Vagal Augmentation with Transcutaneous Stimulation: a phase II, explanatory, randomised controlled trial

Statistical Analysis Plan

Version 1.0; Date: 28.6.2022

Contents

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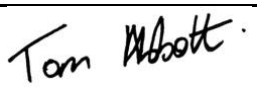
Signature	
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Administrative information

REC number:	21/LO/0272
Trial Sponsor:	Queen Mary University of London
Trial Funder:	King Edward VII Hospital;
Trial registration:	researchregistry
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Protocol version (date):	Version 2.0 (22/11/2021)

Members of the writing committee

Tom EF Abbott(AP) wrote the statistical analysis plan, with input from Gareth Ackland (GA) and AP

Timing of the SAP

Version 1.0 of the SAP was written before AP had access to unblinded data (i.e. trial dataset with the variables for treatment allocation included).

Remit of the SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the VATS trial. It is important to set these out and to agree them in advance of inspecting the outcome data for the trial, so that data derived decisions in the analysis are avoided. Any exploratory, post hoc or unplanned analysis will be clearly identified as such in the respective study analysis report.

Background and trial design

Study objectives	**Primary Objective** Absolute pain score 24h after surgery, assessed by 100mm visual analogue score (VAS). **Secondary Objectives** Minimal Clinically Important Difference [MCID] in visual analogue score; VAS adjusted for pain severity; postoperative morbidity; opioid use; heart rate variability [explanatory variable].
Study design	Phase II, single-centre, two-arm, parallel group randomised controlled trial
Setting	Surgical services of hospitals undertaking major trauma orthopaedic surgery.
Participants	**Inclusion criteria** • Scheduled to undergo major elective or urgent (not requiring intervention in <24h) noncardiac (orthopaedic) surgery under general and/or spinal anaesthesia, expected to take >120 minutes from the induction of anaesthesia. • American society of Anaesthesiologists (ASA) grade I–III. • Aged 18 years and over. **Exclusion criteria** • Requiring invasive mechanical ventilation and/or new renal replacement therapy during hospitalization. • Cardiac arrhythmia requiring therapy prior to/during hospitalization. • Dementia. • Cancer requiring active/ongoing therapy. • Postural orthostatic tachycardia syndrome. • Lower limb neuromuscular disorders. • Auricular dermatitis. • Day-case surgery, not requiring overnight hospital admission.
Interventions	**Sham Group:** Patients randomised to receive sham treatment will receive no current via the bilateral auricular leads for 50 minutes. **Stimulation Group:** Patients randomised to receive stimulation will receive a sub-threshold current via the bilateral auricular leads for 50 minutes.
Primary outcome measure	The primary outcome is absolute pain score 24h after surgery, assessed using the 100mm visual analogue score.

Outcome measures

Primary outcome measure

The primary outcome will be the absolute VAS pain score 24h after surgery.

Secondary outcome measures

Minimally Clinical Important Difference: The proportion of participants who achieve a minimally clinical relevant reduction >10mm using the 100 mm pain Visual Analogue Score will be compared before and after the period of stimulation in each group, before and after surgery.[1]

VAS stratified by pain intensity: Absolute changes in pain score before and after sham/stimulation will be compared before and after the period of stimulation in each group before and after surgery, stratifying for mild, moderate, and severe pain intensity before the intervention. A pain VAS score of 30, 70, and 100 indicates the upper boundaries of mild, moderate, and severe pain intensity.[1]

Postoperative morbidity: Defined by the Post Operative Morbidity Survey (POMS) before (preoperative) and after (postoperative days 3 and 7) surgery. The POMS is an 18-item survey which examines nine domains (pulmonary, infection, renal, gastrointestinal, cardiovascular, neurological, haematological, wound, pain) of postoperative morbidity.[2] The POMS is a reliable and valid measure of short-term postoperative morbidity following major surgery.[20] The hospital electronic patient management system will be used to prospectively record POMS on postoperative days 0 (preoperative), 3 and 7. Clavien-Dindo grades for complications during hospital stay will also be reported.

Opiate use: Opiate consumption [expressed as morphine equivalents] before and for three days after surgery.

Explanatory measures

Autonomic function, as assessed by time and frequency domain measures of heart rate variability 10 minutes before and 10 minutes after each stimulation session, before and after surgery.[3]

Sample size and randomisation

Sample size calculation

Consensus perioperative guidelines recommend that the Visual Analogue Score should be used to assess pain intensity.[4] 72 patients are required to have a 90% chance of detecting, significant at the 1% level, a decrease in mean VAS (the primary outcome measure) from 34mm in the control group to 23mm in the experimental group after surgery (standard deviation of outcome 12mm). Allowing for 10% dropout per group, a final sample size of 86 participants is required, analysed by intention to treat.

Randomisation procedure

Randomisation will occur after the participant has provided informed consent before the surgical procedure is due to start. Participants are randomly assigned (1:1) by block randomisation to receive stimulation or sham stimulation to ensure a balance in sample size across groups over time (Power

Analysis & Sample Size (PASS) 2021, Utah, USA). Investigators will log on to a secure web-based randomisation file to obtain a unique patient identification number and allocation to a treatment group.

Analysis methods

General analysis principles

Analyses will follow the intention-to-treat principle: all randomised patients with a recorded outcome will be included in the analysis and analysed according to the treatment to which they were randomised [5, 6]. Patients will be included in the analysis, regardless of whether the treatment they received was compliant with the protocol. Definitions of what constitutes a recorded outcome for each outcome can be found in Appendix 1. Patients with missing outcome data will be excluded from the analysis. Missing data for baseline covariates to be included in the analysis model will be accounted for using mean imputation for continuous variables and the missing indicator approach will be used for missing data for categorical variables [7, 8].

For the analysis of the primary outcome, each secondary outcome, and all process measures, we will present the following information:

The number of patients included in each analysis, by treatment group

A summary statistic of the outcome (e.g. mean (SD), number (%)), by treatment group

The estimated treatment effect

A 95% confidence interval for the estimated treatment effect

A two-sided p-value

For all analyses, a significance level of 5% will be used.

Representativeness of patients

A log of eligible patients not recruited to the trial will be kept. Reasons for non-participation will be categorised and summarised. Participation in the trial, treatment allocation and completeness of follow-up will be illustrated by a CONSORT flow diagram [9].

Baseline characteristics

Baseline characteristics will be summarised for each treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. The following baseline characteristics will be summarised by treatment group:

- Demographic: age (years), gender (male/female)
- Co-morbid disease: Hypertension; Ischaemic heart disease; Cardiac failure; Cardiac valvular disease
- Stroke/TIA; Peripheral vascular disease; Diabetes mellitus, type I; Diabetes mellitus, type II ; COPD; Asthma Smoker; Interstitial or other respiratory disease; Liver cirrhosis; GI pathology-other; Osteoarthritis; Rheumatoid arthritis; Inflammatory disease; Active cancer; Previous cancer
- ASA grade

- Medications: Statin; Anticoagulant; Antiplatelet; Beta-blocker; Calcium channel antagonist; Heart rate limiting calcium channel antagonist; Doxazosin; Diuretic; Nitrate; Angiotensin converting enzyme inhibitors; Angiotensin II Receptor Blockers; Other hypertensives; Other heart failure Rx; Digoxin/anti-arrythmic; Other Rx Asthma Rx; Opioids-oral; Opioids- parental; NSAIDs; Paracetamol' Steroids; Metformin; Insulin; Any other diabetic medication
- Pre-operative blood test results (within 1 week before surgery or most recent): Haemoglobin; Serum Albumin; Creatinine; white cell count; Neutrophil count; Lymphocyte count; CRP
- Anxiety: GAD-7 and Amsterdam preoperative anxiety score.

Analysis software

All analyses will be conducted in NCSS 2021 (NCSS 2021 Statistical Software (2021). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.).

Analysis of primary outcome

Primary analysis

Difference in absolute pain score 24h after surgery, assessed by 100mm visual analogue score (VAS), under the ITT principle [10]. Repeat-measures ANOVA will be used to compare VAS before versus after stimulation/sham, with post hoc Tukey-Kramer testing.

Analysis of secondary outcomes

Minimally clinical relevant reduction before and 24h after surgery: The proportion of participants who achieve a minimally clinical relevant reduction >10mm using the 100 mm pain Visual Analogue Score will be compared before and after the period of stimulation in each group, before and after surgery.[1] Paired t-test will compare between sham and stimulation groups.

VAS stratified by pain intensity: Absolute changes in pain score before and after sham/stimulation will be compared before and after the period of stimulation in each group before and after surgery, stratifying for mild, moderate, and severe pain intensity before the intervention. Repeat-measures ANOVA will be used to compare VAS before versus after stimulation/sham, with post hoc Tukey-Kramer testing.

Postoperative morbidity: Absence of POMS will be compared between groups serially [time to become free of morbidity after surgery]. Individual POMS will be reported in a separate table but not tested formally.

Opiate use: Opiate consumption [expressed as morphine equivalents] will be presented before and for three days after surgery, between stimulation/sham, but not tested formally.

Explanatory measures

The effect of stimulation/sham on time and frequency domain measures of heart rate variability 10 minutes before and 10 minutes after each stimulation session, before and after surgery.[3] . Repeat-

measures ANOVA will be used (group: stimulation/sham X experimental timepoint X before/after surgery), with post hoc Tukey-Kramer testing.

Exploratory analyses

Exploratory analyses will be repeated to examine the relationship between autonomic parameters and achieving MCID, independent of group allocation to stimulation/sham.

Sensitivity analysis

The amount of missing primary outcome data is anticipated to be minimal but will be accounted for in a sensitivity analysis if missing data is greater than 5%.

Other analyses, data summaries and graphs

Clinical management

Clinical management for sham/stimulation groups will be summarised but not subjected to statistical testing. Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group. The sham/stimulation groups will be compared for the following clinical management characteristics:

- Anaesthetic technique
- level of care on the first night after surgery

Process measures

Summary measures will be presented separately for each treatment group. All patients with recorded data will be included in the summary. Formal statistical analysis will not be performed. Duration of hospital stay after surgery (days) will be summarised using median (IQR).

Safety analyses

Adverse events and serious adverse events will be presented as a number (%) by treatment group. All patients with a recorded outcome will be included in the summary. In addition to this, 'other' adverse events will be reported separately if prevalence is more than 5% across all participants in the trial.

- Arrhythmia
- Headache
- Pain
- Skin irritation at the stimulation site
- Dizziness
- Other
- None

Protocol deviations

Numbers and percentages of protocol deviations will be reported. Protocol deviations will be reported as participants who stopped therapy either during the stimulation period, before and/or after surgery. Stimulation current, as applicable, will be reported to demonstrate variation in protocol parameters.

Complications within 30 days after surgery

The number and percentage of patients experiencing each of the following complications will be presented by treatment allocation. These summaries will not be subjected to any statistical testing. These complications are defined by the Clavien-Dindo grade.[11]

References

1. Myles, P.S., et al., *Measuring acute postoperative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state.* Br J Anaesth, 2017. **118**(3): p. 424-429.
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10. Yelland, L.N., et al., *Applying the intention-to-treat principle in practice: Guidance on handling randomisation errors.* Clinical Trials, 2015. **12**(4): p. 418-423.
11. Clavien, P.A., et al., *The Clavien-Dindo classification of surgical complications: five-year experience.* Ann Surg, 2009. **250**(2): p. 187-96.

Appendix 1: Derived outcomes and variables

Variables

Primary outcome

VAS 24h after surgery: Expressed as 0-100mm.

Secondary outcomes

Minimally Clinical Important Difference: Expressed as 0-100mm.

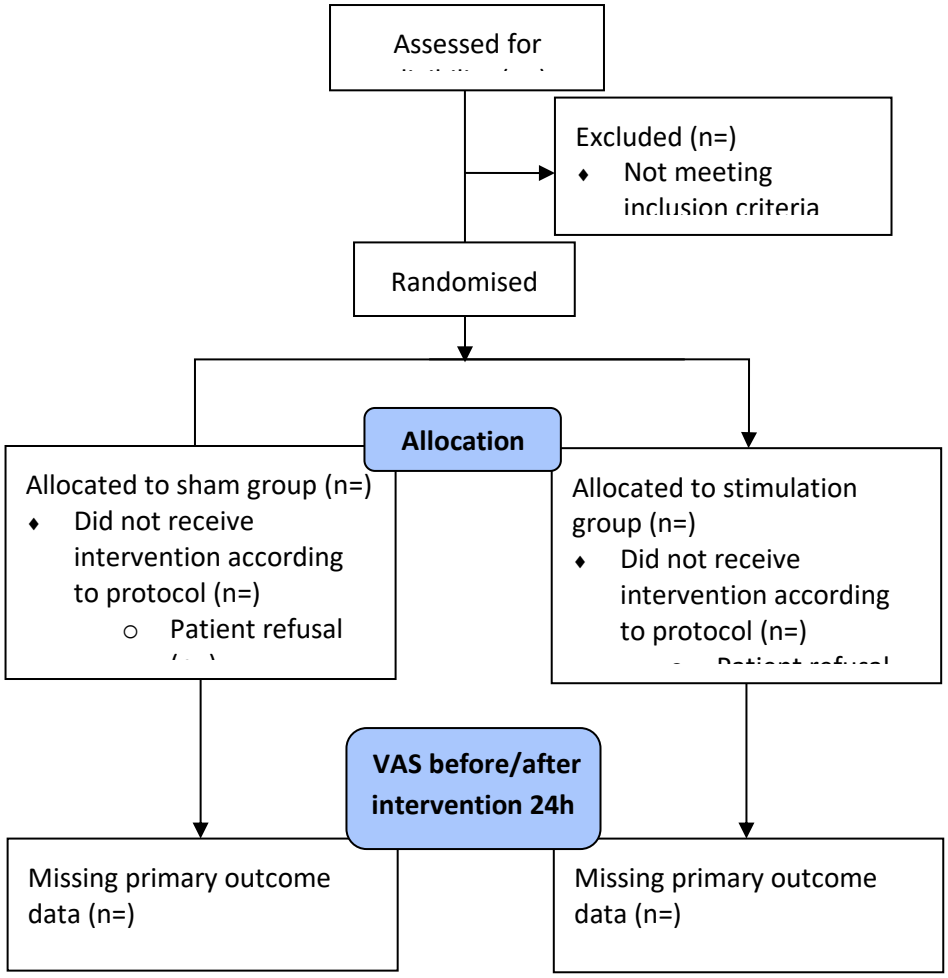
VAS stratified by pain intensity: Expressed as 0-100mm.

Postoperative morbidity: 18-item survey reporting nine domains (pulmonary, infection, renal, gastrointestinal, cardiovascular, neurological, haematological, wound, pain) of postoperative morbidity.[2]

Opiate use: Opiate consumption – morphine equivalents [mean SD]

Appendix 2: CONSORT flow diagram

The following information will be provided in the CONSORT flow diagram:



Appendix 3: Dummy tables

Table 1: Baseline Characteristics

Baseline Characteristics	Number of patients with available data - no. (%)		Summary measure	
	Sham (n=XX)	Stimulation (n=XX)	Sham	Stimulation
Gender - no. (%)				
Male				
Female				
Age (years)				
Mean (SD)				
Median (IQR)				
Current Smoker - no. (%)				
American Society of Anaesthesiology grade >II - no. (%)				
GAD-7 score				
Amsterdam preoperative anxiety score				
Chronic comorbid disease - no. (%)				
Hypertension				
Ischaemic heart disease				
Cardiac failure				
Cardiac valvular disease				
Stroke/TIA				
Peripheral vascular disease				
Diabetes mellitus, type I				
Diabetes mellitus, type II				
COPD				
Asthma				
Smoker [ex/current]				
Interstitial or other respiratory disease				
Liver cirrhosis				
GI pathology-other				
Osteoarthritis				
Rheumatoid arthritis				
Inflammatory disease				
Active cancer				
Previous cancer				
Planned surgical procedure - no. (%)				
Pre-operative blood tests results				
Haemoglobin (d/DL)				
Mean (SD)				
Creatinine (µmol/L)				
Albumin				
White cell count				
Neutrophil count				
Lymphocyte count				
C-reactive protein				
Medication - no. (%)				

Statin				
Anticoagulant				
Antiplatelet				
Beta-blocker				
Calcium channel antagonist (amlodipine/felodipine				
Heart rate limiting calcium channel antagonist				
Doxazosin				
Diuretic				
Nitrate				
ACE inhibitors				
Angiotensin II Receptor Blockers (ARBs)				
Other hypertensive				
Other heart failure Rx				
Digoxin/anti-arrythmic.				
Asthma Rx				
Opioids-oral				
Opioids- parental				
NSAIDs				
Steroids				
Paracetamol				
Metformin/ Insulin/ Any other diabetic medication				

Abbreviations: SD, standard deviation; IQR, Interquartile range; COPD, chronic obstructive pulmonary disease.

Haemoglobin

Table 2: Clinical management

Clinical management characteristics	**Number of patients with available data - no. (%)**		**Summary measure**	
	Sham (n=XX)	**Stimulation (n=XX)**	**Sham**	**Stimulation**
Surgery - no. (%)				
Ortho-lower limb Ortho-upper limb				
Duration of surgery [minutes]				
Anaesthetic technique - no. (%)				
General anaesthesia alone				
General anaesthesia + epidural/spinal				
General anaesthesia + spinal				
General anaesthesia + other regional				
Regional anaesthesia + sedation				

Abbreviations: SD, standard deviation; IQR, Interquartile range

Table 3: Protocol Adherence before and after surgery

Adherence and contamination - no. (%)	**Sham (n=XX)**	**Stimulation (n=XX)**
≥1 treatment deviation		
Current before		
Current after		
Other deviation		

Table 4: Primary and secondary outcomes.

Outcomes	Number of patients with available data and included in analysis - no. (%)		Summary measure		Treatment effect (95% CI)	P-value
	Sham (n=XX)	Stimulation (n=XX)	Sham	Stimulation		
Primary outcome						
VAS 24h after surgery						
Secondary outcomes						
MCID						
VAS before surgery						
VAS [pain intensity]						
Opiate use						

Table 5: PostOperative Morbidity survey: reported before surgery, 3 and 7 days after surgery.

Complication	Number of patients with available data - no. (%)		Summary measure	
	Sham (n=XX)	Stimulation (n=XX)	Sham	Stimulation
De novo requirement for supplemental oxygen.				
Respiratory support.				
Currently on antibiotics.				
Temperature >38°C/ blood cultures in last 24h.				
Oliguria (< 500 mL/day),				
Serum creatinine (>30% from baseline value)				
Unable to tolerate normal enteral diet				
Nausea/vomiting.				
Myocardial infarction or ischemia				
Hypotension (drug therapy/fluid >200 mL/h)				
Atrial or ventricular arrhythmia				
Pulmonary edema				

De novo focal neurological deficit				
Coma.				
Confusion/delirium.				
Wound dehiscence requiring surgical exploration				
Wound drainage/pus.				
Blood, platelets, fresh frozen plasma or				
cryoprecipitate.				
Surgical wound pain-parenteral opiates				
Regional anesthesia.				
Not mobilising alone				
None				

Table 6: Process measures

Process measures	**Number of patients with available data - no. (%)**		**Summary measure**	
	Sham (n=XX)	**Stimulation (n=XX)**	**Sham**	**Stimulation**
Re-admission to hospital within 30 days of surgery – no. (%)				
Duration of hospital stay after surgery (days) - Median (IQR)				
Number of patients admitted to a critical care unit - no. (%)				

Table 7: Adverse events

Adverse Events - no. (%)	**Sham (n=XX)**	**Stimulaton (n=XX)**
Patients with ≥ 1 adverse event		
Total number of adverse events		
Type of adverse events		
Arrhythmia [a]		
Headache		
Pain [b]		
Skin irritation at the stimulation site		
Dizziness		
Other		
None		

[a] Defined as clinically detected arrythmia during or after day of intervention.

[b] Defined as localised pain to auricular region