



Clinical trial results:

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

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2016-003144-36 |
| Trial protocol | NL |
| Global end of trial date | 29 October 2018 |

Results information

| | |
|-----------------------------------|---------------------------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2022 |
| First version publication date | 13 July 2022 |
| Summary attachment (see zip file) | article RAPM (rapm-ARTIKEL.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | NAC.TEP16 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03354572 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | RadboudUMC |
| Sponsor organisation address | Geert Grooteplein Zuid 10, Nijmegen, Netherlands, 6525GA |
| Public contact | Head of department Anesthesiology, Radboud UMC, Kris.Vissers@radboudumc.nl |
| Scientific contact | Head of department Anesthesiology, Radboud UMC, Kris.Vissers@radboudumc.nl |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 December 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 October 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of intravenous N-Acetylcysteine 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

Protection of trial subjects:

Pain scores were measured with Visual Analogue Scale (VAS) on a 0 to 100mm scale in rest and during movement. Preoperative measurement was done during the first questionnaire, just before the study medication was administered. After surgery, a 0 to 10 Numeric Rating Scale (NRS) was obtained by experienced nurses on the recovery ward, since a VAS is unreliable directly after general anesthesia. This NRS score was multiplied by 10 for easy comparison with the VAS. Subsequently, VAS scores were obtained twice a day (morning and evening) by self-reported questionnaires starting the evening of surgery and for 3 consecutive days.

Background therapy:

General anesthesia with propofol, sufentanil, rocuronium and sevoflurane was provided according to the local protocol for laparoscopic IHR. Local wound infiltration with bupivacaine 2.5 mg/ml with a total of 20 ml was applied by the surgeon in all patients. For postoperative analgesia, all patients were allowed to take oral acetaminophen 1000 mg, 4 times a day, and naproxen 500 mg, twice a day. In addition, if this was insufficient, they were allowed to take 5 mg immediate-release opioid oxycodone (e.g. OxyNorm) with a maximum of 6 times a day

Evidence for comparator:

There is increasing evidence that NAC induces analgesia in animal models of inflammatory and neuropathic pain. Its analgesic effects are also demonstrated in humans, although these studies were methodologically poor and relatively low doses were used compared to the animal models.^{12, 22} When effective, NAC can become a new safe and cheap inexpensive co-analgetic in postoperative multimodal pain strategies. Therefore, we hypothesized that the administration of pre-emptive intravenous NAC can reduce postoperative pain and opioid use after laparoscopic inguinal hernia repair. We compared it to placebo (saline).

| | |
|---|------------------|
| Actual start date of recruitment | 03 November 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 60 |
| Worldwide total number of subjects | 60 |
| EEA total number of subjects | 60 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 40 |
| From 65 to 84 years | 20 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

participants were 18 or above with an American Society of Anesthesiologists (ASA) physical status I or II, scheduled for primary unilateral or bilateral laparoscopic IHR by a total extraperitoneal technique between 1 November 2017 and 15 October 2018 in the Máxima Medical Center, Veldhoven, The Netherlands

Pre-assignment

Screening details:

From 1 November 2017 to 15 October 2018, we screened 198 patients of whom 49 patients met exclusion criteria in their electronic chart, 70 patients declined participation and 19 patients were excluded due to organizational aspects. 53 patients received study medication and 7 patients were excluded because of different reasons

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | overall trial |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

participants were randomly assigned using a computer-generated random number table with block size of 30, stratified by unilateral or bilateral procedure. Study medication was prepared according to allocation by the pharmacy in ready to use infusion bags with identical look. Participants and investigators were blinded to treatment allocation. Treatment allocation was performed by the research unit in the Radboud University Center, which was not involved in patient care.

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Acetylcysteine |

Arm description:

NAC 150 mg/kg in 250 mL NaCl 0,9%

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | N-Acetylcysteine |
| Investigational medicinal product code | |
| Other name | Fluimucil, NAC |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

NAC 150 mg/kg in 250 mL NaCl 0,9% intravenous in 15 minutes.

| | |
|------------------|---------|
| Arm title | placebo |
|------------------|---------|

Arm description:

placebo

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Saline 0,9% |
| Investigational medicinal product code | |
| Other name | NaCl 0,9% |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

NaCl 0.9% with equal volume as the NAC group

| Number of subjects in period 1 | Acetylcysteine | placebo |
|---|----------------|---------|
| Started | 30 | 30 |
| Completed | 26 | 27 |
| Not completed | 4 | 3 |
| met exclusion criteria | 1 | - |
| Consent withdrawn by subject | 1 | 1 |
| logistics (medication not there) | - | 2 |
| logistics (did not receive studymedication) | 2 | - |

Period 2

| | |
|------------------------------|---------------------------------|
| Period 2 title | after receiving studymedication |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Acetylcysteine |

Arm description:

NAC 150 mg/kg in 250 mL NaCL 0,9%

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | N-Acetylcysteine |
| Investigational medicinal product code | |
| Other name | Fluimucil, NAC |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

NAC 150 mg/kg in 250 mL NaCL 0,9% intravenous in 15 minutes.

| | |
|------------------|---------|
| Arm title | placebo |
|------------------|---------|

Arm description:

placebo

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Saline 0,9% |
| Investigational medicinal product code | |
| Other name | NaCl 0,9% |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

NaCl 0.9% with equal volume as the NAC group

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: we analysed the data of the patients who actually received study medication

| Number of subjects in period 2 ^[2] | Acetylcysteine | placebo |
|---|----------------|---------|
| | | |
| Started | 26 | 27 |
| Completed | 23 | 23 |
| Not completed | 3 | 4 |
| wrong study medication | - | 1 |
| Adverse event, non-fatal | 1 | 1 |
| received wrong medication | 1 | - |
| Protocol deviation | 1 | 2 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: not all patients were given the study medication due to various reasons

Baseline characteristics

Reporting groups

| | |
|---|----------------|
| Reporting group title | Acetylcysteine |
| Reporting group description: NAC 150 mg/kg in 250 mL NaCL 0,9% | |
| Reporting group title | placebo |
| Reporting group description: placebo | |

| Reporting group values | Acetylcysteine | placebo | Total |
|---|----------------|---------|-------|
| Number of subjects | 26 | 27 | 53 |
| Age categorical | | | |
| age | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 16 | 18 | 34 |
| From 65-84 years | 10 | 9 | 19 |
| 85 years and over | 0 | 0 | 0 |
| not recorded | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| geometric mean | 54 | 61 | |
| standard deviation | ± 15.7 | ± 11.7 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 1 | 2 |
| Male | 25 | 26 | 51 |
| ASA classification | | | |
| ASA, American Society of Anesthesiologists | | | |
| Units: Subjects | | | |
| ASA 1 | 19 | 14 | 33 |
| ASA 2 | 7 | 13 | 20 |

End points

End points reporting groups

| | |
|---|----------------|
| Reporting group title | Acetylcysteine |
| Reporting group description: NAC 150 mg/kg in 250 mL NaCL 0,9% | |
| Reporting group title | placebo |
| Reporting group description: placebo | |
| Reporting group title | Acetylcysteine |
| Reporting group description: NAC 150 mg/kg in 250 mL NaCL 0,9% | |
| Reporting group title | placebo |
| Reporting group description: placebo | |

Primary: VAS during movement

| | |
|--|---------------------|
| End point title | VAS during movement |
| End point description: VAS filled in an electronic or paper questionnaire the morning after surgery by the patient him/her self at home | |
| End point type | Primary |
| End point timeframe: morning after surgery | |

| End point values | Acetylcysteine | placebo | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 ^[1] | 23 ^[2] | | |
| Units: 0-100 | 34 | 26 | | |

Notes:

[1] - 1 had violation of protocol
1 had an allergic reaction (AE)
1 had wrong studymedication
[2] - 2 had violation of protocol
1 needed CPR in OR
1 had wrong studymedication

| | |
|-----------------------------------|---|
| Attachments (see zip file) | database used for analysis/my.data.xlsx |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | VAS movement 24h |
| Statistical analysis description: A sample size of 25 patients in each group was calculated to find a difference of 10 mm on the VAS at 24 hours after surgery based on a mean VAS of 58 mm, a SD of 12.2, a power of 80% and an alpha of 0.05 (double sided). | |
| Comparison groups | Acetylcysteine v placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≥ 0.05 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 48 |
| upper limit | 68 |
| Variability estimate | Standard deviation |
| Dispersion value | 12.2 |

Secondary: VAS in rest

| | |
|--|-------------|
| End point title | VAS in rest |
| End point description: | |
| VAS filled in an electronic or paper questionnaire the morning after surgery by the patient him/her self at home | |
| End point type | Secondary |
| End point timeframe: | |
| morning after surgery | |

| End point values | Acetylcysteine | placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 23 | | |
| Units: 0-100 | 19 | 17 | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | VAS rest 24 h |
| Comparison groups | Acetylcysteine v placebo |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 58 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 48 |
| upper limit | 68 |
| Variability estimate | Standard deviation |
| Dispersion value | 12.2 |

Other pre-specified: Time to discharge

| | |
|--|---------------------|
| End point title | Time to discharge |
| End point description: | |
| Time calculated from end of surgery till discharge from the hospital | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Time calculated from end of surgery till discharge from the hospital | |

| End point values | Acetylcysteine | placebo | | |
|---------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 23 | | |
| Units: minutes | | | | |
| median (inter-quartile range (Q1-Q3)) | 239 (206 to 266) | 200 (171 to 244) | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Time to discharge |
| Statistical analysis description: | |
| Kaplan Meier | |
| Comparison groups | Acetylcysteine v placebo |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | Logrank |

Other pre-specified: Opioid use day 1

| | |
|---|---------------------|
| End point title | Opioid use day 1 |
| End point description: | |
| number of patients that used opioids in 1 day after surgery | |
| End point type | Other pre-specified |

End point timeframe:
opioid use in days after surgery

| End point values | Acetylcysteine | placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 23 | | |
| Units: 0-23 | 5 | 9 | | |

Statistical analyses

| Statistical analysis title | opioid use day 1 |
|---|--------------------------|
| Comparison groups | placebo v Acetylcysteine |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | Fisher exact |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

patients were monitored up until the fourth day after surgery

Adverse event reporting additional description:

patient were monitored (ECG/NIBD/SpO2) during administration of the studymedication and for >2 hours after (during surgery and recovery as well). Also they received a daily questionnaire.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Acetylcysteine |
|-----------------------|----------------|

Reporting group description:

NAC 150 mg/kg in 250 mL NaCL 0,9%

| | |
|-----------------------|---------|
| Reporting group title | placebo |
|-----------------------|---------|

Reporting group description:

placebo

| Serious adverse events | Acetylcysteine | placebo | |
|---|---|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 1 / 27 (3.70%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Bradycardia | Additional description: patient had bradycardia after surgery and a collapse at his parking space; his stay in the hospital was prolonged | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 27 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradyarrhythmia | Additional description: extreme bradycardia after start of surgery; patient was given cardiac massage/ CPR. | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Haematoma | Additional description: patient had pain and swelling postoperative; ultrasound: haematoma. patient was readmitted. | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 27 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|----------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Oxygen saturation decreased | Additional description: after receiving studymedication, desaturation to 90-92% and mild hypotension occurred. Patient received tavegyl and was operated on 90 min later. No complaints after surgery | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 27 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Acetylcysteine | placebo | |
|---|--|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 26 (53.85%) | 0 / 27 (0.00%) | |
| Gastrointestinal disorders | | | |
| Nausea | Additional description: nausea (but not vomiting) during or direct after receiving studymedication | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 0 / 27 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | Additional description: did not need additional oxygen therapie | | |
| subjects affected / exposed | 4 / 26 (15.38%) | 0 / 27 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | 0 / 27 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Endocrine disorders | | | |
| Flushing | Additional description: feeling of flushing during or direct after infusion of studymedication | | |
| subjects affected / exposed | 14 / 26 (53.85%) | 0 / 27 (0.00%) | |
| occurrences (all) | 14 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 20 September 2017 | the investigator on site was changed to Dr. Slooter due to not being GCP certified of the previous investigator. This was filled as an amendment, and was approved. |
| 10 November 2017 | Bilateral hernia inguinalis were also included in the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

We did not reach the calculated 25 patients per group since only 23 patients per group could be analyzed. The high prevalence of side effects seen after intravenous NAC might have resulted in unblinding and could have influenced the treatment effect.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34446544>