

RESEARCH PROTOCOL

Pilot study: postoperative pain reduction by pre emptive N-Acetylcysteine

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TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE	10
2. OBJECTIVES.....	11
3. STUDY DESIGN	12
4. STUDY POPULATION	14
4.1 Population (base).....	14
4.2 Inclusion criteria	14
4.3 Exclusion criteria	14
4.4 Sample size calculation.....	14
5. TREATMENT OF SUBJECTS	16
5.1 Investigational product/treatment.....	16
5.2 Use of co-intervention (if applicable)	16
5.3 Escape medication (if applicable).....	16
6. INVESTIGATIONAL PRODUCT	17
6.1 Name and description of investigational product(s)	17
6.2 Summary of findings from non-clinical studies.....	17
6.3 Summary of findings from clinical studies	17
6.4 Summary of known and potential risks and benefits	17
6.5 Description and justification of route of administration and dosage.....	17
6.6 Dosages, dosage modifications and method of administration	17
6.7 Preparation and labelling of Investigational Medicinal Product	17
6.8 Drug accountability.....	17
7. NON-INVESTIGATIONAL PRODUCT	19
8. METHODS	20
8.1 Study parameters/endpoints.....	20
8.1.1 Main study parameter/endpoint	20
8.1.2 Secondary study parameters/endpoints (if applicable)	20
8.2 Randomisation, blinding and treatment allocation	20
8.3 Study procedures	20
8.4 Withdrawal of individual subjects.....	21
8.5 Replacement of individual subjects after withdrawal.....	22
8.6 Follow-up of subjects withdrawn from treatment.....	22
8.7 Premature termination of the study.....	22
9. SAFETY REPORTING	23
9.1 Temporary halt for reasons of subject safety	23
9.2 AEs, SAEs and SUSARs.....	23
9.2.1 Adverse events (AEs).....	23
9.2.2 Serious adverse events (SAEs).....	23
9.2.3 Suspected unexpected serious adverse reactions (SUSARs)	24
9.3 Annual safety report	25
9.4 Follow-up of adverse events.....	25
9.5 Data Safety Monitoring Board (DSMB) / Safety Committee	25

10.	STATISTICAL ANALYSIS.....	27
10.1	Primary study parameter(s).....	27
10.2	Secondary study parameter(s).....	28
10.3	Interim analysis (if applicable).....	28
11.	ETHICAL CONSIDERATIONS.....	29
11.1	Regulation statement.....	29
11.2	Recruitment and consent.....	29
11.3	Objection by minors or incapacitated subjects (if applicable).....	29
11.4	Benefits and risks assessment, group relatedness.....	29
11.5	Compensation for injury.....	29
11.6	Incentives (if applicable).....	30
12.	ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION.....	31
12.1	Handling and storage of data and documents.....	31
12.2	Monitoring and Quality Assurance.....	31
12.3	Amendments.....	31
12.4	Annual progress report.....	32
12.5	End of study report.....	32
12.6	Public disclosure and publication policy.....	32
13.	STRUCTURED RISK ANALYSIS.....	33
13.1	Potential issues of concern.....	33
13.2	Synthesis.....	34
14.	REFERENCES.....	35

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
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)
NAC	N-Acetylcysteine (Fluimucil)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie 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
VAS	Visual Analog scale
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Title: postoperative pain reduction by pre emptive N-Acetylcysteine.

Rationale: Despite current available analgesic drugs, post-surgical pain management remains challenging. A potential new target for analgesic drugs are group-II metabotropic glutamate receptors subtypes (mGlu2 and mGlu3 receptors), since growing evidence from animal models show that activation of these receptors produce s analgesic effects in inflammatory and in neuropathic pain states. . N-Acetylcysteine (NAC) is a safe agent and with little to no side effects. NAC can induce analgesia by activating the glutamate:cystein antiporter, causing endogenous activation of the mGlu 2/3 receptors. However, this has only been investigated once in the peri-operative setting, were it showed preliminary promising result of reduction in opiate necessity. In healthy subjects there was a significant reduction in pain ratings to laser stimuli and amplitudes of laser evoked potentials after NAC. Based on these promising results, we hypothesize that pre emptive intravenous NAC can reduce postoperative pain and thereby cause less necessity for escape analgesics like opiates.

Objective: In patients receiving NAC we hope to see less postoperative pain and thereby less usage of escape pain medication compared to patients receiving placebo.

Study design: This pilot study will be a multi centre randomised, double blinded, placebo controlled pilot study. Subjects will be randomized to placebo or NAC treatment before surgery and will be followed till 1 week after surgery.

Study population: 60 patients with informed consent for surgical unilateral inguinal hernia repair, otherwise ASA 1-2 classification and age > 18 years, will be enrolled.

Intervention (if applicable): Group 1 receives a bolus of 150 mg/kg NAC intravenous 1 hour prior to surgery. Group 2 receives saline in equivalent volumes also 1 hour prior to surgery.

Main study parameters/endpoints:

Primary objective

To evaluate the efficacy of intravenous NAC in comparison with placebo in terms of pain relief after unilateral inguinal hernia repair measured by a visual analogue scale (VAS 0-100) at day 1 after surgery.

Secondary objectives

1. Difference in pain scores (VAS 1-100) between NAC and placebo direct after surgery, before discharge and in following 3 days postoperative.
2. Difference in time before first pain medication is administered postoperative between NAC and placebo.
3. Difference in total consumption of opiates in the hospital (mg) between NAC and placebo.
4. Difference in time from surgery to discharge between NAC and placebo.
5. Difference in postoperative pain medication at home necessary to reach adequate pain relief between NAC and placebo (Acetaminophen /NSAID's/opiates).
6. If there is a difference in 5, is there also a difference in adverse effects of pain medication (like nausea, obstipation) between NAC and placebo.
7. safety of intravenous NAC 150 mg/kg in terms of nausea, vomiting, anaphylactoid or allergic reactions (presenting as dyspnea, urticaria)

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will need to be admitted earlier in the hospital prior to surgery, to make sure they receive study medication in time.

An intravenous line will be placed on the holding to be able to administer study medication, however, this same line can be used during and after surgery. During administration of the study medication subjects will be monitored respiratory and hemodynamically, to ensure possible side effects of NAC are captured.

Oral NAC is safe agent and even over the counter available in the Netherlands. Subjects will have little extra risks due to the intravenous NAC given in this concentration. The main risk is the occurrence an anaphylactoid reaction, which is easily treated by antihistaminic and seldom described as serious in the literature. [1-5] Careful monitoring of subjects will ensure any potential side effect or adverse event are noticed and treated as quickly as possible. Side effects will be documented and presented.

After discharge patient receive a diary and will record: 1) VAS at predetermined time, 2) pain medication used, 3) side effects of pain medication (nausea, obstipation, dizziness) and 4) overall satisfaction.

Total time investment of participants should not exceed more than 2 hours in total.

1. INTRODUCTION AND RATIONALE

In 2008 it was estimated that approximately 240 million surgical procedures were done worldwide on a yearly basis, and over the last years this number has probably grown even further.[6] Inguinal hernia repair is one of the most performed surgeries in ambulatory setting.[7] Despite currently available analgesic drugs, post surgical pain management remains challenging in this group of patients, as the pain score appears inadequate (mean VAS of 5.8 +/- 1.22 cm) one day after surgery with the use of common analgesics.[8, 9] Beside accounting for patient discomfort, pain is also a major contributor to prolonged length of hospital stay and is a health care quality indicator.[10, 11]

With multimodal pain management the intention is to reduce pain with less side effects of analgesics. Multimodal pain management is the combination of different pharmacologic mechanisms of action, which work by acting at different sites within the central and peripheral nervous system, thereby having an additive or synergistic effect and reducing the necessity of opiates. [12]

With this in mind, a potential new target for analgesic drugs are group- II metabotropic glutamate receptors subtypes (mGlu2 and mGlu3 receptors) localized in the spinal cord and other regions of the nociceptive system. Growing evidence from animal models show that activation of these receptors occur via the glutamate:cystein antiporter and can induce analgesia in models of inflammatory and neuropathic pain.[13-17] They depress pain transmission at synapses between primary afferent fibers and second order sensory neurons on the dorsal horn of the spinal cord.[18]

N-Acetylcysteine (NAC) is on the market since 1968 and is an over the counter available agent, mostly known for its role as mucolytic agent in cystic fibrosis and for the treatment of acetaminophen intoxication. It is a safe agent with little to no side effects. [1-5] Recent studies have shown NAC can inhibit nociceptive transmission in rats and in healthy humans.[15, 19] NAC can induce analgesia by activating the glutamate:cystein antiporter, causing endogenous activation of the mGlu2/3 receptors.

Therefore, NAC can potentially become a cheap and safe additive in the multimodal pain management. However, evidence for usage of NAC in the context of multimodal pain management is still lacking. Only one available study in humans evaluated the effect of NAC in the perioperative setting.[19] Despite being a randomised controlled trial, there are several limitations in this study; the study arms are too small and only morphine consumption is presented. Also, blinding might have not as good as suggested since oral NAC has a typical flavour and the placebo was lemonade. Due to these limitations, still no answer on the question whether NAC can be an additive in current multimodal painmanagement is provided.

Therefore, we would like to conduct a randomised, double blinded, placebo controlled pilot study to investigate whether pre emptive intravenous NAC can reduce postoperative pain after surgical inguinal hernia repair. Primary endpoint will be pain score on day one after surgery, and secondary outcomes postoperative analgesic consumption, time to first necessity for pain medication, hospital stay and adverse effects of analgesic medication.

2. OBJECTIVES

Primary Objective:

To evaluate the efficacy of intravenous NAC in comparison with placebo in terms of pain relief after unilateral inguinal hernia repair measured by a visual analogue scale (VAS 0-100) at day 1 after surgery.

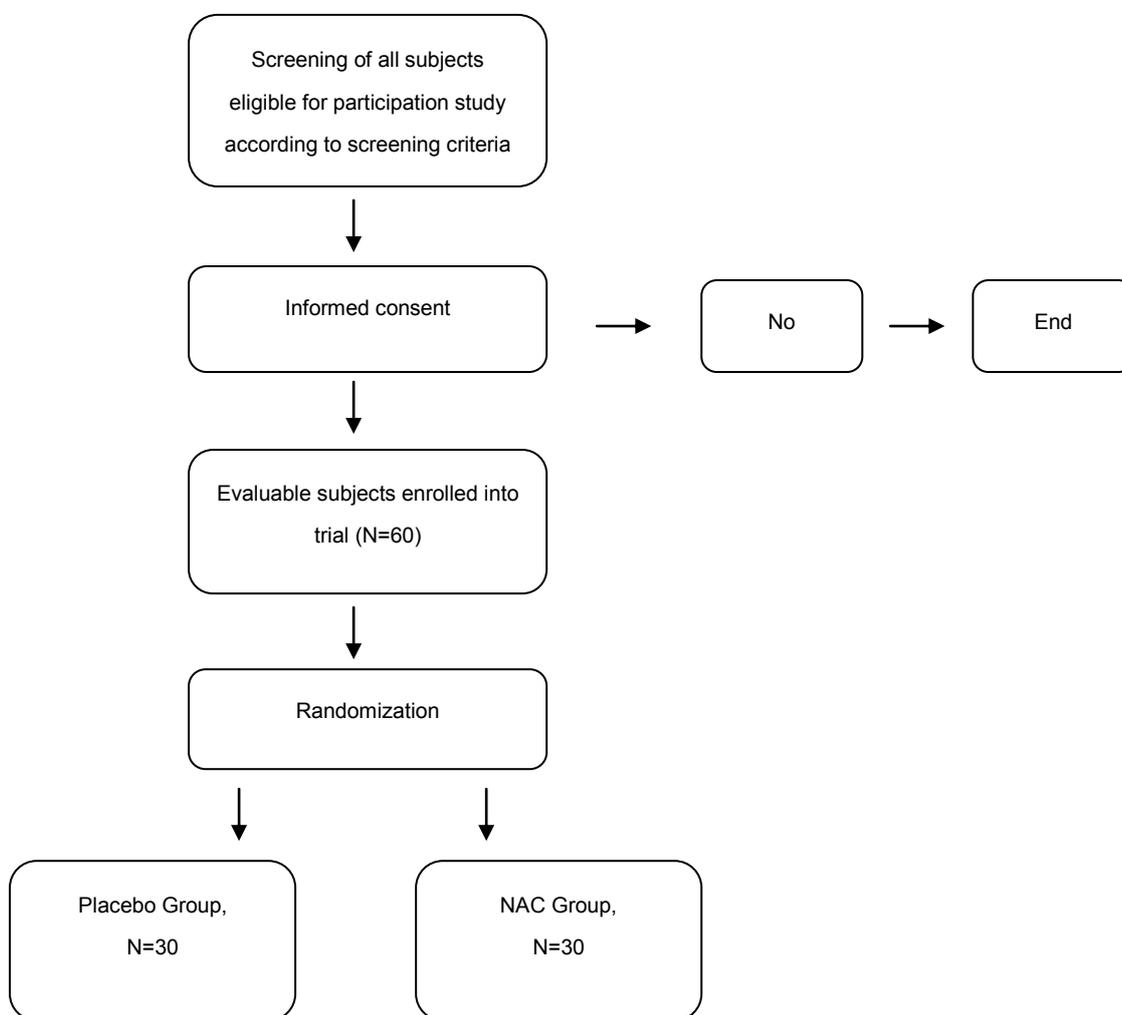
Secondary Objective(s):

1. Difference in pain scores between NAC and placebo direct after surgery, before discharge and in following 3 days postoperative.
2. Difference in time before first pain medication is administered postoperative between NAC and placebo.
3. Difference in total consumption of opiates in the hospital (mg) between NAC and placebo.
4. Difference in time from surgery to discharge between NAC and placebo.
5. Difference in postoperative pain medication at home necessary to reach adequate pain relief between NAC and placebo (Acetaminophen /NSAID's/opiates).
6. If there is a difference in 5, is there also a difference in adverse effects of pain medication (like nausea, obstipation) between NAC and placebo.
7. safety of intravenous NAC 150 mg/kg in terms of nausea, vomiting, anaphylactoid or allergic reactions (presenting as dyspnea, urticaria)

3. STUDY DESIGN

The study will be a multi centre double blinded randomized placebo controlled trial, which will be conducted at the Maxima Medical Centre, Veldhoven and Radboudumc, Nijmegen. We will investigate whether pre-emptive intravenous NAC will reduce postoperative pain in patients with unilateral inguinal hernia repair. Subjects who are scheduled for laparoscopic inguinal hernia repair will be screened at the pre-operative screening clinic according to screening criteria (see section 4). After patients have given oral and written informed consent (IC), subjects will be randomized to either NAC or placebo and will be prospectively followed till 1 week after surgery. Participants and investigators enrolling subjects can not foresee assignment because of central allocation is used to conceal allocation.

We expect this pilot study will take 6 months, starting at first inclusion.



Consequences for patients

At specific time points the following measurements will be performed.

History taken: is part of standardized care, and will be done during the preoperative screening.

Study medication: subjects will receive an intravenous line to administer either NAC or placebo intravenously. Oral NAC is safe agent and even over the counter available in the Netherlands. Subjects will have little extra risks due to the intravenous NAC given in this concentration. The main risk is the occurrence an anaphylactoid reaction, which is easily treated by antihistaminic and seldom described as serious in the literature. [1-5] Careful monitoring of subjects will ensure any potential side effect r adverse event are noticed and treated as quickly as possible.

Physical examination: is part of standardized care, and will be done during the pre operative screening (measurement of bloodpressure and pulse).

Diary: Patient will record VAS on predetermined time, analgesic medication taken, side effects of analgesic medication, overall satisfaction.

Vital signs: is part of standard care peri operatively, however, extra measurements of heartrate (HR), bloodpressure (BP) and oxygenation (SpO2) during administration of study medication will take place to ensure possible side effects of NAC are captured.

4. STUDY POPULATION

4.1 Population (base)

Subjects will be identified at the pre operative screening at the Maxima Medical Centre, Veldhoven, the Netherlands or at the pre operative screening at Radboudumc, Nijmegen, the Netherlands. Sixty evaluable subjects (male or female) will be enrolled in the trial.

We will randomize patients in one of the following two groups:

1. Receive intravenous placebo prior to inguinal hernia repair.
2. Receive intravenous NAC prior to inguinal hernia repair.

4.2 Inclusion criteria

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

Subjects scheduled for laparoscopic unilateral inguinal hernia repair.

- ASA 1 or 2.
- Age >18 years.

4.3 Exclusion criteria

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

- Pregnancy or lactating
- Allergy to NAC
- History of chronic pain
- Use of opioids or neuropathic analgesics
- Use of NAC prior to trial (< 1 month of planned surgery)
- Contra indication for the use of NSAID's
- Previous inguinal hernia repair on the same side (a redo operation)
- Alcoholism
- Diabetes Mellitus
- Asthma or Chronic Obstructive Pulmonary Disease
- Known renal function disorders (MDRD <60)
- Known liver failure (bilirubine >1.5x upper limit of normal)
- No written IC by patient

4.4 Sample size calculation

The sample size is powered to find a significant difference in pain 24 hours after surgery. The primary outcome will be the VAS between the two groups. Assuming a clinical relevant difference of 1(cm) on the VAS between groups, with a mean of 5.8 and a standard deviation of 1.22 after 24 hours and a power of 80%, then 25 patients are needed in each group (t-test, alpha=0,05; double sided), taking in to account a possible loss to follow up of 20%, a total of 30 patients will be included in each group.

If this pilot study shows promising results we aim to set up a further larger study where there will be an extended focus on NAC and reduction of postoperative pain.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The following NAC infusion regimen will be conducted. One hour prior to surgery, the patients will receive 150 mg/kg in 200 ml intravenous bolus over 15 minutes.

During NAC infusion, patients vital signs will be adequately monitored.

Patients who are not included in the treatment arm of the study will receive intravenous saline instead with identical look of NAC in the same timeframe and dosage (200ml).

5.2 Use of co-intervention (if applicable)

Subjects will receive standard recipes for postoperative analgesics, which they can take at home if they experience pain. Standard regime for postoperative pain will be:

Acetaminophen 4 dd 1 gram oral

Naproxen 2 dd 500 mg oral

Oxynorm 5 mg oral, only on request with a maximum of 6 times a day

5.3 Escape medication

During hospital stay escape medication for acute pain will be the regimen as described above. If this regimen is insufficient, sufentanil or morphine intravenously can be given with on the recovery ward by judgement of the anaesthesiologist to achieve adequate pain reduction.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

N-Acetylcysteine, concentrate for intravenous admission 200 mg/ml.

6.2 Summary of findings from non-clinical studies

The summary is provided in the SPC for N-Acetylcysteine supplied with this protocol.

6.3 Summary of findings from clinical studies

The summary is provided in the SPC for N-Acetylcysteine supplied with this protocol.

6.4 Summary of known and potential risks and benefits

Oral NAC is an over the counter agent in the Netherlands. Intravenous NAC is almost exclusively used for Acetaminophen intoxication. Side effects of intravenous NAC are rare. In 0,1-1% anaphylactoid reactions occur like bronchospasm, dyspnea, pruritis, flushing or rash. In the literature this incidence is higher, 8.4% with a higher incidence in asthmatics.[4] However, the side effects are easily managed with antihistaminic and non were life threatening.[5]

6.5 Description and justification of route of administration and dosage

Although preferred route of administration is oral, since this is cheaper and less anaphylactoid reactions are seen (2% vs 6%), we choose for the intravenous admission after good consultation with the clinical pharmacist. [1]The main reason to choose for the intravenous route is primary a problem with blinding the oral route. Also, the oral bioavailability of NAC is only 4%, and since there appears to be a dose-response curve we hypothesized that if there is no effect seen after high dose intravenously, none will be seen in the oral route. [20]

6.6 Dosages, dosage modifications and method of administration

The given dosage will be 150 mg/kg in 200 ml of saline intravenously over a period of 15 minutes. This is the same bolus as is given intravenously for acetaminophen intoxication and therefore well described and investigated in the literature.[1, 2, 4, 5]

6.7 Preparation and labelling of Investigational Medicinal Product

Preparation will be done by the hospital pharmacy or pharmacist.

6.8 Drug accountability

NAC will be delivered by the producer of NAC, Zambon Nederland BV. The delivered NAC has a concentration of 200 mg/ml. After randomization of the patient, the hospital

pharmacy or pharmacist will prepare the medication for reconstitution in the clean room according to local protocol. Reconstitution shall be understood as a simple process of diluting the NAC with saline for the purpose of administering it. Normally this process can be done by a nurse on the ward, however to extend shelf life and ensure blinding this will be done in the clean room by the pharmacy.

The medication will be stored (with a maximum of seven days as described by manufacturer) according protocol until surgery of the patient. Study medication will be labelled with "NAC or placebo", together with patient identity. The pharmacy or pharmacist will deliver the appropriate study label to the clinic on the day the patient is planned for his/ her surgery. After administration the medication bags will be stored and collected 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

Primary objective is to evaluate the efficacy of intravenous NAC in comparison with placebo in terms of pain relief after unilateral inguinal hernia repair measured by a visual analogue scale (VAS 0-100) at day 1 after surgery.

8.1.2 Secondary study parameters/endpoints (if applicable)

- Pain scores (VAS 1-100) direct postoperatively , before discharge and in following 3 days postoperative.
- Time to first necessity of pain medication after surgery.
- Total consumption of in hospital opiates/ analgesics.
- Time to discharge.
- Analgesic medication taken at home by patient (registered by patients in diary).
- Adverse effect of analgesic medication (nausea, obstipation, sedation)
- Safety of intravenous NAC (nausea, vomiting, dyspnea, urticaria)

8.2 Randomisation, blinding and treatment allocation

Participants and investigators enrolling subjects can not foresee assignment because of central allocation is used to conceal allocation. We used blocked randomization to form the allocation list for the two comparison groups because of the small sample size. We used a computer random number generator to select random permuted blocks and an equal allocation ratio.

Breaking of the randomization code will be done in case of any SAE or SUSAR. Study medication will be administered by blinded personnel. Patients, hospital staff that are involved in the care of the patient (surgeon, anaesthetist, nurses) and outcome investigators (including primary data collectors) are all blinded for treatment allocation.

8.3 Study procedures

Patients shall be informed about the study during their visit to the surgery outpatient clinic and if they are scheduled for unilateral laparoscopic inguinal hernia repair. . Patients will be asked if they consent to be approached by the investigator and if so they will receive study information and the informed consent form. The patients will be asked by the investigator over the phone if they have any questions and in case of informed consent they will be asked to fill in the form and sent this back in the provided envelope.

Measurements at baseline

Patient characteristics are obtained through history taking and physical exam (and if thought necessary by anaesthetist also laboratory values) during the regular preoperative screening. This is part of standard care.

- Date of birth
- Gender
- Medical history
- Current pain score (VAS 0-100)
- Intoxication (smoking, alcohol, drugs)
- Allergies
- Medication
- Physical examination (heart sounds, breath sounds, airway, baseline bloodpressure and pulse)

Administration of study medication

Patient will be admitted to the day clinic prior to his/ her surgery. For the administration of the study medication, they will be admitted to the recovery ward, where patients will receive an intravenous canula. The administration of study medication will start an hour before surgery and infusion will take 15 minutes. During administration of study medication vital signs (saturation, non invasive bloodpressure and pulse) will be registered every 5 minutes. Also injection site will be monitored for reaction. In case of an anaphylactoid reaction to NAC, the protocol "anaphylatoide reactie" will be followed.

Surgery

Prior to surgery patient will receive general anesthesia according to the local protocol of the Maxima Medical Centre. This will be standard care that the patient would receive also without being included in this study.

All patients receive premedication with acetaminophen and naproxen.

General anesthesia will consist of anti emetic (granisetron), propofol, sufentanil, rocuronium and for maintenance sevoflurane. No dexamethasone will be administered. In case of residual muscle relaxants, sugammadex will be given. Dosage of analgesic medication will be recorded.

After surgery

Patients will be monitored on the recovery ward according to local protocol. Pain scores (VAS 1-100) will be registered as well as need for analgesic medication.

Adverse effects of analgesic medication (nausea, sedation) will be recorded.

Discharge from the recovery ward will be no different than according to local protocol after surgery. On the ward also pain scores (VAS 0-100) will be registered every hour till discharge home. Need for analgesic medication and adverse effects will be recorded. In case of nausea droperidol 1.25 mg or metoclopramide 10 mg can be given.

Home

Patients will be asked to fill in a diary for the first 3 days after surgery. In this diary they are asked to fill in pain scores (VAS 0-100) on certain times, as well as used analgesic medication and, in case of adverse effects of this medication, also these adverse effects. Patients will receive a call on day 1 to make sure the diary is filled in and not forgotten. The diary is, and if not received patients will be called at home after 1 week. If patients don't have internet or prefer a paper diary this is also possible. Data filled in online will be directly saved in the secured database of castor, where only authorized personnel has access to.

8.4 Withdrawal of individual subjects

Subjects 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.

8.5 Replacement of individual subjects after withdrawal

If subjects decide to withdraw before receiving the study medication, they will be omitted from the data collection and will be replaced by a new study object. If the subject had received study medication, they will be included in the analysis for the arm where the subject was allocated to (intention to treat analysis).

8.6 Follow-up of subjects withdrawn from treatment

After withdrawal subjects will not be followed for research purposes, but will continue to receive normal, standard of care follow-up by their treating physician.

8.7 Premature termination of the study

The data safety monitoring board will be informed in case of a serious adverse event. The trial will be terminated prematurely after consulting the DSMB if there might be an increased risk to the subjects enrolled, for example if the treatment causes unanticipated harm to the subject or in case of a SUSAR. Subject safety will continue to be monitored by the investigator for the duration of the trial.

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 investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events..

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) / Safety Committee

According to the NFU-classification this trial has a low risk. For this reason a Data Safety Monitoring Board will be established to perform ongoing safety surveillance and interim analyses on the safety data.

The DSMB will consist of: Dr. J. Hofland (Anesthesiologist), Dr. C. Slagt (Anesthesiologist) and Dr. A. Morariu (Anesthesiologist). None of these persons have a conflict of interest with Drs. C.E. Mulken.

The advice(s) of the DSMB will only be sent to the principal investigator and

coordinating investigator of the study. Should the investigator 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 Rstudio software. Descriptive analysis will be carried out for baseline characteristics: age, gender, ASA-classification, intoxications and co-morbidities. Also length of surgery and used anaesthetic technique of both groups will be described. Nominal and ordinal data will be presented by number and percentage. Continuous data will be presented depending on normal distribution with either mean and standard deviation or (in case of no normal distribution) median with range.

Inferential statistics will be performed for both primary and secondary outcomes. We will determine if data is normally distributed or not and do statistical analysis accordingly. In case of normal distribution we will use an unpaired t-test. In case of a non normal distribution we will perform a log transformation on the data, however, if still no normal distribution we will use the non parametric test Mann Whitney U (Wilcoxon rank sum). P values <0.05 will be considered significant. P values will be calculated with various tests depending on presence of normal distribution or not.

Statistical analysis will be based on an intention-to-treat analysis.

Missing data will be described thoroughly, and will be investigated on whether it is missing completely at random (MCAR), missing at random (MAR) or not missing at random (NMAR). In case patients received treatment the data known will be used in analysis. We expect to not have many missing data due to the follow up by phone. We expect that in case of missing data this will be completely at random. Therefore, we chose not to use imputating techniques but listwise deletion in case of missing data. In case there is more missing than 5% or a suspicion of MAR, we will rethink the use of imputating techniques.

10.1 Primary study parameter(s)

The primary outcome will be the mean VAS (1-100) between the two groups at day 1 after surgery. Pain scores are ordinal data and therefore a non parametric test should be used. However, one can discuss whether the VAS can't be interpreted as continuous data, and therefore (if normally distributed) parametric tests can be used with more statistical power. Here we decided to treat VAS as continuous data and therefore use parametric test, the unpaired t- test..

10.2 Secondary study parameter(s)

- Pain scores (VAS 1-100) direct postoperatively, before discharge and in following 3 days postoperative. Ordinal data, but like with the primary outcome we will treat VAS as continuous data and therefore in case of normal distribution unpaired t test. Time to first necessity of pain medication after surgery. Continuous data, two groups; depending on normal distribution unpaired t test or Mann Whitney U.
- Cumulative consumption of in hospital opiates. Continuous data, two groups; depending on normal distribution unpaired t test or Mann Whitney U.
- Time to discharge. Continuous data, two groups; time to event; Kaplan Meier analysis.
- Analgesic medication taken at home by patient. Continuous data, two groups; depending on normal distribution unpaired t test or Mann Whitney U.
- Adverse effect of analgesic medication (nausea, obstipation, sedation) Dichotomous data, unpaired and 2 groups; Fisher exact.
- safety of intravenous NAC 150 mg/kg in terms of nausea, vomiting, anaphylactoid or allergic reactions (presenting as dyspnea, urticaria)

10.3 Interim analysis (if applicable)

there will be no interim analysis.

11. ETHICAL CONSIDERATIONS Regulation statement

The current pilot study will be conducted according to the principles of the declaration of Helsinki, current version 2008, and in accordance with the legislations issued by the WGBO, WMO, WBP and BIG

11.2 Recruitment and consent

Patients shall be informed about the study during their visit to the surgery outpatient clinic and if they are scheduled for unilateral laparoscopic inguinal hernia repair. Patients will be asked if they consent to be approached by the investigator and if so they will receive study information and the informed consent form. The patients will be asked by the investigator over the phone if they have any questions and in case of informed consent they will be asked to fill in the form and sent this back in the provided envelope.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

Oral NAC is safe agent and even over the counter available in the Netherlands. Subjects will have little extra risks due to the intravenous NAC given in this concentration. The main risk is the occurrence of an anaphylactoid reaction, which is easily treated by antihistaminic and seldom described as serious in the literature. [1-5] Careful monitoring of subjects will ensure any potential side effect or adverse event are noticed and treated as quickly as possible.

The possible benefit for subjects lays in the fact that NAC can reduce postoperative pain and reduce the necessity of opioids postoperatively.[19]

The burden for the subjects is, next to receiving study medication, minimal. They receive no different care during surgery, or after surgery. The subject is asked to fill in a diary for the first 3 days after surgery, which should not take more than 1 hour in total in time investment and is non-invasive.

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 (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be handled anonymously through coding. Subjects will only be able to be linked to the coded investigation product through the source document which contains the linking between subject and investigation number. The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: de Wet Bescherming Persoonsgegevens, WBP). All subject data will be stored 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 subjects that may be published in abstracts, scientific journals, marketing material or presented at medical meetings will reference an unique subject code and will not reveal the subjects 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, “kwaliteitsborging mensgebonden onderzoek 2.0” this study will be of low risk because of the administration of NAC intravenously. The given dosage is considered safe and is extensively been investigated previously. Extra monitoring of the subjects will take place. The medication will all be prepared by the pharmacy/ pharmacist so the chance of dosage error is limited to a minimum. However, the nurses are not used to NAC intravenously and they will receive training before the trial starts. The expected possible side effect however are no different than of most other medication given intravenously.

We will monitor according to the NFU criteria.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

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 fully anonymised. 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 pain and anesthesiology.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Much is known about NAC and its action in the human body. However, not much is known about the possible new effect on postoperative pain. There have been many reasons to subscribe NAC in the past. It is an frequently used drug, which nowadays is even for sale in local drugstores without subscription in the Netherlands. Although not to investigate a probable role as new analgesic agent, there have been many studies to investigate the same dosage of intravenous NAC in acetaminophen intoxication, in which no life threatening adverse events occurred. Beside those studies we refer to the supplied SPC/IB of NAC.

Study materials will be supplied by the hospital pharmacy or pharmacist.

a. Level of knowledge about mechanism of action

There is a high level of knowledge of this medicine. It is first choice in acetaminophen intoxication and therefore frequently applied in the used dosage.

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

See references [15, 19, 21]

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

There are several articles which show the effect of NAC on the group-II metabotropic glutamate receptors subtypes (mGlu2 and mGlu3 receptors) and the effect of this on pain behaviour in animals. [13-15, 17] Pre-emptive NAC can reduce nocifensive behaviour and this analgesic effect was abrogated by the Sxc- inhibitor sulphalazaline as well as by adding the mGlu2/3 receptor antagonist.[17]

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

see references [20, 22]

e. Analysis of potential effect

The potential effect is that through activation of the endogenous mGlu 2/3 receptors via the glutamate:cystein antiporter, post operative pain is reduced and therefore the necessity for opiates. In animal studies there is a dosage- response curve, were the higher the dosage (30 mg/kg, 100 mg/kg or 300 mg/kg) the less pain behaviour was observed. [14] This is why we chose to use a higher dosage and intravenous administration than previous studies in human did, and this hopefully reduces postoperative pain.

f. Pharmacokinetic considerations

NAC is mainly metabolized in the liver. In plasma NAC can be present in its intact, reduced form as well as in various oxidized forms. It can be oxidized to a disulphide and form mixed disulphides by reacting with other low molecular weight thiols such as cysteine and glutathione. Based on total NAC concentration, its volume of distribution (V_{ss}) was $0.47 \text{ l}\cdot\text{kg}^{-1}$. The terminal half life was 5.58h after intravenous administration. Elimination is renal

g. Study population

Subjects are scheduled for an elective laparoscopic unilateral inguinal hernia repair. They will be screened for contraindications for receiving NAC (see exclusion criteria).

h. Interaction with other products

In vitro inactivation of antibiotics is seen. Therefore it is not advised to combine antibiotics with NAC. Antibiotics are given in the operating room before incision, and therefore no interaction is suspected.

i. Predictability of effect

The evaluation if NAC indeed causes postoperative pain reduction will be measured via VAS score, which is a validated measurement to evaluate pain treatment. Values can be compared with normals in a database.

j. Can effects be managed?

Most effects will be monitored in the day clinic. Side effects of the NAC intravenously are rare, and if they occur this will be on the ward. Most side effects can be treated with tavegyl 1 mg intravenously, since a canula is already in place. Administration of the study medication will be done by trained personel to ensure subject safety.

13.2 Synthesis

Postoperative pain management is still a challenging manner. Although development in surgical techniques has drastically improved chronic pain after inguinal hernia repair, acute pain is still not optimized. Due to infiltration with local anesthetics, peripheral nerve blockage and analgesics patients leave the hospital with acceptable pain scores. However, a day after surgery this no longer provides analgesia and patients report pain scores less acceptable.

With this pilot for pre emptive NAC we hope to improve this patient important outcome. The risk for subjects in this study is experiencing side effects of the NAC intravenously, which we find an acceptable risk since side effects are never reported to be life threatening and there is an extensive history of NAC given intravenously.

Subjects with an increased risk of NAC side effects are excluded and all subjects are monitored during NAC infusion.

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