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 studymedication

Number of subjects in period 2[2]	Acetylcysteine	placebo
Started	26	27
Completed	23	23
Not completed	3	4
wrong studymedication	-	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 studymedication 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 calcutaled from end of surgery till discharge from the hospital	
End point type	Other pre-specified
End point timeframe: Time calcutaled 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 untill 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 collaps 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 beeing 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