Postoperative pain reduction by pre-emptive N-acetylcysteine: an exploratory randomized controlled clinical trial

Chantal Elise Mulkens,[1] Marieke Staatsen,[2] Lucie van Genugten,[3] Barbara A M Snoeker,[4] Kris C P Vissers,[1] Jörgen Bruhn,[5] Martin J L Bucx[1]

[1]Department of Anesthesiology, Pain and Palliative Medicine, Radboudumc, Nijmegen, Gelderland, The Netherlands
[2]Department of Anesthesiology, Maxima Medical Centre, Eindhoven, Noord-Brabant, The Netherlands
[3]Department of Anesthesiology, Slingeland Hospital, Doetinchem, The Netherlands
[4]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, University of Amsterdam, Amsterdam, The Netherlands
[5]Anesthesiology, Radboudumc, Nijmegen, The Netherlands

Correspondence to
Chantal Elise Mulkens, Department of Anesthesiology, Pain and Palliative Medicine, Radboudumc, Nijmegen, Gelderland, Netherlands; chantal.mulkens@radboudumc.nl

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ABSTRACT

Background A new potential target for multimodal pain management is the group-II metabotropic glutamate receptor subtypes, which can be activated by N-acetylcysteine. We investigated whether pre-emptive administration of N-acetylcysteine leads to a reduction in postoperative pain after laparoscopic inguinal hernia repair.

Methods Sixty American Society of Anesthesiologists I-II patients scheduled for elective inguinal hernia repair were randomized to receive either N-acetylcysteine (150 mg/kg) or placebo intravenously 1 hour before surgery. The primary outcome was the visual analogue score during movement in the morning (approximately 24 hours) after surgery. Among secondary outcomes were postoperative opioid consumption and safety of intravenous N-acetylcysteine.

Results In total, 23 patients were analyzed per group. Pain scores were similar at all timepoints with a 24 hours median score of 34 (IQR of 19.0 to 42.5) in the N-acetylcysteine group and a median score of 26 (16.0 to 50.0) in the placebo group. The percentage of patients using opioids after surgery was 22% versus 39% day 1 (p=0.63); 9% versus 26% day 2 (p=0.14); 9% versus 17% day 3 (p=0.35) in the N-acetylcysteine group compared with placebo group. Side effects resembling anaphylactoid reactions in response to the administration of N-acetylcysteine were present in more than half of the patients.

Conclusions Without finding important differences between N-acetylcysteine and placebo group in pain scores postoperatively, but with a high percentage of bothersome side effects for the N-acetylcysteine group, we would not recommend the use of pre-emptive intravenous N-acetylcysteine to reduce postoperative pain in laparoscopic inguinal hernia repair patients based on this study.

Trial registration number NCT03354572.

INTRODUCTION

Acute postoperative pain (APP) is a worldwide problem causing patient discomfort and suffering. APP is associated with higher postoperative complication rates,[1] causing delayed recovery and discharge[2–7] and having major economic impact. Severe pain is reported in 20%–40% of postoperative patients even today; hence, a high priority should be given to improve perioperative care.[8]

Opioids are still a powerful cornerstone in current perioperative pain management. However, their use is associated with significant side effects such as nausea, vomiting, respiratory depression, constipation and addiction.[9] To reduce these unwanted effects, a multimodal pain strategy is attractive.[7]

Recently, a potential new target for analgesic drugs was identified; the group-II metabotropic glutamate receptor subtypes (mGlu2 and mGlu3 receptors) were localized in the spinal cord and other regions of the nociceptive system in both humans and animals.[10] When activated, these receptors depress pain transmission in the dorsal horn of the spinal cord.[11]

One pharmaceutical agent that is able to activate these receptors is N-acetylcysteine (NAC).[12] NAC is well known for its use in patients with acetaminophen intoxication, where it safely can be administered orally or intravenously in high doses, with only rash being a commonly described side effect.[13–17]

There is increasing evidence that NAC induces analgesia in animal models of inflammatory and neuropathic pain.[18–21] Its analgesic effects are also demonstrated in humans, although these studies were methodologically poor and relatively low doses were used compared with the animal models.[12 22] When effective, NAC can become a new safe and inexpensive coanalgetic in postoperative multimodal pain strategies.

Therefore, we hypothesized that the administration of pre-emptive intravenous NAC can reduce APP and opioid use after laparoscopic inguinal hernia repair (IHR).

METHODS

Study design

The trial was registered prior to patient enrollment at ClinicalTrials.gov (Principal investigator Kris C.P. Vissers, Date of registration: 25 October 2017) and EudraCT (2016-003144-36).

Participants and treatment groups

Eligible 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.

Exclusion criteria were pregnancy, lactation, chronic obstructive pulmonary disease, diabetes, renal or hepatic failure, contraindication for the use of non-steroidal anti-inflammatory drugs or NAC, a history of chronic pain or opiate use before surgery or if a laparoscopic repair was not possible.

After written informed consent, participants were randomly assigned using a computer-generated random number table with block size of 30, stratified by unilateral or bilateral procedure, in a 1:1 ratio to the NAC group (NAC 150 mg/kg in 250 mL NaCL 0,9%) or placebo group (NaCl 0.9% with equal volume as the NAC group). One hour prior to surgery, patients received the study medication intravenously over 15 min. In case of experiencing possible adverse events (eg, flushing, dyspnea) during or after infusion of study medication, 2 mg clemastine was ready for use.[23] 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.

Outcomes

Our primary outcome was pain measured during movement the morning after surgery. Pain scores were measured with Visual Analogue Scale (VAS) on a 0 to 100 mm scale at rest and during movement. Baseline 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 two times a day (morning and evening) by self-reported questionnaires for 3 consecutive days, starting the evening of surgery. Reported time is an approximation due to the self-reported questionnaires.

For postoperative analgesia, all patients were allowed to take oral acetaminophen 1000 mg, four times a day, and naproxen 500 mg, two times a day. If insufficient, they were allowed to take 5 mg immediate-release opioid oxycodone with a maximum of 6 times a day. The patient self-decided whether to take analgesics.

The dose and type of analgesics were evaluated once a day, starting the evening after surgery.

In addition to the pain scores and analgesic use, in the daily evening questionnaire, the following symptoms were registered in conformity with the Opioid-Related Symptom Distress Scale; nausea, vomiting, constipation, difficulty passing urine, difficulty concentrating, drowsiness, dizziness, confusion, fatigue and itchiness. Each item was scored on a 4-point scale for frequency, severity and bothersomeness after which a composite score was calculated.[24]

All questionnaires were filled out on paper or on an electronic device, according to the patient's preference. Electronic questionnaires were automatically saved in the Good Clinical Practice-compliant Castor Electronic Data Capture platform (www.castoredc.com, Ciwit B.V., The Netherlands). The paper questionnaires were returned by the patient and filed into Castor electronic data capture by the researcher.

Study procedure

Patients received information about the study after the indication for surgery was made. Patients filled out the first questionnaire together with one of the two researchers (authors CEM and LvG), after which they received the study medication.

All patients were premedicated with oral acetaminophen 1000 mg and naproxen 500 mg.

Additional data collected were age, gender, weight, ASA classification, tobacco use, time between the end of administration of study medication and start of surgery, duration of surgery, laterality of surgery, if the procedure was performed laparoscopically (with or without open peritoneum) or had to be converted to an open procedure, dose of analgesics administered during surgery, time to administration of first analgesic, total dose of analgesics and time of discharge from the hospital (based on local criteria).

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. Surgery was performed by one of three surgeons, specialized in laparoscopic hernia repair, using a self-adhering Bard mesh.

During the administration of study medication, surgery and the recovery period, vital signs, heart rate, non-invasive arterial blood pressure, pulse oximetry and respiration rate, were monitored.

Statistical analysis

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) (G*power V.3.1.9.2, Franz Faul, Universität Kiel, Germany).[25 26]

Taking into account a loss to follow-up of 20%, the aim was to include a total of 30 patients in each group.

The descriptive statistics were used for nominal and ordinal data by absolute and relative frequencies. Continuous outcomes were summarized with mean and SD if normally distributed, or with median and IQR if not.

Analyses are performed based on modified intention to treat analysis, where patients who did not receive the study medication or had a serious violation of protocol (eg, procedure converted to open Lichtenstein procedure or additive surgery performed) were excluded from analysis. Exclusion from analysis was determined before unblinding.

Inferential statistics were performed for both primary and secondary outcomes. Continuous variables were analyzed by Student's t-test or non-parametric Mann-Whitey U test, depending on normality. Nominal and ordinal data were analyzed using Fisher's exact test. Time-related outcomes were analyzed with Kaplan-Meier and log-rank test. Mean cumulative score of other symptoms was analyzed using mixed analysis of variance (ANOVA) with a correction for sphericity violation according to Greenhouse-Geisser. All statistical analyses were performed using R software (Rstudio V.3.5.0, Boston, USA) and graphs were made with GraphPad Prism (GraphPad Software V.5.03, San Diego, USA).

RESULTS

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. The remaining 60 patients were randomly assigned to two groups (30 patients in both groups). Ultimately, 53 patients received study medication

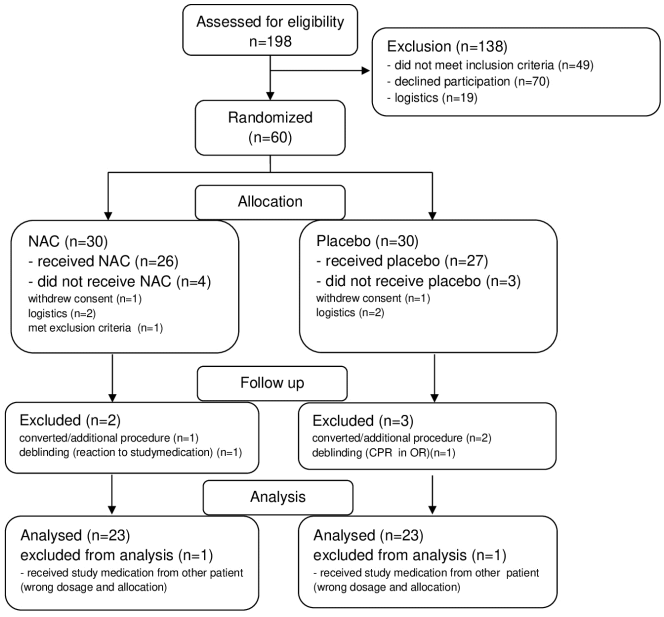

Figure 1 Consort flow diagram This figure represents a CONSORT flow diagram of participants. CONSORT, Consolidated Standard Of Reporting Trials; NAC, N-acetylcysteine.

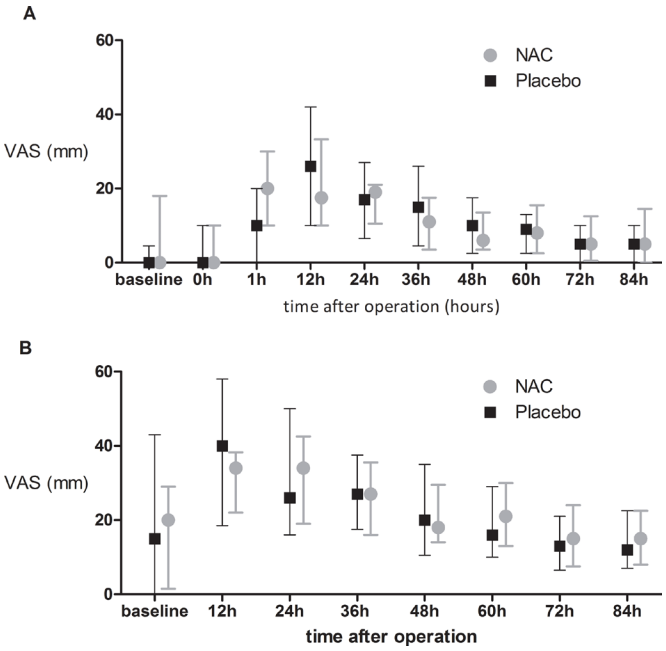

Figure 2 Postoperative pain scores at rest (A) and during movement (B). Postoperative pain scores in millimeters on VAS. Dots represent the median and whiskers the IQR. Baseline scores were obtained before surgery, 0 hour and 1 hour were NRS scores obtained at the recovery ward after surgery and converted to a scale of 0–100. All other pain scores were obtained by a self-reported questionnaire and time is therefore an approximation. Pain scores at baseline, 0 hour, 1 hour and 12 hours were obtained on day of surgery. Pain scores at 24 hours (morning) and 32 hours (evening) were obtained on the first day after surgery. Pain scores at 48 hours (morning) and 60 hours (evening) were obtained on the second day of surgery and pain scores at 72 hours (morning) and 86 hours (evening) were obtained on the third day after surgery. At all timepoints, both during rest and movement, no statistical significant difference was seen (Mann-Whitney U test). NRS, Numeric Rating Scale; VAS, Visual Analogue Scale.

and 7 patients were excluded because of different reasons, consequently 46 patients were included in the analysis (figure 1).

No important difference between treatment groups was observed at baseline, except that patients in the placebo group were classified more often ASA II compared with the NAC group (table 1). There were no missing data in the records during hospital stay, and no missing data for the primary outcome. There was one missing questionnaire in the NAC group of the evening after surgery.

Pain scores and use of analgesics

For our primary outcome, median (IQR) VAS the morning after surgery was 34.0 (19.0 to 42.5) in the NAC group versus 26.0 (16.0 to 50.0) in the placebo group during movement (p=0.92). At rest, these respective values were 19.0 (10.5 to 21.0) and 17.0 (6.5 to 27.0) (p=0.77). We ran a sensitivity analysis, as an intention to treat, and found no appreciable differences for the primary outcome of pain the morning after surgery. Figure 2 depicts the course of VAS at rest (A) and during movement (B) for both groups.

Table 1 Patient demographic and baseline characteristics

	NAC	Placebo
Sample size, n (%)	26 (49)	27 (51)
Mean age (SD) in years	54 (15.7)	61 (11.7)
Sex, n (%)		
Male	25 (96)	26 (96)
Female	1 (4)	1 (4)
ASA classification, n (%)		
I	19 (73)	14 (52)
II	7 (27)	13 (48)
Smoking, n (%)	6 (23)	5 (19)
Mean weight (SD) in kg	79.3 (11.1)	83.6 (13.6)

ASA, American Society of Anesthesiologists; NAC, N-acetylcysteine.

The median (IQR) dose of intraoperative sufentanil was in the NAC group 25 (20 to 27.5) μg and in the placebo group 25 (25, 32.5) μg.

Median (IQR) postoperative time to first analgesic consumption was 210 (112 to 220) min in the NAC group and 213 (114 to 203) min in the placebo group (log rank p=0.70).

Over the total study period, the cumulative dose of acetaminophen per patient in the NAC group was 10.1 g versus 9.2 g in the placebo group (p=0.52). The respective values for naproxen were 2409 mg versus 2500 mg (p=0.97) and for oxycodone 6 mg versus 10 mg (p=0.58). On the day of surgery, oxycodone was used in 50% of patients in the NAC group and 39% in the placebo group (p=0.37). For the 3 consecutive days after surgery, the percentages of patients using oxycodone were 22% versus 39% on day 1 (p=0.63), 9% versus 26% on day 2 (p=0.14) and 9% versus 17% on day 3 (p=0.35) in the NAC group compared with placebo group.

Side effects of NAC infusion

During or after infusion of NAC, more than half of the patients experienced side effects. In the 26 patients receiving NAC, the most frequently observed side effect was flushing (53.8%), half the time combined with urticaria (23.1%). Four (15.4%) of the patients experienced dyspnea, one of whom (3.8%) required the

administration of oxygen because saturation dropped below 93% without oxygen. More than one-third (34.6%) of patients experienced two or more side effects. Because of their side effects, 11 (42.3%) patients received clemastine (2 mg). In one patient, mean arterial pressure decreased more than 20% of baseline, for which ephedrine 5 mg was given successfully to restore blood pressure. None of the side effects were considered life threatening, however, one surgery was postponed for an hour due to dyspnea.

The incidence and severity of the anaphylactoid like reactions during or after infusion of study medication led us to consult our safety board in an early stage, which concluded that these reactions were in range of to be expected side effects and the study was continued.

None of the patients was receiving any placebo-experienced side effects.

Other postoperative symptoms

For other postoperative symptoms, 12 of the 184 questionnaires were not completed with a total of 20 (0.3%) missing items. Given the low percentage of missing data, an available case analysis was performed.

In the NAC group, mean (SD) cumulative symptom scores preoperative, on the first (12 hours), second (36 hours), third (60 hours) and fourth (84 hours) postoperative evening, were 0.20 (0.66), 0.43 (0.90), 0.35 (0.82), 0.17 (0.58) and 0.13 (0.55), respectively. These respective values in the placebo group were 0.04 (0.26), 0.25 (0.64), 0.19 (0.57), 0.15 (0.53) and 0.11 (0.44). In both groups, mixed ANOVA revealed a difference over time ($p=4.74e^{-5}$), but not between groups (p=0.20).

The mean (SD) time between end of administration of study medication and start of surgery in the NAC group was 62.6 (22.3) min and 55.6 (19.2) min in the placebo group (p=0.26). The mean (SD) duration of surgery in the NAC group was 36.7 (14.7) min and 38.9 (17.0) min in the placebo group (p=0.63).

Median (IQR) time between end of surgery and hospital discharge was in the NAC group 239 (206 to 266) min and in the placebo group 200 (171 to 244) min (p<0.01). Sensitivity analysis revealed that this difference persisted when the only patient in this study that had to stay overnight (NAC group) was excluded from analysis.

In the NAC group 6 (26%) of the patients had a bilateral procedure, compared with four (17%) patients in the placebo group (p=0.72). The peritoneum was opened in five (22%) patients in the NAC group and three (13%) patients in the placebo group (p=0.70).

DISCUSSION

The results of this explorative study indicate that in contrast to the hypothesis, preoperative intravenously administered NAC does not seem to have a significant impact on postoperative pain scores in patients having laparoscopic IHR. Moreover, the use of NAC resulted in relevant side effects in more than half of the patients and a prolonged length of stay.

These conclusions were not in line with our hypothesis. First, because in both animal and human studies, an analgesic effect was recently demonstrated. In the studies in humans, oral NAC was demonstrated to reduce pain ratings to laser stimuli and laser-evoked potentials in healthy subjects and to reduce postoperative morphine consumption in patients after knee ligamentoplasty.[12 22]

An important explanation might be a blinding problem in the previous studies. Since NAC was orally administrated without masking its specific taste and odor, this route of administration would have resulted in instantaneous unblinding and possibly overestimation of subjective study endpoints like pain ratings.[27 28] This was the reason that in the present study, NAC was administered intravenously.

A second explanation might be related to the pain ratings of our patients, which were much lower than anticipated on the basis of postoperative pain scores of an open surgical technique.[26] Although there are studies in which postoperative pain is comparable with open surgeries, the use of minimally invasive surgery usually results in less postoperative pain.[29–32] The high level of experience of the three surgeons with this procedure in the present study, and the standard infiltration with bupivacaine during surgery, might have added to the low pain ratings. In addition, it is shown that pain levels experienced by a participant determine analgesic efficacy, with higher pain levels resulting in higher absolute pain score reductions following analgesic administration.[33]

We observed a high incidence of side effects resembling anaphylactoid reactions in response to the administration of NAC. These reactions to intravenous NAC have been observed in earlier studies concerning acetaminophen intoxications[34] but were seldom described as serious and reacted well to antihistaminic.

Although none of our patients had life-threatening anaphylactoid reactions and all reacted favorably to clemastine (a commonly used anti-histamine in Europe), the frequency and intensity of these reactions were a major reason for concern and led us to consult our safety board in an early stage, which concluded that these reactions were in range of to be expected side effects and the study was continued.

Many studies have shown that the combination of dose and speed of infusion used in the present study can be considered safe.[34–37] We have chosen to administer NAC over 15 min for logistic reasons and several studies have shown that slower infusion rates do not appear to give a reduction in adverse effects.[34 35] The reason to choose for a high dose in the present study was that the bioavailability of oral NAC is only 9.1%, whereas it is 100% for the intravenous route.[38] Despite higher serum levels in the present study, we did not find any effect of NAC on pain ratings.

It may be important to realize that the safety of our dosing of NAC was demonstrated in patients with acetaminophen intoxication. In a study in acetaminophen intoxication, more anaphylactoid NAC side effects were detected in patients with lower serum concentrations of acetaminophen, which resulted in the hypothesis that acetaminophen itself might be protective.[16]

LIMITATIONS

First, we did not reach the calculated 25 patients per group since only 23 patients per group could be analyzed. We could have compensated for this drop out by including additional patients. However, the relatively high percentage of anaphylactoid reactions led us to decide not to. In contrast, the percentage of missing items in our included sample was only 0.3%. An addition of patients would not likely have changed our results and conclusion.

A second limitation is that this study was performed in a very homogeneous population, almost exclusively consisting of male patients with little or no comorbidity having only one type of surgery. This limits the generalizability of the conclusions of this study. On the other hand, a potential treatment effect will be

more readily detected in a homogeneous population, which can be considered an advantage.

A third limitation is that we excluded patients using preoperative opioids. Since this is an important predictor for postoperative pain, we might have selected low-pain responders, in which a potential effect of NAC might be difficult to detect.

Finally, the high prevalence of side effects seen after intravenous NAC might have resulted in unblinding and could have influenced the treatment effect. The same holds for the medication to treat the side effects.

CONCLUSIONS

The results of the present study not only demonstrate the absence of a beneficial effect of high-dose intravenous NAC on postoperative pain ratings in this homogenous population of patients having laparoscopic IHR but also show a high prevalence of non-life-threatening anaphylactoid side effects. Therefore, we do not recommend this treatment in these patients, although a beneficial effect in other patients cannot be excluded.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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