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Clinical Investigation

CLINICAL INVESTIGATION

Effect of transauricular nerve stimulation on perioperative pain: a single-blind, analyser-masked, randomised controlled trial

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Abstract

Background: Activation of central autonomic pathways, including those regulating the arterial baroreflex, might reduce acute pain. We tested the hypothesis that transcutaneous auricular nerve stimulation (TAN) reduces pain after orthopaedic trauma surgery through autonomic modulation.

Methods: A total of 86 participants aged >18 yr were randomly assigned to 50 min of either sham or active bilateral TAN, undertaken before, and again 24 h after, surgery for orthopaedic trauma. The primary outcome was absolute change in pain 24 h postoperatively, comparing the 100 mm visual analogue scale (VAS) before and after TAN. Secondary outcomes included the minimal clinically important difference in pain (>10 mm increase or reduction in VAS) before/after surgery, using intention-to-treat analysis. Holter monitoring, the analysis of which was masked to allocation, quantified autonomic modulation of heart rate.

Results: From June 22, 2021 to July 7, 2022, 79/86 participants (49 yr; 45% female) completed TAN before and after surgery. For the primary outcome, the mean reduction in VAS was 19 mm (95% confidence interval [CI]: 12–26) after active TAN (n=40), *vs* 10 mm (95% CI: 3–17) after sham TAN (n=39; P=0.023). A minimally clinically important reduction in postoperative pain occurred in 31/40 (78%) participants after active TAN, compared with 15/39 (38%) allocated to sham TAN (odds ratio 5.51 [95% CI: 2.06–14.73]; P=0.001). Only active TAN increased heart rate variability (log low-frequency power increased by 0.19 ms^2 [0.01–0.37 ms^2]). Prespecified adverse events (auricular skin irritation) occurred in six participants receiving active TAN, compared with two receiving sham TAN.

Conclusion: Bilateral TAN reduces perioperative pain through autonomic modulation. These proof-of-concept data support a non-pharmacological, generalisable approach to improve perioperative analgesia.

Keywords: autonomic modulation; complications; inflammation; neuromodulation; orthopaedic surgery; pain; perioperative; postoperative pain

Editor's key points

- This single blind sham controlled proof of concept study shows the feasibiity and efficacy of bilateral transauricular nerve stimulation on postoperative pain in patients receiving opioid analgesia through enhanced autonomic function.
- These data suggest a role for autonomic changes in the regulation of postoperative pain and highlight the potential for this noninvasive cost-effective neuromodulation technique for postoperative pain.

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Activation of the central autonomic network by noxious stimuli modulates both descending analgesic pathways and adaptive autonomic responses to pain.[1] Systemic inflammation,[2] regional[3] and general[4] anaesthesia disrupt autonomic control during the perioperative period, thereby disrupting neural pathways that harness pain and autonomic control. Acute perioperative pain contributes to the development of morbidity[5] through several parallel mechanisms.[6] Preventing the loss of, or restoring, autonomic regulation limits pain directly,[7,8] and through reducing systemic inflammation[9] that is initiated by cell damage after surgical tissue trauma.[10,11] Activation of the arterial baroreflex, the dysfunction of which is common perioperatively,[10] reduces pain in experimental models[12] and is associated with hypoalgesia in humans.[1,13] Central[14] and efferent (vagal)[15] components of the baroreflex may therefore reduce pain after major surgery for trauma, which potentially limits the adverse effects of opioid prescribing.[16]

Autonomic neuromodulation using transcutaneous auricular nerve stimulation may reduce pathological pain, but the observed effects in models of evoked pain are variable. Notably, there is a paucity of interventional studies that specifically investigate the correlation between acute pain and autonomic measures.[17,18] Transcutaneous auricular neuromodulation may exert analgesic effects through numerous mechanisms, including reducing inflammation, subcortical modulation of locus coeruleus–noradrenergic signalling, and activation of serotonergic and endorphinergic analgesic pathways.[19]

Proof-of-concept studies in human volunteers using noninvasive electrical stimulation of the (putative) auricular branch of the vagus nerve offer a feasible, accessible approach[17] to restore—or minimise—perioperative autonomic dysregulation and hence potentially impact on acute pain.[18] However, randomised controlled trials in acute traumatic pain before or after noncardiac surgery are lacking. Here, we report a phase 2b study addressing the hypothesis that transauricular nerve stimulation (TAN) reduces pain, morbidity, or both through autonomic modulation quantified by serial changes in heart rate variability before and after TAN.

Methods

Study design and participants

This single centre, single-blind phase 2b randomised controlled trial was undertaken at The Royal London Hospital, Barts Health NHS Trust between June 22, 2021 and July 7, 2022. The study was approved by the NHS Research Ethics Committee (21/LO/0272) and registered publicly on January 18, 2022 (researchregistry7566). A statistical analysis plan was made publicly available on June 28, 2022 before the database was locked.

Inclusion criteria

All patients provided written informed consent before enrolment. Patients with American Society of Anesthesiologists physical status 1–3, aged at least 18 yr were eligible, provided they were scheduled for major elective or urgent (i.e. not requiring intervention in <24 h) orthopaedic surgery for traumatic upper or lower limb fractures requiring open reduction internal fixation (ORIF). Only procedures that were expected to last >120 min from the induction of anaesthesia (general, spinal, or both) were eligible.

Exclusion criteria

Exclusion criteria were requiring invasive mechanical ventilation, new renal replacement therapy during hospitalisation, or both, cardiac arrhythmia requiring therapy before/during hospitalisation, dementia, cancer requiring active/ongoing therapy, postural orthostatic tachycardia syndrome, neuromuscular disorders, auricular dermatitis. For pragmatic reasons, we also excluded patients who were incidentally positive for COVID-19 on either positive rapid antigen or polymerase chain reaction testing.

Randomisation and masking

Eligible patients were identified by their surgical teams either in preoperative assessment clinics or on the orthopaedic trauma ward. The study protocol was explained to all enrolled patients before randomisation. After written informed consent was obtained, patients were allocated randomly (1:1) to receive either active or sham stimulation. Randomisation was performed 1 h before the first intervention before surgery, with a random block size of four. A randomisation sequence was created by a biostatistician who did not participate in the implementation or statistical analysis of the trial. Assessors and the trial statistician were blinded to treatment allocation throughout data collection and analysis. Interventions were performed at the same time of day (in the morning) before and after surgery to minimise the possible influence of circadian rhythms on heart rate variability (autonomic) outcomes.

Perioperative management

Surgical approach and anaesthetic management were undertaken according to local practice. The use of regional and local anaesthesia intraoperatively was determined by the consultant anaesthetist in charge of the operating list. Analgesia was prescribed according to local protocols/attending clinician decision.

Electrocardiography

To examine the autonomic effects of TAN, continuous three-lead electrocardiogram recordings were made in the semi-recumbent position for the 50 min intervention period (Spacelabs Lifecard, Hertford, UK), with no external disturbances permitted. Patients remained quiet and were not allowed to eat, drink, or receive additional nursing or therapeutic interventions during this period.

Pain assessment

Participants completed the 100 mm visual analogue score (VAS) to quantify pain at rest 10 min before and after the intervention period. Pain assessment with movement was impractical because of the type of orthopaedic trauma sustained. Anxiety, an established modifier of pain severity[20] and common after surgery,[21] was assessed using the GAD-7 questionnaire at the time of the intervention before and after surgery. In addition, the Amsterdam preoperative anxiety and information scale was calculated.[22]

Sham intervention

Using a CE-marked device (Totally TENS, Well-Life Healthcare Ltd™, New Taipei City, Taiwan), two conductive clips were

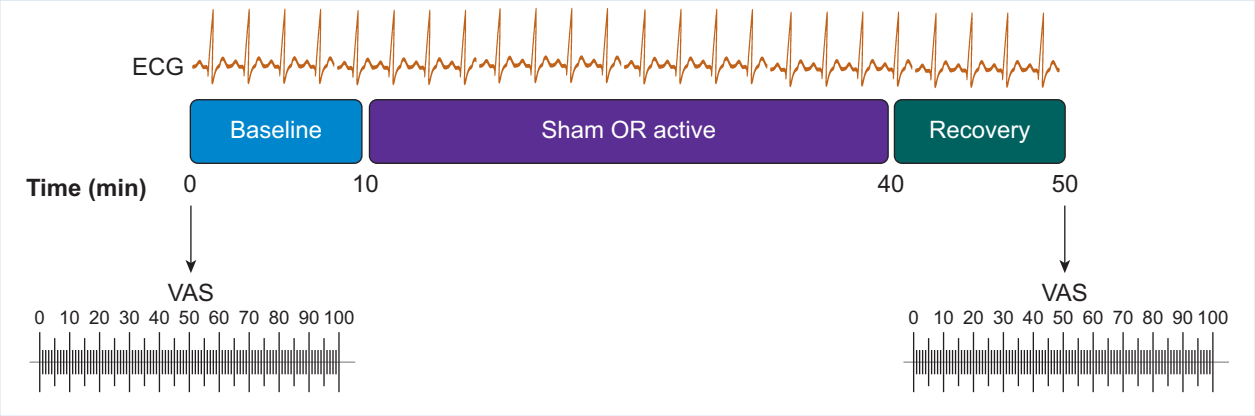

Fig 1. Study intervention. Transauricular ear stimulation protocol (performed between 0900 and 1100 h each day). Visual analogue score is recorded at 0 and 50 min. ECG monitoring records heart rate (HR) throughout the 50 min; baseline HR from 0 to 10 min (10 min period), HR during recovery from 40 to 50 min (10 min period). Sham or active stimulation is administered between 10 and 40 min (30 min period). Heart rate variability is subsequently calculated offline from analyses of RR intervals.

placed securely on both the left and right tragus areas of the outer ear for a total of 50 min. Using parameters we have identified through systematic review,[18] electrical stimulation (pulse width: 200 μs; frequency: 30 Hz) was initiated at 10 mA, until the participant reported a 'tingling' sensation within 20 s of commencing (Fig 1). At this point the current was switched off (sham group).

Active intervention

For active stimulation, electrical stimulation (pulse width: 200 μs; frequency: 30 Hz) was initiated at 10 mA. Once the participant reported a 'tingling' sensation within 20 s of commencing, the current was reduced to a level just below this threshold (20–60 mA) and continued for 30 min.

Blinding and concealment

Investigators and participants were blinded by ensuring the device settings were both invisible and imperceptible to all participants. Both participants and investigators were blinded to Holter data, which were analysed offline by a separate investigator not involved with patient recruitment/device application.

Primary outcome

The primary outcome measure was the difference in visual analogue score (VAS pain score 24 h after surgery, recorded at 10 min before, and at 10 min after the 30 min period of TAN.

Secondary outcomes

Secondary outcomes were the proportion of participants who achieve a minimal clinical relevant reduction >10 mm in VAS before and after surgery[23] and the absolute changes in VAS stratified by pain intensity before the intervention.[23] We recorded opioid use (calculated as morphine milligram equivalents)[24] and postoperative morbidity[25] but did not subject these secondary outcomes to formal statistical testing. Pre-specified adverse events directly related to the trial intervention were recorded (Table 1).

Explanatory measures

Heart rate recordings were obtained under similar environmental conditions and duration.[26] We quantified serially both time- and frequency-domain measures of heart rate variability.[27] For time-domain measures, standard deviation of heart rate, SDNN (standard deviation of NN intervals—estimate of overall heart rate variability), and RMSSD (root mean square of successive differences between normal heartbeats) were quantified 10 min before, and 10 min after each stimulation session. For frequency-domain measures derived by parametric autoregressive modelling, high-frequency (vagal activity) and low-frequency (closely reflecting arterial baroreflex sensitivity in humans)[28] were quantified 10 min before, and 10 min after each stimulation session.

Statistical analysis

Categorical variables are presented as *n* (%) and continuous variables are presented as the mean (standard deviation [SD] or 95% confidence intervals [95% CI]) or median (inter-quartile range). Analyses were conducted using the intention-to-treat

Table 1 Prespecified adverse events.

	Sham TAN	Active TAN
Patients with ≥1 adverse event	2 (4.7)	6 (14.0)
Type of adverse events		
Arrhythmia[a]	0	0
Headache	0	1 (2.3)
Pain[b]	0	0
Skin irritation at the stimulation site	2 (4.7)	5 (11.6)
Dizziness	0	0
Other	0	0

All data presented as *n* (%).
TAN, transauricular nerve stimulation.
[a] Defined as clinically detected arrythmia during or after day of intervention.
[b] Defined as localised pain to auricular region.

principle, where all patients with a recorded outcome are analysed according to the treatment group to which they were randomised. Baseline patient characteristics are presented, stratified by allocation to sham *vs* active treatment. No imputation for missing data and the actual observed data were used to perform the analysis.

The primary outcome (visual analogue score for pain) was analysed using repeat-measures analysis of variance (stimulation/sham allocation × intervention period (before *vs* after stimulation/sham). For secondary outcomes, the proportion of patients in each group with >10 mm change in the 100 mm visual analogue pain intensity scale (VAS) 24 h after surgery, was assessed (Fisher's exact test).[23] Absolute pain scores were analysed controlling for mild, moderate, and severe pain intensity before the intervention before and after surgery (repeated measures analysis of variance); VAS scores of 30, 70, and 100, respectively, indicate the upper boundaries of mild, moderate, and severe pain intensity.[23]

For explanatory analyses, heart rate variability variables[26] before and after stimulation/sham were compared before and after surgery (repeat-measures analysis of variance (stimulation/sham allocation × intervention period × before/after surgery). Two-tailed tests were used, with the significance level set at 0.05 (NCSS 2021, Stata version 14). A full statistical analysis plan was developed before analysis and study completion, and published online at https://www.qmul.ac.uk/ccpmg/sops–saps/statistical-analysis-plans-saps. The statistical analysis was conducted in a blinded fashion with unmasking only after the analysis was completed and the analysis was done in duplicate by two investigators working independently.

Sample size estimation

Consensus guidelines in perioperative medicine recommend that the visual analogue score should be used to assess pain intensity.[29] We designed this trial to determine whether the primary outcome, pain intensity at rest, differed between active and sham stimulation 24 h after surgery. Patients undergoing more extensive surgery report higher pain scores after surgery (mean VAS=34 [SD 22]).[23] Pain studies using patient-controlled analgesia typically titrate analgesia to achieve VAS of ~30,[23] with a VAS=33 equating to a positive patient response after orthopaedic surgery.[23] We calculated that 72 patients were required to have a 90% chance of detecting, significant at the 1% level, a decrease in mean VAS from 34 mm after sham therapy, compared with 23 mm after active stimulation (standard deviation of outcome 12 mm). Allowing for 10% dropout rates in each group, a final sample size of 86 participants was required, analysed by intention to treat.

Results

Subject characteristics

From June 22, 2021 to June 22, 2022, 125 patients requiring urgent ORIF orthopaedic surgery for upper or lower limb traumatic fractures were assessed for eligibility (Fig 2). Of these, 27 were excluded because they did not meet the inclusion criteria, and 12 declined to participate (Fig 2). The remaining 86 patients were randomly assigned to receive active (n=43) or sham (n=43) TAN (Fig 2; Table 2). After randomisation, all 86 patients underwent the intervention before

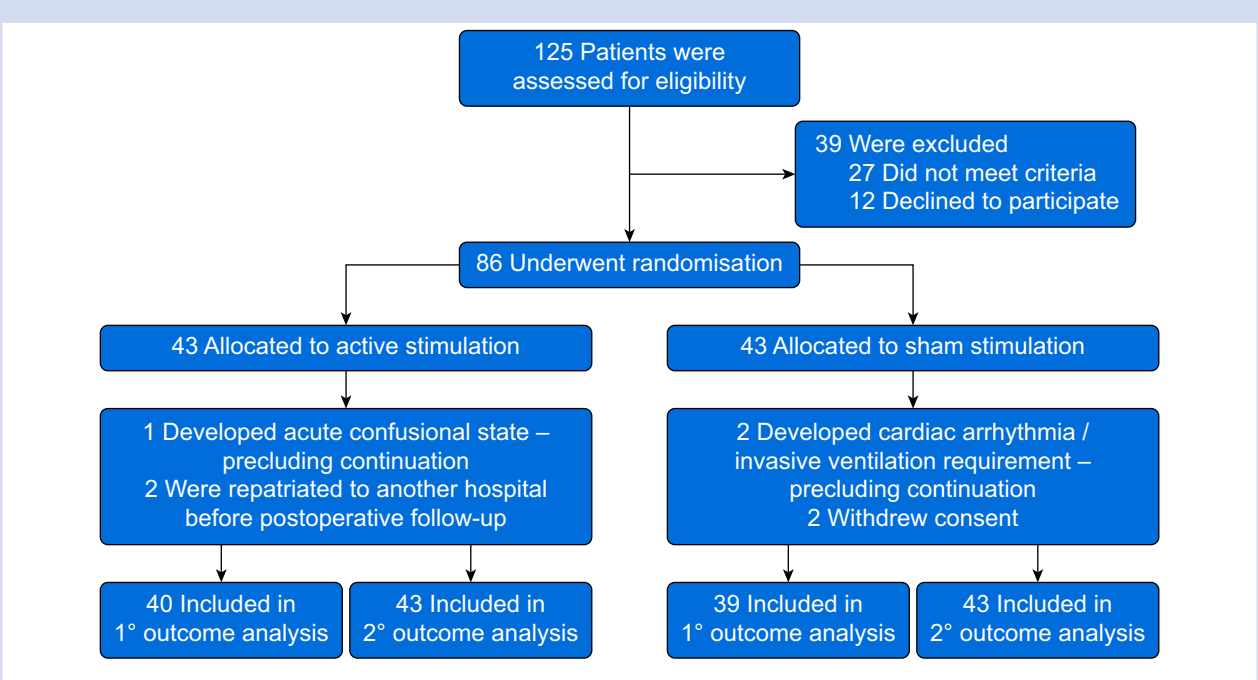

Fig 2. Study enrolment. CONSORT diagram illustrating flow of participants enrolled into the VATS (Vagal Augmentation with Transcutaneous Stimulation) study, detailing numbers of participants included in primary (n=79) and secondary analyses (n=86) for changes in visual analogue score for pain intensity.

Table 2 Participant characteristics.

	Sham (n=43)	Active (n=43)
Female sex	22 (51)	17 (40)
Age (yr)	53 (34–60)	47 (33–54)
Race (white)	30 (70)	28 (65)
American Society of Anaesthesiologists physical status ≥2	30 (70)	27 (63)
GAD-7 score	6 (4–9)	7 (5–9)
Amsterdam preoperative anxiety score	14 (10–17)	15 (11–20)
Chronic comorbid disease		
Hypertension	7 (16)	7 (16)
Ischaemic heart disease	0	3 (7)
Cardiac failure	1 (2)	2 (5)
Cardiac valvular disease	0	1 (2)
Stroke/TIA	0	2 (5)
Peripheral vascular disease	1 (2)	3 (7)
Diabetes mellitus, type 1	1 (2)	1 (2)
Diabetes mellitus, type 2	2 (5)	2 (5)
COPD/asthma	6 (14)	4 (9.3)
Smoker (ex/current)	13 (30)	14 (33)
Interstitial or other respiratory disease	2 (5)	0
Liver cirrhosis	4 (9)	1 (2)
GI pathology—other	2 (5)	2 (5)
Osteoarthritis	2 (5)	2 (5)
Rheumatoid arthritis	2 (5)	1 (2)
Inflammatory disease	1 (2)	4 (9)
Active cancer	1 (2)	1 (2)
Previous cancer	2 (5)	2 (5)
Preoperative blood tests results		
Haemoglobin (g dl^{-1})	127 (111–146)	133 (108–149)
Creatinine (μM)	70 (57–84)	66 (53–79)
Albumin (g L^{-1})	36 (32–43)	39 (36–46)
White cell count (× 10^9 L^{-1})	9.7 (7.3–15.3)	10.5 (8.2–13.4)
Neutrophil count (× 10^9 L^{-1})	6.6 (4.8–12.2)	7.1 (4.9–10.6)
Lymphocyte count (× 10^9 L^{-1})	1.8 (1.3–2.3)	1.5 (1.1–2.2)
C-reactive protein (g L^{-1})	9 (4–50)	18 (4–44)
Preoperative medication		
Statin	5 (12)	8 (19)
Anticoagulant	1 (2)	1 (2)
Antiplatelet	1 (2)	5 (12)
Beta blocker	2 (5)	3 (7)
Calcium channel antagonist	6 (14)	5 (12)
Doxazosin	1 (2)	0
Diuretic	1 (2)	1 (2)
ACE inhibitor	3 (7)	2 (5)
Angiotensin II receptor blocker (ARB)	2 (5)	0
Other hypertensive/antiarrhythmic	0	0
Asthma/COPD medication	5 (12)	5 (12)
Steroids	1 (2)	1 (2)
Metformin	2 (5)	2 (5)
Insulin	1 (2)	2 (5)
Any other diabetic medication	2 (5)	0
Opioids—oral	34 (79)	35 (81)
Opioids—parental	5 (12)	4 (9)
NSAIDs	13 (30)	18 (42)
Paracetamol	43 (100)	41 (95)
Surgery		
lower limb	36 (84)	29 (67)
upper limb	3 (7)	9 (21)
other	4 (9)	5 (12)
Duration of surgery (min)	195 (13–215)	170 (116–260)
Anaesthetic technique		
General anaesthesia alone	8 (19)	7 (16)
General anaesthesia + regional/local	33 (77)	34 (79)
General anaesthesia + peripheral nerve block	12 (28)	10 (23)
Regional anaesthesia + sedation	0	2 (5)

All data presented as n (%); median (IQR; inter-quartile range) unless otherwise indicated.
ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; TIA, transient ischaemic attack.

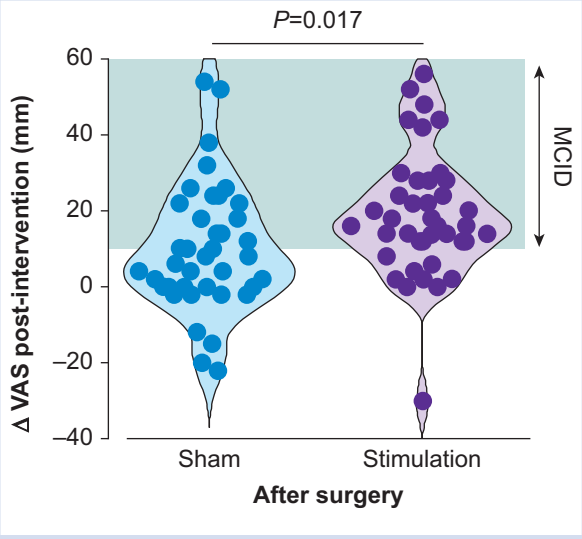

Fig 3. Pain intensity 24 h after surgery, before and after active *vs* sham TAN. Violin plot showing difference between VAS 10 min before and 10 min after sham TAN or active stimulation, after surgery. The shaded area depicts changes that fulfil the requirement for the minimal clinically important difference (MCID) (reduction as shown by grey area).

surgery, mostly under general anaesthesia with regional/local anaesthesia for intraoperative analgesia (Table 2). After surgery, seven patients (four sham, three active TAN) were either unwilling or unable to participate, or had their postoperative care relocated.

Primary outcome: pain after surgery

Mean VAS was reduced by 19 mm (95% CI: 12–26) after active TAN, compared with 10 mm (95% CI: 3–17) reduction after sham TAN (P=0.023; Fig 3; Supplementary Fig. S1, which also includes sensitivity analysis for missing data).

Secondary outcomes

Minimal clinically important difference in visual analogue score

After surgery, active TAN resulted in 31/40 (77.5%) patients reporting a minimal clinically important reduction in VAS >10 mm, compared with 15/39 (38.4%) receiving sham TAN (odds ratio 5.51 [2.06–14.73]; P=0.001). Before surgery, active TAN resulted in 23/43 (53.5%) patients reporting a reduction in VAS >10 mm, compared with 17/43 (39.5%) receiving sham TAN (odds ratio 1.76 [0.75–4.14]; P=0.196; Supplementary Fig. S1). After surgery, pain intensity before the intervention did not influence the effect of TAN (Supplementary Table S1).

Postoperative morbidity and opioid requirements

There were similar numbers of complications after sham and active TAN (Supplementary Table S2). Before surgery, 25/43 (58.1%) participants randomly allocated to sham TAN were receiving opiates for analgesia, compared with 30/43 (69.8%) randomly allocated active TAN. The mean difference between active and sham TAN in morphine equivalents being administered up to the day of surgery after the first intervention was 362 mg (−128 to 852). Some 24 h after surgery, the mean difference between active and sham TAN in morphine equivalents being administered was 64 mg (−51 to 180) (Supplementary Fig. S2).

Adverse events

There were six adverse events in the active TAN group, compared with two after sham TAN, with seven/eight adverse events attributable to skin irritation at the tragus ear site where the stimulation leads were attached. Headache was the other single adverse event. No serious adverse events occurred (Table 1).

Effect of TAN on cardiac autonomic modulation

Time-domain measures: there was 100% capture of Holter data for autonomic analyses during TAN. For time-domain measures, mean R-R interval was shorter after surgery in both active and sham TAN groups (Table 3). Active TAN increased the standard deviation in heart rate by 0.22 beats min^{-1} (0.02–0.42), compared with no change after sham TAN (0.13 [−0.08 to 0.33]). TAN had similar effects on RMSSD and SDNN, both of which were lower after surgery (RMSSD declining by 8 ms [4–11]; SDNN declining by 7 ms [4–10]). Higher minimal clinically important difference values were independently associated with time-domain measures indicative of preserved or higher heart rate variability (Supplementary Table S3).

Frequency-domain measures: surgery reduced high (HF_{log}: −0.53 ms^2 (−0.23 to −0.82); P=0.001) and low frequency power (LF_{log}: −0.49 ms^2 (−0.25 to −0.73); P=0.0001). Active TAN increased low-frequency power (log LF) by 0.19 ms^2 ([0.01 to 0.37]; P=0.033), compared with no change (0.15 ms^2 [−0.04 to 0.33]; P=0.17) after sham TAN (Table 3). No other frequency-domain measures were altered by TAN. Higher minimal clinically important difference values were independently associated with frequency-domain measures indicative of preserved or higher heart rate variability (Supplementary Table S3).

Discussion

This prospective randomised controlled trial demonstrates that active peripheral neuromodulation via the auricular nerve reduces pain in patients already treated with opioid analgesia, over and above the expected placebo effect of device-based interventions.[30]

Meta-regression analyses of placebo interventions for all clinical conditions report larger effects of physical placebo interventions (e.g. sham placement of devices) and subjective, patient-involved assessment of outcomes (including visual analogue scores).[31] Moreover, we identify that active peripheral neuromodulation alters autonomic function contemporaneously with reductions in pain intensity. Our phase 2b study provides new insights that demonstrate the feasibility and efficacy of TAN in reducing pain by boosting autonomic function and potentially accelerating functional rehabilitation.

Several contributory mechanisms underpin the relationship between pain intensity early after noncardiac surgery and distant organ injury. Failure to minimise acute pain impairs mobilisation, which in turn promotes pulmonary infections, prolongs urinary catheterisation, and delays the return of normal bowel function.[6] Established—or acquired autonomic dysregulation—impacts on a wide range of interconnected

Table 3 Heart rate variability before and after sham and active transauricular nerve stimulation (TAN) undertaken preoperatively and 24 h after surgery.

	Sham TAN				Active TAN			
	Before surgery (n=43)		After surgery (n=40)		Before surgery (n=43)		After surgery (n=39)	
	Pre TAN	Post TAN	Pre TAN	Post TAN	Pre TAN	Post TAN	Pre TAN	Post TAN
Time domain								
RR interval (ms)	793 (688–868)	770 (671–867)	744 (636–835)	727 (667–843)	806 (698–892)	760 (693–900)	709 (627–803)	700 (639–804
SDNN (ms)	25.1 (14.4–35.9)	29.0 (17.0–39.3)	20.8 (12.5–31.4)	22.3 (13.6–33.6)	22.0 (15.5–36.1)	23.1 (16.9–42.1)	19.1 (8.2–27.5)	20.9 (11.6–31.5)
RMSSD (ms)	17.4 (10.8–30.7)	16.9 (12.5–34.4)	15.2 (9.1–23.8)	16.6 (8.3–23.0)	15.5 (9.6–28.3)	17.0 (9.8–32.7)	12.0 (4.9–23.9)	13.6 (6.9–23.6)
SDHR (beats min^{-1})	2.59 (1.58–3.60)	2.88 (1.60–4.01)	2.27 (1.59–3.13)	2.15 (1.48–3.31)	2.57 (1.68–3.18)	2.83 (1.75–3.65)	2.35 (1.43–3.06)	2.54 (1.48–3.35)
Frequency domain (AR)								
[log] Low frequency (ms^2)	5.8 (4.8–6.5)	6.1 (4.7–6.7)	5.7 (4.1–6.3)	5.4 (3.6–6.1)	5.6 (4.7–6.4)	5.6 (4.8–6.7)	5.4 (3.6–6.1)	5.5 (4.1–6.2)
[log] High frequency (ms^2)	4.6 (3.5–5.6)	4.6 (3.7–5.8)	4.5 (3.2–5.1)	4.5 (3.3–5.2)	4.8 (3.4–5.5)	4.7 (3.5–5.8)	3.9 (2.6–5.3)	4.1 (2.9–5.1)

All data presented as n (%); median (IQR; inter-quartile range).
AR, parametric autoregressive (AR) modelling; RMSSD, root mean square of successive differences between normal heartbeats; RR, pulse interval; SDHR, standard deviation of heart rate; SDNN, standard deviation of NN intervals.
See Supplementary Material for heart rate variability parameters for each 5 min epoch of sham and active intervention period.

neurohormonal and immune pathways, resulting in prolonged, more intense pain, impaired resolution of inflammation, and delayed organ repair.[18] Our findings suggest that TAN may also have a role in reducing perioperative opioid consumption. Greater preoperative opioid use is associated with increased risk of postoperative readmissions.[32] Persistent opioid exposure is also associated with increased overall expenditure on readmissions and ambulatory care visits.[33]

Although our study identifies that cardiac autonomic modulation is altered by TAN, the precise neurophysiological mechanism cannot be addressed by this study design. Some healthy volunteer studies have demonstrated that a short period of TAN reduces experimental acute pain.[34–37] However, the exact mechanisms linking autonomic neuromodulation and analgesia are unclear, and there is a paucity of evidence investigating the correlation between autonomic changes and pain outcomes.

Human studies incorporating measures of cardiac sympathetic neurotransmitter release suggest that low frequency reflects baroreflex function rather than cardiac sympathetic tone.[38] However, experimental data from conscious sheep challenges whether the low frequency (LF) component of heart rate variability is a robust measure of baroreflex sensitivity, postulating that LF represents a composite autonomic measure between cardiac sympathetic nerve activity and baroreflex control.[39] Nevertheless, our data are consistent with a role for autonomic changes occurring at the same time as modulation of the perception of pain.

Autonomic interventions in humans show that increases in either arterial or venous blood pressure in subjects with preserved baroreflex sensitivity are associated with hypoalgesia.[1] Even in healthy normotensive individuals, pain sensitivity decreases as resting arterial blood pressure increases.[40] Chronic arterial hypertension is associated with an increased tolerance to pain in humans.[41] Experimental models of acute and chronic hypertension show that disruption of sinoaortic afferent input attenuates or abolishes hypertension-associated hypoalgesia, in part by augmenting ascending pain pathways.[41] Experimental hypertension induces reduced sensitivity to pain through attenuation of the nociceptive signal at the spinal level.[41] Analogous to our trial, daily auricular nerve stimulation for 30 min for 27 days inhibited the development of neuropathic pain in Zucker diabetic fatty rats with type II diabetes mellitus.[42] Experimental interventions in humans, such as baroreceptor activation by neck suction,[43] are impractical in the acute surgical setting. Given we now provide the first data consistent with an autonomic effect likely related to baroreflex control, TAN offers a low cost, noninvasive intervention with a very low potential risk-to-benefit ratio.

A strength of our study was the use of the visual analogue scale (VAS) to evaluate postoperative pain, which is consistent with consensus guidelines.[23] The use of absolute and cut-off values to define clinically significant reductions in pain minimises the drawbacks with subjective assessments.[23] Whereas our results suggest that TAN may be useful for acute postsurgical pain, it remains unclear whether this may accelerate the resolution of pain to facilitate more effective physical therapy, mobility, or both. Indeed, there is a paucity of evidence researching the effects of autonomic neuromodulation on chronic pain. Using a sham stimulation protocol is critical since meta-regression analyses show that physical placebo interventions, in combination with patient-reported outcomes in pain such as the visual analogue score, are far more likely to be associated with placebo effects.[31,44] The masked analysis of

the very high rate of Holter data acquisition was a further strength of this study. Although the results of this trial are concordant with systematic review of TAN parameters that alter heart rate variability,[18] there remains uncertainty regarding dose-response characteristics, frequency of dosing, and the timing of this intervention. A limitation of this study is that we cannot rule out that there are minimum thresholds for the frequency of the intervention, and the duration, intensity, or both of stimulation parameters that are required to be optimally clinically effective; these may differ according to surgical population and autonomic endotype. For example, a longer course of treatment after surgery may be more effective. Pivotal to the interpretation of these results is mapping pain to alterations in autonomic function by an investigator masked to treatment allocation. Additional measures of autonomic function and/or baroreflex sensitivity[10] would add further weight to our observations, but these conventional techniques are frequently severely hampered by the constraints of the perioperative environment.

In summary, this phase 2b perioperative study shows that noninvasive auricular neuromodulation reduces acute pain in parallel with autonomic changes that are mechanistically implicated in favourably modulating pain perception. Optimising pain control is strongly linked to the prevention of developing new, or additional, multimorbidity. Transcutaneous auricular nerve stimulation is a novel, noninvasive, low-cost analgesic intervention, which offers the potential for self-administration at scale.

Authors' contributions

Designed the study protocol, recruitment and intervention: ABUP, GLA
Recruitment and intervention: PWMB
Data extraction: JIMA
Recruitment and intervention: ZM
Masked Holter data cleaning/collation: WLG
Statistical design: TEFA
Contributed to the first manuscript draft and subsequent revisions: all authors
All authors had full access to the data in the study and gave the final approval of the manuscript and agree to be accountable for all aspects of work.

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Declaration of interest

TEFA and GLA are editors of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.12.025.

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