4 is not involved in the metabolism of propofol.[17]
Alfentanyl is mainly metabolized in the liver by CYP3A4.[18] No known interactions between alfentanyl and lidocaine are reported.

i. Predictability of effect

Since it is clearly demonstrated that lidocaine reduces opioid dosage during abdominal surgery, we highly expect that lidocaine reduces the need of alfentanyl during colonoscopy

j. Can effects be managed?

The risk of neurotoxic side effects of lidocaine in the prescribed dosages is low. Patients are monitored during the procedure and in the recovery room. Nurses are trained to treat negative side effect from PSA.

13.2 Synthesis

Colonoscopy is a commonly performed procedure to diagnose or follow up an inflammatory bowel disease. For some patients, this can be a very painful procedure. Propofol in combination of a short-acting opioid i.e. alfentanyl is commonly used for PSA.[5]
However, alfentanyl can induce some serious adverse effects like hypotension, bradycardia, and respiratory depression.
Perioperative administration of lidocaine, has a proven beneficial effect in abdominal surgery: reduction of postoperative pain scores, per- and postoperative opioid dosage.[8]

According to the NFU-classification this trail has a low risk.
The risk for patients for participating in this study is experiencing side effects of lidocaine.
This is a low risk due to the known low and non-toxic plasma levels with this infusion regimen of lidocaine.
We excluded patients with an increased risk for local anesthetic side effects.
Monitoring of patients will ensure that any potential side effect or adverse event are noticed and treated as quickly as possible.
There is a Data Safety Monitoring Board established to perform ongoing safety surveillance and interim analyses on the safety data.

In our opinion it is important to develop strategies for PSA to minimize the risk for adverse cardiorespiratory complications and increase patients comfort during colonoscopy.

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