RESEARCH PROTOCOL

Peri-operative slow-paced breathing - a non-invasive technique to reduce anxiety in breast cancer surgery patients

Slow-PACE trial

Peri-operative slow-paced breathing - a non-invasive technique to reduce anxiety
Slow PACE trial

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Laboratory sites	*N/A*

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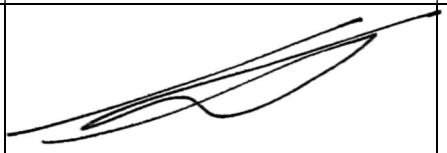
Principal Investigator: Dr. Sabrine N.T. Hemmes, PhD Department of Anesthesiology		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
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
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
(S)AE	(Serious) Adverse Event
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.
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: In the perioperative period anxiety for anesthesia and the surgical procedure is common. Breast cancer surgery patients have a higher level of anxiety compared to other patients undergoing (cancer) surgery. Relaxing breathing techniques, such as deep belly breathing are easy to learn and can have a beneficial effect on postoperative recovery. The quality of evidence in the perioperative setting is low. Slow-paced breathing at a frequency around 6 breaths per minute stimulates vagal activity and can possibly decrease anxiety, reduce mean blood pressure, postoperative pain and postoperative nausea and vomiting (PONV).

Objective: We aim to examine the effects of a guided slow-paced breathing technique (Slow PACE breathing) performed at induction of anesthesia in patients undergoing surgery for breast cancer on anxiety, compared to usual care. We further aim to explore effects on pre-operative blood pressure, per-operative need of hypnotics, postoperative pain and opioid use, PONV and patient satisfaction.

Study design: Single center, two-group, prospective, randomized controlled trial.

Study population: Patients scheduled for breast cancer surgery in the Antoni van Leeuwenhoekziekenhuis.

Intervention: Performance of pre-trained guided Slow PACE breathing by the patient at induction of anesthesia for breast surgery.

Main study parameters: Anxiety scored by Spielberger's State Anxiety Inventory (STAI-S).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There are no physical risks related to the intervention. Participants randomized in the intervention group are trained in Slow PACE breathing and will follow this short daily routine until the day of surgery. All participants are asked to complete two questionnaires at baseline, and one short questionnaire on the day of surgery and at day 1.

1. INTRODUCTION AND RATIONALE

1.1 Perioperative anxiety in breast cancer surgery patients

In the perioperative period anxiety for anesthesia and the surgical procedure is common. In a survey of ~16.000 patients in the U.K. fear for anesthesia was the most important source of perioperative anxiety.[1] Breast cancer surgery patients have a higher level of anxiety compared to other patients undergoing (cancer) surgery, such as surgery for urological cancer.[2]

Perioperative anxiety has a strong influence on different aspects of anesthetic care. It has a negative influence on the induction and maintenance of anesthesia,[3,4] postoperative pain,[5] and postoperative nausea and vomiting (PONV).[6]

1.2 Rationale

Relaxation techniques can have a beneficial effect on anxiety, postoperative pain and possibly length of hospital stay, but the quality of evidence is low. Breath focus with deep belly breathing is a well-known relaxation technique that is easy to learn. It can disengage the mind from distracting thoughts and sensations.[7] The respiratory system is closely connected to the autonomic nerve system (ANS) via the vagal nerve.[8] When breathing is manipulated to a slow frequency, it can increase vagal activity, decrease anxiety and reduce mean blood pressure.[7,8] Stimulation of the vagal nerve is also known to decrease hyperalgesia[10] and mitigate release of pro-inflammatory cytokines.[11] The maximum effect is typically observed at a respiratory frequency around 6 breaths per min (0.1 Hz).[8] This breathing technique is endorsed by the National Health Service (NHS) of the United Kingdom (U.K.) to reduce stress and anxiety.[12] The application of slow-paced breathing and its vagus-mediated effect on has not yet been investigated in the clinical perioperative setting.

1.3 Aim

Slow-paced breathing in this trial is deep belly breathing around a frequency of 6 breaths per min and called Slow PACE breathing in this study. Participants will be trained in Slow PACE breathing pre-operatively and will practice the relaxation technique daily. We aim to examine the effects of Slow PACE breathing in breast cancer patients undergoing surgery on perioperative anxiety, performed at induction of anesthesia.

Performance at induction of anesthesia is chosen as defined intervention to be able to closely monitor non-compliance. If a participant does not manage to perform Slow PACE breathing after training at induction, she will be considered non-compliant.

We further aim to explore effects on blood pressure, per-operative need of hypnotics, postoperative pain and opioid use, PONV and patient satisfaction.

2. OBJECTIVES

Primary Objective: The present study aims to examine the effects of pre-trained Slow PACE breathing performed at induction of anesthesia in patients undergoing surgery for breast cancer on anxiety, scored by Spielberger's State-Trait Anxiety Inventory, state scale (STAI-S),[13] compared to usual care.

Secondary Objectives: To examine the effect of pre-operative Slow PACE breathing compared to usual care on:

- mean blood pressure before induction
- need of hypnotics during induction
- post-operative pain and need of opioids
- postoperative nausea and vomiting (PONV)
- patient satisfaction
- compare anxiety trait scored by Spielberger's State Anxiety Inventory (STAI-T)[13] and general anxiety scored by the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A)[14] at baseline

2.1 HYPOTHESIS

Pre-trained Slow PACE breathing performed at induction of anesthesia attenuates perioperative anxiety.

3. STUDY DESIGN

Single center, two-group, prospective, randomized controlled trial of patients scheduled for surgery for breast cancer. The trial will be conducted according to Good Clinical Practice (GCP) Guidelines and comply with the principles of the Declaration of Helsinki, all applicable national (WMO) and general data protection regulations (GDPR).

4. STUDY POPULATION

4.1 Population (base)

We aim to include patients undergoing surgery for breast cancer in the Antoni van Leeuwenhoekziekenhuis.

4.2 Inclusion criteria

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

- Female
- Undergoing surgery for breast cancer in the Antoni van Leeuwenhoekziekenhuis

4.3 Exclusion criteria

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

- Age < 18 years
- ASA ≥ 4
- History of severe pulmonary illness: severe asthma or severe chronic obstructive pulmonary disease (COPD) GOLD III or IV
- Unable to give written or oral informed consent
- Patient refusal
- Not able to understand Dutch
- No internet access
- Visual or hearing impairments interfering with reading and listening to the online material

4.4 Sample size calculation

With 75 patients per arm, 96% power would be achieved to detect a difference of 5 points in STAI-S score between intervention and control, with a mixed model analysis of repeated measures, at the two-sided 5% significance level in a design with 3 measurements per patient (baseline before surgery, at pre-operative holding and on day 1 post-operatively) having an autoregressive order 1 covariance structure when the standard deviation is 10 and the correlation between observations within the same patient is 0.6.[15] The PASS software module for the test of two means in a repeated measures design was used for this calculation. Accounting for 5% drop-outs/non-compliant patients, 79 patients per arm (total 158) would be needed.

Feasibility analysis

After inclusion of 30 patients, we plan to assess the compliance to Slow PACE breathing just before induction. A failure to compliance is when a patient in the intervention group does not perform the guided Slow PACE breathing at induction of anesthesia, defined as breathing at rate of ≥ 10 breaths per minute. Assuming 95% patients will comply, the lower limit of a binomial exact 95% confidence interval for the compliance rate will be 80%. If the lower limit of the 95% confidence interval for the compliance rate is below 80%, then additional strategies will be deployed to ensure patients adhere to the training of the breathing technique (e.g. weekly calls to check-up and remind the patients) and patients with failure to compliance will be reviewed for point of improvement to increase compliance.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Intervention group:
The intervention consists of performance of pre-trained Slow PACE breathing by the patient at induction of anesthesia for breast cancer surgery.

Slow PACE breathing
Slow PACE breathing is a simple technique of deep belly breathing in a low frequency (0.1 Hz = 6 breaths per minute), performed in supine position, synchronizing the breath with a breath pacer provided by an audio-guide.

Training
Patients will be trained pre-operatively in the Slow PACE breathing technique using an instruction video combined with a personal instruction by video-call.
Thereafter patients are requested to practice Slow PACE breathing once daily for at least 5 minutes using a provided audio-guide, which patients can listen on their portable device (e.g. phone, tablet or laptop).

5.2 Use of co-intervention

Patients in both groups will not receive pre-medication with a benzodiazepine (e.g. oxazepam).

6. INVESTIGATIONAL PRODUCT

No investigational product or treatment is used in this study.

7. NON-INVESTIGATIONAL PRODUCT

No investigational product or treatment is used in this study.

8. METHODS

8.1 Study parameters

8.1.1 Main study parameter

Anxiety scored by Spielberger's State Anxiety Inventory (STAI-S)[13]

8.1.2 Secondary study parameters

- Mean arterial pressure (MAP) just before induction
- Total dose of hypnotics (propofol in milligrams) needed for induction of anesthesia
- Highest numerical rating score for pain (NRS – a linear 11 point scale for self-reported pain) during admission in the recovery room
- Mean cumulative intravenous opioid dose administered during admission in the recovery room – converted to morphine equivalent dose (MEQ)
- Occurrence of postoperative nausea and vomiting in the recovery room requiring anti-emetics
- Patient satisfaction on a scale of 0 (extremely unsatisfied) to 10 (extremely satisfied)
- Anxiety Trait scored by Spielberger's State Anxiety Inventory (STAI-T)[13] at baseline
- General anxiety scored by the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A)[14] at baseline

8.1.3 Other study parameters

Procedure related

- Patient participation to the daily pre-operative practice of Slow PACE breathing

Baseline and surgery parameters

- Age
- Length and weight
- American Society of Anesthesiologists classification (ASA class)
- Sociodemographic status (household, marital state, employment, education)
- Intoxications
- History of sedative or anti-depressive medication use
- Type of breast cancer and type of breast cancer surgery
- Underlying disease(s)

Intraoperative

- The following vital signs are scored at baseline (e.g. measured on the outpatient department), at arrival on the operation room, just before induction and at the first measurement after induction:
  - Systolic-, diastolic-, and mean blood pressure (mmHg)
  - Heart rate (beats per minute)
  - Oxygen saturation (SpO2 in %)
  - Respiratory rate (breaths per minute)
- Type and dose of anesthetic medication used for induction of anesthesia
- Type and dose of vasoactive medication used during or within five minutes after induction
- Anesthetic medication used for maintenance of anesthesia
- Type and dose of administered opioids
- Type and dose of other analgesia
- Anti-emetics used
- Perioperative anesthesiological management regarding locoregional techniques
- Duration of anesthesia
- Duration of surgery

Postoperative - recovery room

- Vital signs
- Highest NRS during admission in the recovery room
- Mean cumulative intravenous opioid dose administered during admission in the recovery room (MEQ)
- Postoperative nausea or vomiting (Y/N)

8.2 Randomisation, blinding and treatment allocation

Randomisation

Patients will be randomly allocated to the study arms (usual care or Slow PACE breathing) using blocked randomization with age (<50 versus ≥50) as randomisation stratification factor in Castor.

Blinding

In this trial it is not possible to blind the patient or the investigators.

8.3 Study procedures

8.3.1 General

To benefit patient comfort and because our easy-to-learn intervention is very low risk and low burden, we aim to provide all contact for this study online, supported by additional contact by (video)phone. We also aim to obtain informed consent digitally (see §11.2). We want to prevent unnecessary visits to the hospital just for the study, because many breast surgery patients do not live nearby the Antoni van Leeuwenhoekziekenhuis.

8.3.2 Measures of anxiety

Baseline (T0)
After obtaining informed consent participants will fill out the baseline questionnaires online: STAI and HADS-A.

Spielberger's State-Trait Anxiety Inventory (STAI) is a well validated and widely used method of measuring an individual's temperament or normal anxiety levels (Trait Anxiety) as well as their current or situational anxiety levels (State Anxiety).[13] Each scale is comprised of 20 statements. The participant scores each question on a 4-point scale ranging from 1 (not at all) to 4 (very much so), with the total score ranging from 20 to 80. Higher scores indicate higher levels of anxiety symptoms. A cut-off score of 40 is commonly used to define probable clinical levels of anxiety. In this study, we will ask participants to complete both Trait and State subscales at baseline. The STAI-T will give an estimation of patients at high risk for anxiety.

Besides the STAI-T we will also take the HADS-A subscale at baseline to identify breast cancer patients with high anxiety levels.[14] The Hospital Anxiety and Depression Scale is a questionnaire that has been found to be a reliable instrument for detecting states of anxiety and depression in a hospital setting. The HADS-A is the anxiety subscale that consists of seven items. Each item is rated on a 4-point scale (ranging from 0 = no not at all, to 3 = yes definitely), for a total score ranging from 0 to 21. A subscale score above 8 denotes anxiety.
The HADS-A is a shorter questionnaire then STAI-T and is used more commonly in the Antoni van Leeuwenhoekziekenhuis to measure general anxiety. We will compare STAI-T to HADS-A in prediction of high general anxiety.

Pre-operative (T1)

On the day of surgery the participant will be asked complete the STAI-S questionnaire just before surgery on the iPad provided by the investigator.

Post-operative (T2)

Post-operatively the participant will be asked complete the STAI-S questionnaire online again. The participant will also be asked to score patient satisfaction on a scale of 0 (extremely unsatisfied) tot 10 (extremely satisfied).

8.3.3 Slow PACE breathing

Training

After completion of the baseline questionnaires, participants randomized in the intervention group will receive a link to the study site with a comprehensive instruction video explaining the Slow PACE breathing technique. Furthermore a 'kick-off' video-call is planned with an investigator to give additional instructions and to answer any questions regarding the breathing technique.

After the initial instructions participants are asked to practice Slow PACE breathing daily for at least 5 minutes, guided by an audio-guide to guide the breathing to a frequency of 6 breaths per minute (0.1 Hz). This audio-file will be available on the site.

The participant will receive the researcher's contact details, so she can always reach us in case of further questions or need for guidance.

Pre-operative

On the day of surgery, the participant will be transported to the operating room, where iv access is obtained and the participant is monitored by electrocardiogram, and pulse oximetry and non-invasive blood pressure will be measure by a cuff every 2-3 minutes (as is the normal procedure). The blood pressure at arrival on the operation will be noted (BP 0).

After the 'time-out procedure' the participant randomized in the intervention group will be asked to start with the Slow PACE breathing technique. This will be guided by the same audio-fragment provided during the training, so the participant has a recognizable breath pacer. The blood pressure (BP 1) and the respiratory rate at the start of induction will be noted in both groups.

8.3.4 Other study procedures

Preoperative

To monitor participation to the daily training sessions, participants in the intervention group will receive a daily email with a reminder and a link to the electronic CRF (Castor), in which they can score if they had time to practice the slow-paced breathing the day before (Y/N).

Intra-operative

Intra-operatively care as usual will be given to all patients. Anesthesia is induced with sufentanil and propofol. The blood pressure directly after induction will be noted (BP 2). Anesthesia is maintained by propofol or sevoflurane at the discretion of the attending anesthetist. Depth on anesthesia will be monitored by the Bispectral index (BIS)-monitor and kept between 40 to 60. Routine general anesthesia, perioperative pain management, anti-emetic prophylaxis and fluid management will be performed and given in the intraoperative and postoperative period according to routine clinical use. Once anesthesia is terminated, patients are transported to the recovery room.

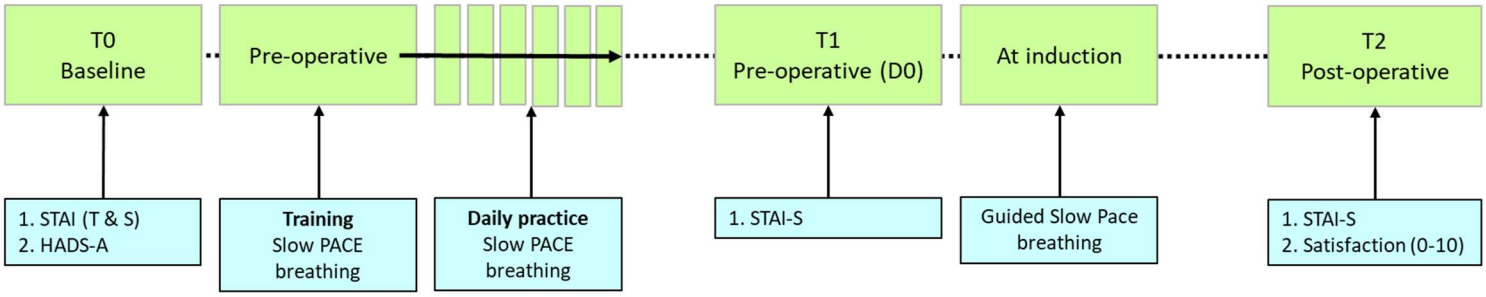
Postoperative

In the recovery room care as usual will be given to all patients. The patient's respiratory rate, SpO_2 and heart rate are measured continuously and a non-invasive blood pressure is measured at least every 15 minutes. Recovery room nurses are aware of the study protocol, but unaware of treatment allocation.
On arrival, the patient is asked to rate their pain on the 11 point Numerical Rating Scale and is asked whether they require any further pain relief. They are also asked for nausea.
All medications given and all pain scores and postoperative nausea or vomiting are noted in the electronic patient record. At least 2 NRS scores are noted for every patient (one on arrival and one before discharge).

End of study period

Data acquisition ends after completion of the post-operative questionnaire (STAI-S) and scoring of patient satisfaction.

Study flowchart



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 subject can either email or call the researcher on the provided email or phone number at any time to inform the researcher. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

Subjects withdrawing consent before any data are collected will be replaced.

8.6 Follow-up of subjects withdrawn from treatment

Patients who are withdrawn by their physician will be subjected to the same follow up as per the study protocol. When a patient withdraws their consent they will not be subjected to follow–up.

8.7 Premature termination of the study

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Reasons for premature termination could be a slow inclusion rate.

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 trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

The investigator will report all AEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following AEs:

- AEs that are a result of the surgical procedure

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, except for the following SAEs:

- SAEs that are a result of the surgical procedure
- SAEs that are unrelated to the breathing technique

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)

Not applicable

9.3 Annual safety report

Not applicable

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)

In this low risk study with no additional risks for the patient, we do not have a DSMB.

10. STATISTICAL ANALYSIS

10.1 Sample size calculation

See Section 4.4 for details.

10.2 Analysis sets

Analyses will be performed on an intention-to-treat (ITT) basis on all randomized patients. A per-protocol analysis set (PPS) will comprise all randomized patients excluding the non-compliant. Additional sensitivity analyses will be performed on the PPS.

10.3 Primary study parameter

For analyzing the STAI-S, a mixed model for repeated measures data (T1= pre-operative, and T2= post-operative) will be used to test for differences between study arms, adjusted for STAI-S at baseline and randomization stratification factor age group. Akaike's information criteria (corrected) and Bayesian information criteria will be used for choosing the correlation structure. Diagnostic residual plots will be used to inspect model assumptions. In a separate exploratory analysis, STAI-T at baseline (dichotomized for anxiety status with cut-off 40 (see protocol Section 8.3.2) will be added as an explanatory variable in the regression, with and without interaction with study arm. The same will be done with HADS-A at baseline, dichotomized using cut-off 8 (Section 8.3.2).

Additional analyses will be performed on the primary study parameter: Differences in STAI-S between measurements T0 and T1, between T1 and T2 and between T0 and T2 will be compared between study arms using linear regression models for each comparison, adjusting for baseline measurements.

10.4 Secondary study parameters

1. MAP just before induction
2. Total dose of hypnotics (propofol) needed for induction of anesthesia
3. Highest NRS during admission in the recovery room
4. Mean cumulative intravenous opioid dose administered during admission in the recovery room – converted to morphine equivalent dose (MEQ)
5. Occurrence of PONV in the recovery room
6. Patient satisfaction on a scale of 0 – 10
7. Anxiety Trait scored by Spielberger's State Anxiety Inventory (STAI-T)[13] at baseline

8. General anxiety scored by the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A)[14] at baseline

Descriptive statistics will include total counts, mean, median, standard deviation (SD), range and interquartile range (IQR. For secondary endpoints 1 to 4, study arms will be compared using a Mann-Whitney U-test or an independent samples t-test, and 95% confidence intervals for the difference of means, or of medians (based on a nonparametric bootstrap procedure) will be obtained, depending on distributional assumptions. For study endpoints 5 and 6 chi-square tests (Fisher's exact test in case of sparse data) will be used for testing for differences between groups. The Cochran-Armitage test might be employed to test for trends in patients satisfaction. Secondary endpoints 7 and 8 will be each analyzed with receiver operating characteristic (ROC) curves, calculating the area under the curve (AUC) and 95% confidence interval and providing sensitivity, specificity, positive predictive value and negative predictive value. The AUCs for endpoints 7 and 8 will be compared using DeLong's test for correlated ROC curves.
To further explore the blood pressure before and after induction of anesthesia between groups, study arms will be compared similarly to the primary endpoint, by using a mixed model for repeated measures data, taking measurements of MAP at arrival on the OR (BP0), at start of induction (BP1) and just after induction (BP2) in an exploratory analysis. Graphical tools will be used to visualize the data (e.g. spaghetti plots) together with descriptive statistics (total opioid dose endpoint) per time point.

10.5 Other study parameters

Demographic data, baseline vital signs, NRS scores, perioperative administered cumulative drugs dosage, applied loco-regional techniques and duration of anesthesia will be reported.

10.6 Interim analysis

No planned interim analysis will be performed

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (7th version of Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and comply with Good Clinical Practice (GCP) Guidelines and all applicable national regulatory requirements and general data protection regulations (GDPR).

11.2 Recruitment and consent

11.2.1 Recruitment

Patients will be screened for eligibility during the routine preoperative consultation. Should a patient be eligible, then she will be contacted by one of the researchers by phone to receive oral information about the study. This contact will take place at least 2 weeks prior to the surgical procedure.

Many patients in this population live far from the hospital and do not frequently visit the Antoni van Leeuwenhoek hospital in person. If receiving neoadjuvant treatment, they often receive this in a hospital near their home address. To benefit patient comfort and because our easy-to-learn intervention is very low risk and low burden, we aim to provide all contact for this study online, supported by additional contact by (video)phone. We used the ‘Handreiking elektronische toestemmingsverlening voor deelname aan medisch-wetenschappelijk onderzoek, 22 augustus 2022’ and the ‘Checklist METC NedMec eConsent (NL) version 1 jan 2023’ provided by the Centrale Commissie Mensgebonden Onderzoek (CCMO) to ensure compliance with article 6 lid 2 WMO.

If a patient is interested in participation, the document with the patient information and informed consent form will be sent digitally in an attachment by email using Zivver. Zivver is a service used in the AvL to send and receive information securely between patients and doctors in end-to-end encrypted emails protected by a personal password. Only the sender and the recipient can open the email and access the attached files. Zivver nor the IT department has access to the personal password, nor to the decryption key. This means that nobody but the sender and the recipient of the message can decrypt the message and read its content. Zivver complies with the concerning privacy and information protection regulations, like GDPR.

In Zivver the researcher can audit if the email has been received and opened by the recipient. The IT department has access to the audit-logs in which they can audit when

and where the email has been accessed and if any settings have been changed, without having access to the content of the email.

11.2.2 Consent

The patients will be given sufficient time, at least 48 hours, to consider their decision and discuss this with their relatives or the independent expert. If the patient is willing to participate, oral consent is obtained by telephone. Hereafter an email with the patient information and informed consent form (IFC), signed and dated by the researcher, will be sent as attachment using Zivver to the email address that the participant personally gives to the researcher during this telephone contact. This email is secured twice with a personal password which the researcher will give to the participant during the same phone call. The participant will sign and date the IFC and send it back as attachment to the researcher by email using Zivver. The participant will thus have a digital copy of the IFC. If the patient prefers to give written consent personally, then an appointment with one of the researchers will be made in the hospital to obtain written informed consent and for further personal contact and information.
The IFC signed by both participant and researcher will be stored digitally and will be safeguarded by the primary investigator digitally and protected by a password (also see §12.1).

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The patient risk is negligible. The patient burden comprises of the training instruction, daily practice and completing the questionnaires is considered minimal.

11.5 Compensation for injury

The sponsor/investigator has been granted a dispensation of the liability insurance by the accredited METC.

11.6 Incentives

As this is an investigator initiated study, without additional funds, no financial incentive is available for patients. The patients in the intervention group are trained a stress reducing breathing technique, which they can apply in other stressful situations. The control group will have access to the training video and audio fragments on request, after the study has finished.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All data will be handled confidentially and anonymously. Every subject will receive a subject identification code that contains no patient identifying data. The code list and key to the code will be safeguarded by the primary investigator digitally and protected by a password. Should other parties, such as a monitor or the Inspectie Gezondheidszorg en Jeugd, require data to be traced back to an individual subject, this code list can be used. All involved parties will handle patient data in a confidential manner. All relevant data will be recorded and stored in an electronic case report form (eCRF) using this identification code. Castor will be used to minimize errors and to ensure traceability. The data will be recorded in the eCRF at the bedside, or they will be extracted from the electronic patient record. All signed digital informed consent forms will be stored digitally, safeguarded by the primary investigator and protected by a password. The local researchers and project leader are responsible for data processing and are the only people that have access to the source data. All data will be stored for the length of the study and for 15 years afterwards, for further publication. All handling of personal data will comply with the Dutch Personal Data Protection Act.

12.2 Monitoring and Quality Assurance

As this trial is a low risk trial, we protocolize for a planned monitoring once a year.

12.3 Amendments

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

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 investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. 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 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.

12.6 Public disclosure and publication policy

This study has been registered with the Netherlands Trial Register under the trial number NL84554.041.23. The results of the study will be published in a peer-reviewed (inter-) national scientific journal. We will submit analyses to scientific journals in the field of anesthesiology. The results of this study will be disclosed unreservedly according to the Central Committee on Research Involving Human Subjects (CCMO) statement on publication policy (http://www.ccmo.nl/attachments/files/ccmo-statement-publicatiebeleid-3-02-en.pdf). Data will be made accessible according to the FAIR guidelines.

13. STRUCTURED RISK ANALYSIS

Not applicable.

14. REFERENCES

1. Walker EMK, Bell M, Cook TM, Grocott MPW, Moonesinghe SR; Central SNAP-1 Organisation; National Study Groups. Patient reported outcome of adult perioperative anaesthesia in the United Kingdom: a cross-sectional observational study. Br J Anaesth. 2016;12;117(6):758-766. Erratum in: Br J Anaesth. 2017;1;119(3):552.
2. Pastore AL, Mir A, Maruccia S, Palleschi G, Carbone A, Lopez C, Camps N, Palou J. Psychological distress in patients undergoing surgery for urological cancer: A single centre cross-sectional study. Urol Oncol. 2017 Dec;35(12):673.e1-673.e7. doi: 10.1016/j.urolonc.2017.08.006. Epub 2017 Sep 5. PMID: 28887095.Laufenberg-Feldmann R, Kappis B. Assessing preoperative anxiety using a questionnaire and clinical ratings: a prospective observational study. Eur J Anaesthesiol. 2013;30(12):758–63.
3. Gras S, Servin F, Bedairia E, et al. The effect of preoperative heart rate and anxiety on the propofol dose required for loss of consciousness. Anesth Analg 2010; 110:89–93.
4. Kalkman CJ, Visser K, Moen J, et al. Preoperative prediction of severe postoperative pain. Pain 2003; 105:415–423.
5. Munafo MR, Stevenson J. Anxiety and surgical recovery. Reinterpreting the literature. J Psychosom Res 2001; 51:589–596
6. Powell R, Scott NW, Manyande A, Bruce J, Vögele C, Byrne-Davis LM, Unsworth M, Osmer C, Johnston M. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database Syst Rev. 2016;26;2016(5):CD008646.
7. Bernardi L, Spadacini G, Bellwon J, Hajric R, Roskamm H, Frey AW. Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure. Lancet. 1998;2;351(9112):1308-11. doi: 10.1016/S0140-6736(97)10341-5.
8. Bernardi L, Porta C, Gabutti A, et al. Modulatory effects of respiration. Auton Neurosci 2001; 90: 47–56.Bernardi L, Gabutti A, Porta C, Spicuzza L. Slow breathing reduces chemoreflex response to hypoxia and hypercapnia, and increases baroreflex sensitivity. J Hypertens. 2001;19(12):2221-9.
9. https://www.health.harvard.edu/mind-and-mood/relaxation-techniques-breath-control-helps-quell-errant-stress-response
10. Chakravarthy, K., Chaudhry, H., Williams, K. et al. Review of the Uses of Vagal Nerve Stimulation in Chronic Pain Management. Curr Pain Headache Rep 2015;19, 54.
11. Sundman and Olofsson, Neural control of the immune system, Advances in Physiology Education 2014 38:2, 135-139
12. https://www.nhs.uk/mental-health/self-help/guides-tools-and-activities/breathing-exercises-for-stress/

13. Spielberger, C.D. (2010). State-Trait Anxiety Inventory. In The Corsini Encyclopedia of Psychology (eds I.B. Weiner and W.E. Craighead).
14. Zigmond A, Snaith R. The hospital anxiety and depression scale. Acta Psychiat Scand 1983;67:361-70.
15. Lin SY, Huang HA, Lin SC, Huang YT, Wang KY, Shi HY. The effect of an anaesthetic patient information video on perioperative anxiety: A randomised study. Eur J Anaesthesiol. 2016 Feb;33(2):134-9.