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Intradermal thumbtack needle buried Neiguan (P6) point for prevention of postoperative nausea and vomiting in patients undergoing craniotomy: study protocol for a randomized controlled trial

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Abstract

Introduction: Postoperative nausea and vomiting (PONV) is among the most common adverse reactions following anesthesia and surgery. Recent clinical studies have reported that the average incidence is about 30%, while in patients specifically undergoing neurosurgery the incidence can be as great as 73%. Studies also suggest that its occurrence increases the risk of intracranial hematoma and hemorrhage**.** The objective of this study is to evaluate the effectiveness of intradermal thumbtack needle buried Neiguan (P6) point therapy in the prevention of PONV in patients undergoing craniotomy under general anesthesia.

Methods and analysis: This is a single-center, three-arm, randomized controlled trial. 180 participants are randomly assigned to either an Acupuncture group, Intradermal thumbtack needle group or Control group in a 1:1:1 ratio. The P6 of the Acupuncture group is punctured at both sides perpendicularly to a depth of 20mm. Needles are retained for 30 minutes and stimulated every 10 minutes to maintain the de qi. The therapy includes 2 treatments; the acupuncture is administered immediately after and 24 hours after surgery. For the Intradermal thumbtack needle group, the intradermal thumbtack needle is quickly inserted into the skin and embedded at P6 acupoints bilaterally. Patients and their families are asked to press the needle point with the onset of

nausea, vomiting, bloating, pain and other reported discomfort. The needle is replaced after 24 hours. The therapy is administered immediately after and 24 hours after surgery. For the Control group, no intervention is carried out. The incidence of PONV within 48 hours after craniotomy across the three groups is observed. Other observations include: (1) assessment of nausea score (severity of nausea) and pain score （VAS) 0-2, 2-6, 6-24 and 24-48 hours after craniotomy under general anesthesia; (2) assessment of total rescue antiemetic dosage 0-48 hours after craniotomy under general anesthesia;（3）length of hospital stay; (4) patient satisfaction score with PONV management. We will perform all statistical analysis following the intention-to-treat principle.

Discussion: The results from this study may potentially confirm that the therapy described can prevent PONV in patients undergoing craniotomy under general anesthesia.

Ethics and dissemination:

Ethics approval has been granted by the Bioethics Subcommittee of West China Hospital, Sichuan University: the approval number is 2018 (Number 231). Results will be expected to be published in peer-reviewed journals.

Trial registration: This study is registered with the Chinese Clinical Trial (ChiCTR1800017173)in July 2018, the registration status was prospective registration.

Keywords: intradermal thumbtack needle, Neiguan, nausea, vomiting, craniotomy.

strengths and limitations of this study

- ►A randomised controlled trial of 180 patients will be conducted to evaluate the effectiveness of intradermal thumbtack needle buried Neiguan (P6) point therapy in the prevention of PONV in patients undergoing craniotomy under general anesthesia. ► The feasibility of the trial has been examined by a pilot randomised trial of 30 patients. ► This trial will be conducted using rigorous methods, such as the blinding of data analyst and outcome assessors, and the implementation of interventions using clearly prespecified approaches. ► The control group lacked placebo effect.

Background

Postoperative nausea and vomiting (PONV), is one of the most commonly observed adverse reactions following anesthesia and surgery[1-3]. It increases the difficulty of medical care, delays the patient's recovery from anesthesia, extends their hospital stay and increases overall healthcare costs[4, 5]. Recently, clinical studies report that there is a high incidence, - about 30% - of patients experiencing PONV. This is much higher in patients who specifically undergo neurosurgery. The incidence in these cases can be as high as 73%. The studies also suggest that the occurrence of PONV can result in an increased risk of intracranial hematoma and hemorrhage[6, 7].

Pharmacological prophylaxis is widely used in clinical practice, and the most commonly used prophylactic antiemetics include serotonin (5-HT3) receptor antagonists, often in combination with either droperidol or

dexamethasone[8-10]. Recently, however, the US Food and Drug Administration (FDA), has reported that droperidol may cause death secondary to arrhythmia or QT prolongation, while other drugs have varying degrees of side effects[11]. At present, no therapy is categorically effective at preventing PONV.

Due to the limited efficacy and many side effects of drug therapy, various non-pharmacological techniques have been used in clinical practice. These therapies include acupuncture[12], acupressure[13], transcutaneous electrical nerve stimulation (TENS)[14, 15], and electro-acupuncture[16], among others[17]. In 2006, the American Society of Peri anesthesia Nurses (ASPAN), recommended pericardium 6 (P6; also known as Neiguan) acupoint stimulation (Class IIb, Grade A) and self-P6 acupoint compression before and after surgery (Grade C) as a complementary intervention for PONV prophylaxis. The 2014 American Anesthesia Outpatient Guide also recommended that acupuncture treatment may be used as an alternative or adjuvant therapy for prevention of PONV[18] . Many recent studies have supported the efficacy of P6 acupoint stimulation in preventing PONV[17, 19-21].

The existing acupuncture treatment is still mainly focused on electro-acupuncture or traditional needle operation. In our clinical practice, however, the limitations of these two acupuncture stimulation methods

(including fixed treatment and fixed treatment time, inconvenience of other medical operations during needle retention, etc.) have resulted in unstable efficacy.

A combination of traditional Chinese and Western medicine, including needle embedding therapy, was put forward in the 1950s. With the developments of acupuncture apparatus, intradermal thumbtack needle has emerged as a new kind of the embedding therapy. The Intradermal thumbtack needle (**Figure 1**), an improved subcutaneous needle, is a type of shallow needling method that reduces pain and prolongs the acupuncture effect via longer needle retention. Also, our previous clinical experience indicates that the time of nausea and vomiting in patients after surgery is uncertain[22-24]. As the Intradermal thumbtack needle has a 24-hour persistent stimulating effect, patients can self-press it at the P6 to relieve gastrointestinal discomfort when needed.

Therefore, we designed a single-center, prospective, double-blind, randomized controlled trial (RCT) to evaluate the efficacy of P6 acupoint stimulation by intradermal thumbtack needle as a non-pharmacological prophylaxis for PONV. This study incorporates the concept of fast tracksurgery, using a prospective randomized controlled method, inspired by the concept of a postoperative analgesia pump, to develop P6 acupoint stimulation treatment by intradermal thumbtack needle with long-term

stimulation characteristics（**Figure 2)**. The study is designed to evaluate the effectiveness and safety of P6 acupoint stimulation for the prevention of PONV in patients who undergo craniotomy under general anesthesia by intradermal thumbtack needle versus acupuncture filiform needles, and versus routine antiemetic. The objective is to compare the effect and safety using different methods.

Methods

Design:

This is a single-center, prospective, single-blind, parallel-group, RCT. The trial protocol strictly follows the principles of the Declaration of Helsinki (version Seoul, 2008) and approval has been obtained from the Sichuan University Ethics and Research Committee. Participants have been and will continue to be recruited from the West China Hospital of Sichuan University (WCHSU) from January 2018 to November 2019. All participants are required to give written informed consent. The study's flow chart is shown in **Figure 3**.

Patient population and setting:

A total of 180 Chinese patients undergoing craniotomy will be sequentially recruited at the WCHSU after fulfilling the eligibility criteria and signing the informed consent. A clinical assistant with institutional review board training will be in charge of patient enrolment.

Eligibility criteria

Inclusion criteria: Patients who fulfill the following conditions will be included: 1) scheduled for neurosurgery requiring opening of the cranium and dura; 2) aged between 18 and 70 years old; 3) American Society of Anesthesiologists (ASA) physical status classification of I or II; 4) undergoing general anesthesia; 5) no history of PONV or motion sickness; 6) no experience with acupuncture therapies; 7) no use of antiemetic 24 hours before surgery; 8) willingness to participate; and 9) having signed an informed consent form.

Exclusion criteria: Participants that meet any of the following criteria will be excluded: 1) nausea or vomiting 24 hours before surgery; 2) pregnant or lactating women; 3) menstruating phase of the menstrual cycle; 4) drug or alcohol abusers; 5) criminals; 6) recipients of chemotherapy or radiation therapy during the previous 7 days before surgery; 7) cardiac pacemaker; 8) refusal to accept acupuncture and TENS treatment; 9) mental disorder; 10) history of epilepsy and still taking an antiepileptic medicine; 11) unconscious before the surgery; 12) cannot normally communicate; 13) undergoing ventricle or brainstem surgery; 14) cerebral perfusion pressure (CPP) of greater than 150mmHg and signs of encephalopathy; 14) poorly controlled diabetes mellitus (fasting plasma glucose greater than 12 mmol/L); 15) bleeding disorders (hemophilia or

afibrinogenemia); and 16) serious systemic disease (AIDS or sepsis).

Dropout criteria: Participants who meet any of the following criteria are withdrawn from the study: 1) death; 2) waking up more than 2 hours after surgery; 3) trachea intubation; 4) persistent coma; 5) cognitive impairment; 6) further surgery or transfer to ICU if necessary for the aggravation of the disease, etc. Patients who are withdrawn are not replaced.

***Randomization and blinding*:**

A randomized grouping plan will be designed using the statistical software named Package for Encyclopedia Medical Statistics 3.1 (PEMS 3.1). Using this plan, the 180 patients will be randomly assigned to either an acupuncture, intradermal thumbtack needle, or control treatment group. The grouping scheme will be kept hidden in an envelope. The included participants will be randomly assigned to each group according to the distribution scheme in the envelope: 60 patients in each group. This study is a single-blind design, mainly for patient unawareness, and the efficacy evaluator and statistician are separated in this study.

Study investigators, acupuncturists and participants will be aware of the treatment allocation. Outcome assessors and data analysts will be blinded and participants will be asked not to reveal their allocation to assessors. In addition, we will have blinded interpretation of the study results to

minimise misleading data interpretation.

***Interventions*:**

The determination of the program and the point of acupuncture is based on previous research and The Name and Location of Acupoints (GB/T 12346-2006). All the practitioners performing the treatment must have an acupuncturist qualification certificate and have performed clinical treatment independently for more than 2 years. The acupuncturists are not replaced during the experiment.

All patients will receive the same anesthesia methods: general anesthesia with endotracheal intubation. Blood pressure, heart rate, pulse oximetry and end tidal CO_2 will be routinely monitored. Induction of anesthesia will be achieved with midazolam 0.05mg/kg, sufentanil 0.3μg/kg, atracurium 0.15mg/kg and propofol 2mg/kg. When endotracheal intubation and gastrointestinal decompression with either an orogastric or nasogastric tube are undertaken, the anesthesia will be maintained with 50% nitrous oxide and 3% sevoflurane. After the operation has commenced, participants will be given sufentanil 0.2μg/kg and atracurium 0.1mg/kg intermittently. 30 minutes before the end of the operation, the patients will be treated with prophylactic antiemetic drugs: Ondansetron Hydrochloride Tablets 8mg according to the advice of doctors. After surgery, patients will be continually monitored in the post-anesthesia care

unit (PACU) after anesthesia to continue the ventilator support. The tracheal tube will be removed after the patients awake. The time from the start of anesthesia induction to the time of removal of the tube will be recorded. Patients who then meet the criteria (Steward Rating Scale $\geqslant$4, and the blood gas index of special patients being normal as judged by the anesthetist) will be sent back to the ward.

For the acupuncture group (acupuncture is added at the base of basic treatment), bilateral Neiguan (P6, located on the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist) (**Figure 4**) will be selected.

The location of the acupoint refers to national standards of PRC published in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints"). After the patients are transported from the post-anesthesia care unit (PACU) to the common ward, the treatment will commence. After skin disinfection with a disposable disinfecting cotton swab, sterile and disposable stainless-steel needles (0.25 × 25 mm, Suzhou Hwato-med, Jiangsu, China) will be quickly and perpendicularly inserted into the skin at P6 acupoints bilaterally to a depth of 20mm. The duration of reinforcing-reducing manipulation of twirling and rotating needle should be used for 1 minute to achieve de qi (a composite of sensations including soreness, numbness, distention, heaviness, and other sensations), which

is recognized to be an essential component for acupuncture efficacy. The needles will be kept in place for 30 minutes and manipulated manually every 10 minutes to maintain the de qi. When the treatment is over, all needles will be carefully removed. The therapy includes 2 treatments, and the acupuncture will be administered immediately after and 24 hours after surgery.

For the group of thumbtack needle stimulation (press-needle is added at the base of conventional therapy), the bilateral P6 acupoint will be selected. The location of the acupoint refers to national standards of PRC published in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints"). Treatment will commence after the patients are transported from the post-anesthesia care unit (PACU) to the common ward. After skin cleansing with a 75% alcohol swab, Japanese SEIRIN PYONEX (0.2mm × 1.5 mm) will be quickly inserted into the skin and embedded at P6 acupoints bilaterally. Patients and their families will be asked to press the needle point when the patient feels nausea, experiences vomiting, bloating, pain and other discomfort. The needle will be replaced after 24 hours. The therapy is given twice as the thumbtack needle stimulation will be given immediately after and 24 hours following surgery.

For the control treatment group of rapid rehabilitation surgery, the benefits, specific measures, prevention of complications, time and cost of

hospitalization will be explained to patients and their families in detail using multimedia presentations and pamphlets prior to the operation. Preoperative measures also include fasting for 6 hours, fasting water for 2 hours and infusing water and carbohydrates 2 hours before surgery. Premedication will not be administered. Fluid volume management and temperature intervention, drainage system, urethral catheter and gastric tube will not be applied during the operation. The postoperative measures include multi-mode control of postoperative pain, early ambulation, early extubation (when tubes are applied), ADR monitoring and prognosis monitoring.

Outcome measures:

Main Outcome:

In this study, patients are monitored for 48 hours post-operatively. The observers will record any episodes of vomiting (criteria based on vomiting action or vomitus in the mouth) 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours following surgery. The incidence of PONV within 48 hours after craniotomy across the three groups is the main criteria to be measured.

Secondary Outcome:

The observers will evaluate the patients' degree of nausea using the WHO's PONV forth class rating scale: 0) no nausea at all; 1) mild nausea

or abdominal discomfort without vomiting; 2) evident nausea without vomitus; 3) extreme nausea and vomitus containing gastric juice, which is uncontrolled by medicine. The pain score adopts a standard visual analogue scale (VAS) during 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after craniotomy under general anesthesia. The assessment of total rescue antiemetic dosage 0-48 hours after craniotomy under general anesthesia will be recorded. The length of stay in the hospital and patient satisfaction score with PONV management will also to recorded.

Adverse event reporting:

Adverse events will be recorded via voluntary reports by neurosurgeons, physical examination, laboratory examination, or other methods. All adverse events must be recorded on the CRF's adverse events page and the following information about adverse events should be provided: 1) severity degree (mild, moderate or severe); 2) the relationship with research therapy (definitely related, probably related, possibly related, probably irrelevant or definitely irrelevant); 3) duration (the start and end dates or if the adverse advent still exists at the last check); 4) serious adverse event (SAE); 5) important medical events (if potentially harmful to patients medical or surgical intervention may be requested).

In order to ensure the safety of each patient, any serious adverse events

that occur from the time the patient gives consent up to 30 days after completion of the study, whether or not associated with the treatment of this research, must be reported to the project director within 24 hours. Severe adverse events that occur 30 days after the cessation of the study do not need to be reported unless the researchers deem it relevant to the treatment. The recurrence, complication, or progression of previous reported serious adverse events must also be reported as first reported follow-up information, as soon as the first serious adverse event occurs. The researchers must report the events within 24 hours once receiving the follow-up information. If a serious adverse event is considered to be completely unrelated to the previously reported one, it should be reported as a new event.

***Sample size calculation and statistical analysis*:**

A German prospective observational study published in 2011 demonstrated an overall incidence of PONV in 47% of patients after craniotomy under general anesthesia. The sample size is determined by using PEMS 3.1 with α= 0.05 (two-sided) and β= 0.1 (90% power). The formula for calculation is as follows:

$$\mathrm{n} = 2\lambda/(2sin^{-i}\sqrt{P_{max}} - 2sin^{-1}\sqrt{P_{min}})^2$$

In order to demonstrate a 30% absolute reduction in the incidence of PONV, the sample size will be 49 patients for each group. Considering the

potential for loss and attrition (20%), 60 patients per group, or a total of 180 patients, should be reasonable. If a patient cannot complete the study due to death, reoperation, unconsciousness or cognitive impairment, the patient will be recorded as an episode of PONV.

All data will be analyzed by a blinded statistician using PEMS 3.1 at a separate location from the WCHSU. The intention-to-treat principal will be used in the data analysis. Baseline data will be collected and compared first. Different statistics are presented differently, for example, continuous data is presented as mean (± standard deviation). Chi-square test is used to compare the incidence of postoperative vomiting, complete response rate, sex difference and other nominal data. Conversely, the Kruskal-Wallis test is used to compare the nausea score, satisfaction score and antiemetic dosage. Additionally, the Nemenyi test and Scheffé's method are used for multiple comparisons between groups. A *P* value <0.05 is considered statistically significant.

Patient and public involvement

The patients and public were not involved in planning and design of this study.

The present trial was developed by acupuncturists based on previous clinical experience and literature. Patients were not involved in the design of the study. The outcomes were commonly used assessments of PONV

in clinical practice. The cost of interventions and outcome measurements were mostly covered by the study funding so it was not thought to be a significant burden and were in line with patient preferences. The results will be disseminated to study participants via the website of our hospital.

Discussion

Our previous studies have shown the effectiveness and safety of acupuncture in the treatment of nausea and vomiting following craniotomy. In the clinic, however, we have found that, as the time of postoperative nausea and vomiting is not fixed, patients are eager to receive treatment when they experience nausea and vomiting. Often, however, acupuncture cannot be administered as there is no qualified practitioner available. In order to improve the availability of treatment, acupuncturists need to formulate new protocols. Seaband© and TENs are effective treatments for postoperative nausea and vomiting. They are easy to administer and non-invasive, though our previous studies have found that their efficacy is inferior to needle therapy. The intradermal thumbtack needle has a piercing effect and can be in place for 24 hours. When the patient is nauseous, pressing the acupuncture point can achieve de-qi sensation. We therefore designed this randomized controlled study in order to demonstrate that intradermal thumbtack needle buried Neiguan point therapy can reduce the nausea and vomiting

after craniotomy. It is conducive to clinical use and improved patient satisfaction.

Ethics and dissemination

Ethics approval has been granted by the Bioethics Subcommittee of West China Hospital, Sichuan University: the approval number is 2018 (Number 231). Results will be expected to be published in peer-reviewed journals.

The case report forms (CRFs) will be stored in a locked cabinet at the hospitals and accessible by the research team only. On completion of the trial and data checking, the CRFs will be transferred to be securely archived at Sichuan university for 5 years before being destroyed. The trial database will be anonymised, password protected and securely held. Patient identifiable data are shared only within the clinical team on a need-to-know basis to provide clinical care and ensure appropriate follow-up. The aggregated research findings will be presented at national and international scientific conferences and be submitted for publication in peer-reviewed journals.

Contributors

Jian-qin lv devised the study question and design. Yi yang developed the idea into the full protocol and wrote the article draft.tianhao xu reviewed the protocol. Lingqi jian calculated the sample size and specified the statistical strategy. Chengwei wang is in charge of conducting all the procedures. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests

Patient consent

Obtained.

Ethics approval

This study protocol with the written informed consent forms has been peerreviewed and approved by Ethical approval of West China Hospital of Si-chuan University clinical trials and biomedical ethics committee 2018 (231) in July 2018.The approval number is 2018(231).

Availability of data and material:

The datasets used and/or analyzed after completing the current study will be available from the corresponding author by reasonable requests.

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Figure Legends

Figure 1: Intradermal thumbtack needle

Figure 2: Intradermal thumbtack needle being inserted into the Neiguan point (P6)

Figure 3: Trial flow chart

Figure 4: Location of P6 acupoint

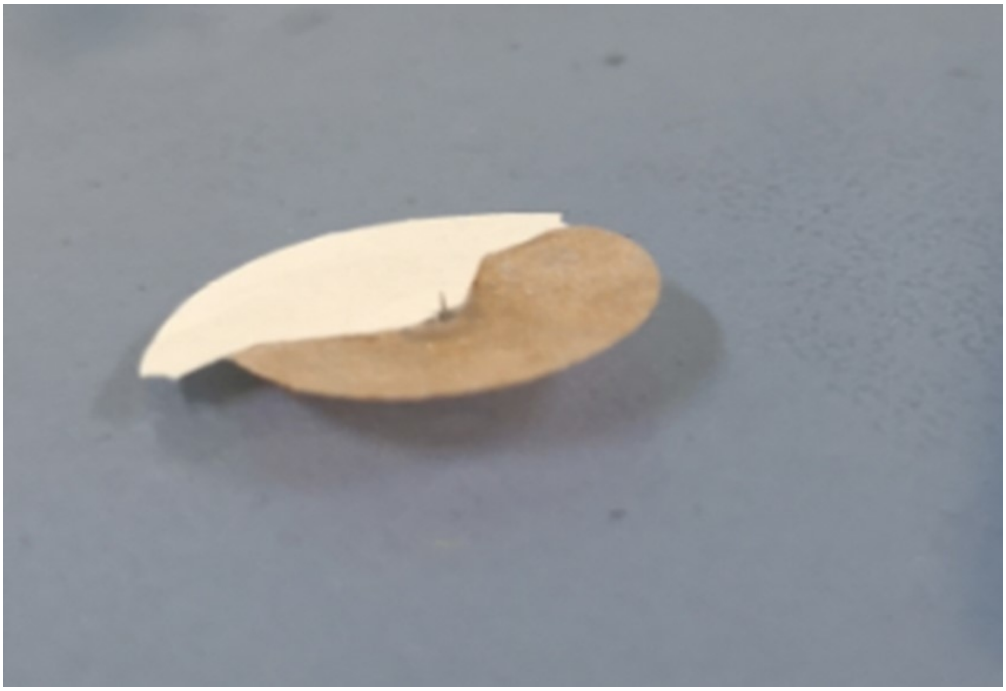
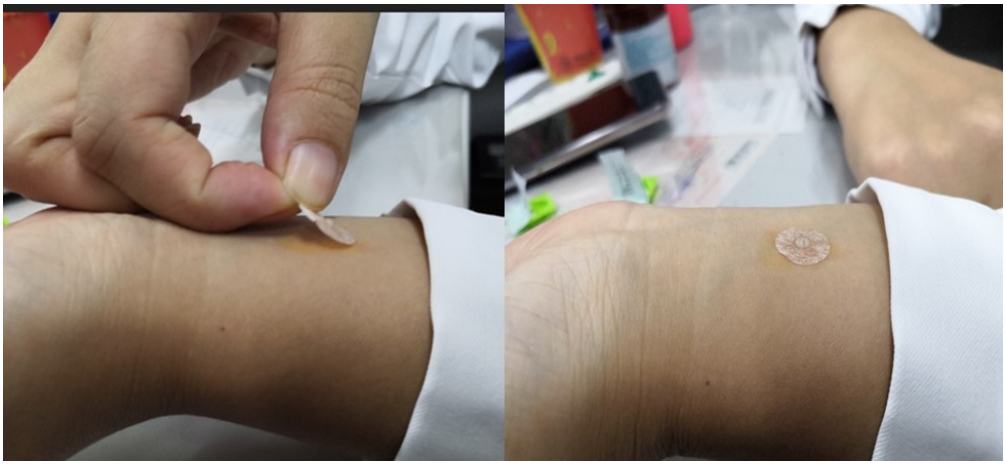


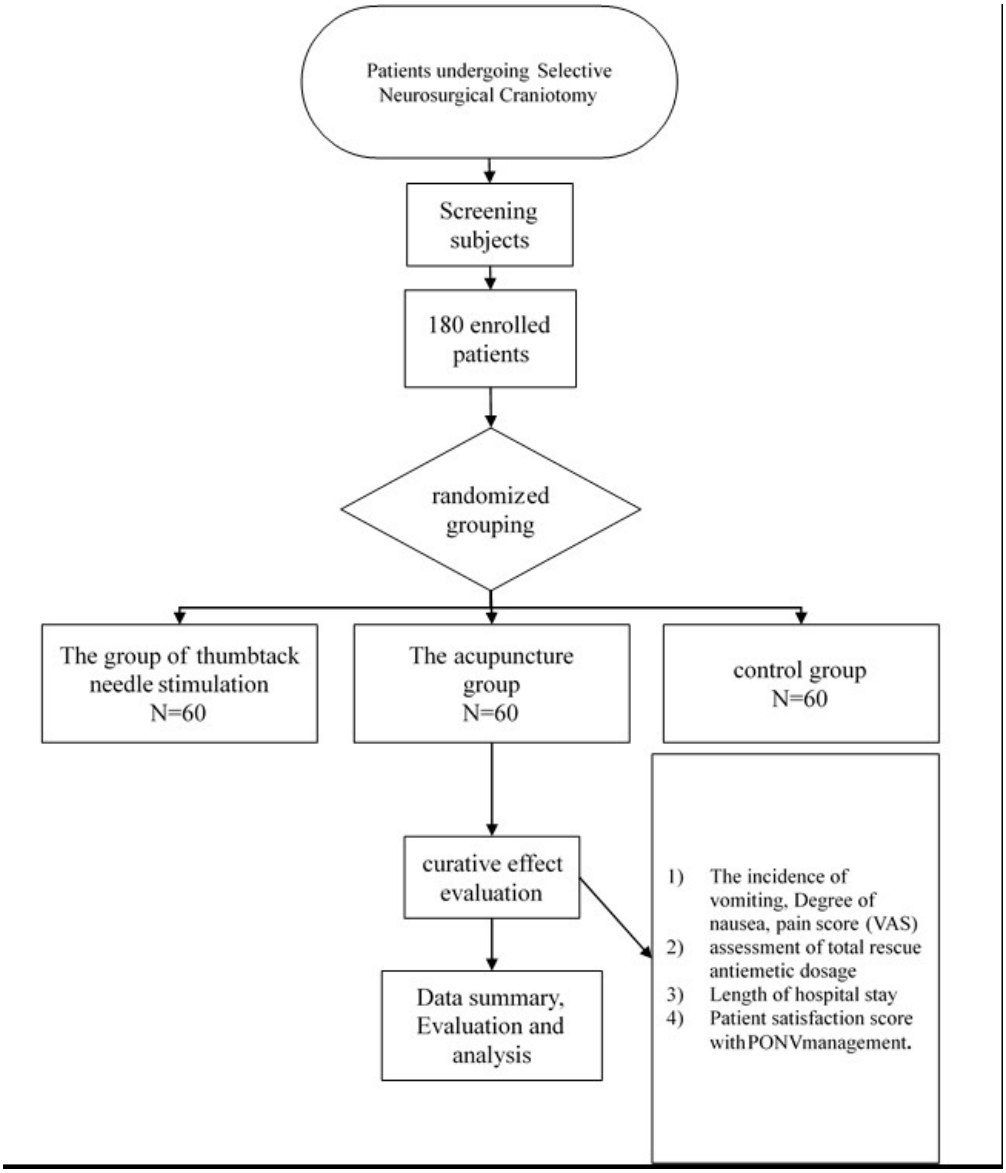
Figure 1 Intradermal thumbtack needle

144x98mm (150 x 150 DPI)



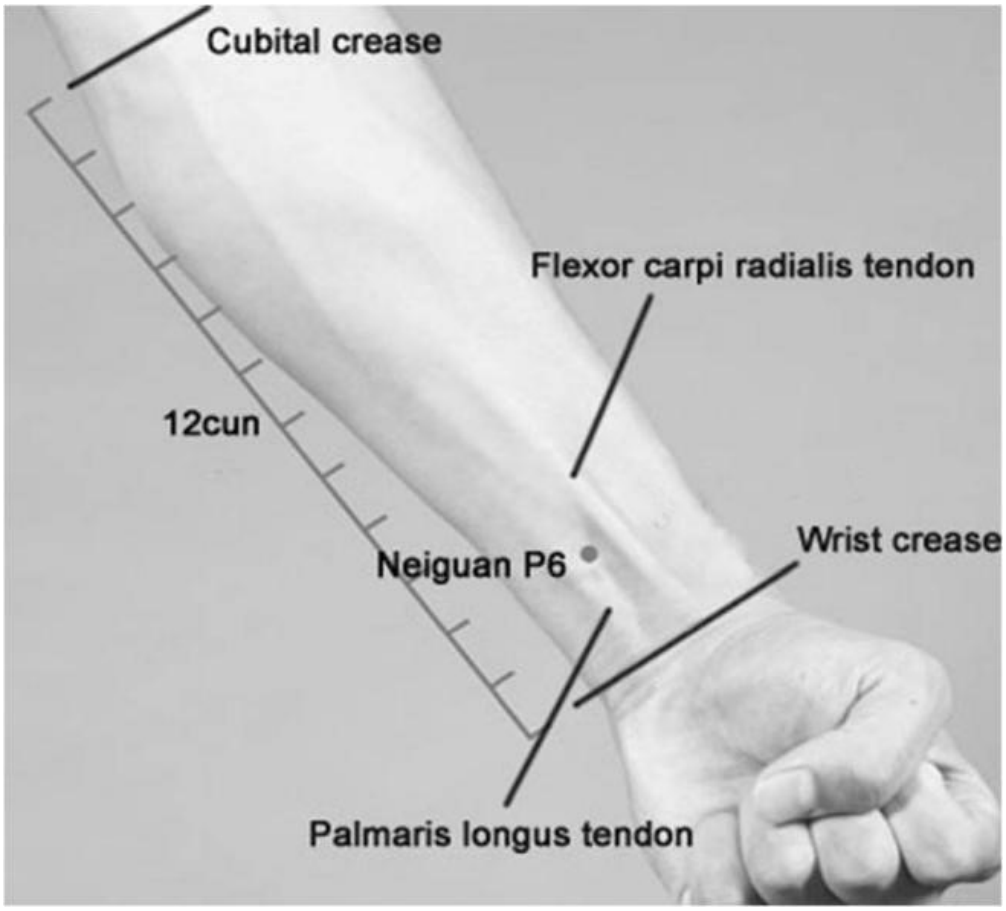
Intradermal thumbtack needle being inserted into the Neiguan point (P6)

165x75mm (150 x 150 DPI)



Trial flow chart

171x200mm (96 x 96 DPI)



Location of P6 acupoint

75x68mm (220 x 220 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	2
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A

	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Intradermal thumbtack needle buried Neiguan (P6) point for prevention of postoperative nausea and vomiting in patients undergoing craniotomy: study protocol for a randomized controlled trial

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Intradermal thumbtack needle buried Neiguan (P6) point for prevention of postoperative nausea and vomiting in patients undergoing craniotomy: study protocol for a randomized controlled trial

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Abstract

Introduction: Postoperative nausea and vomiting (PONV) is among the most common adverse reactions following anesthesia and surgery. Recent clinical studies have reported that the average incidence is about 30%, while in patients specifically undergoing neurosurgery the incidence can be as great as 73%. Studies also suggest that its occurrence increases the risk of intracranial hematoma and hemorrhage**.** The objective of this study is to evaluate the effectiveness of intradermal thumbtack needle buried Neiguan (P6) point therapy in the prevention of PONV in patients undergoing craniotomy under general anesthesia.

Methods and analysis: This is a single-center, three-arm, randomized controlled trial. 180 participants are randomly assigned to either an Acupuncture group, Intradermal thumbtack needle group or Control group in a 1:1:1 ratio. The P6 of the Acupuncture group is punctured at both sides perpendicularly to a depth of 20mm. Needles are retained for 30 minutes and stimulated every 10 minutes to maintain the de qi. The therapy includes 2 treatments; the acupuncture is administered immediately after and 24 hours after surgery. For the Intradermal thumbtack needle group, the intradermal thumbtack needle is quickly inserted into the skin and embedded at P6 acupoints bilaterally. Patients and their families are asked to press the needle point with the onset of

nausea, vomiting, bloating, pain and other reported discomfort. The needle is replaced after 24 hours. The therapy is administered immediately after and 24 hours after surgery. For the Control group, no intervention is carried out. The incidence of PONV within 48 hours after craniotomy across the three groups is observed. Other observations include: (1) assessment of nausea score (severity of nausea) and pain score （VAS) 0-2, 2-6, 6-24 and 24-48 hours after craniotomy under general anesthesia; (2) assessment of total rescue antiemetic dosage 0-48 hours after craniotomy under general anesthesia;（3）length of hospital stay; (4) patient satisfaction score with PONV management. We will perform all statistical analysis following the intention-to-treat principle.

Discussion: The results from this study may potentially confirm that the therapy described can prevent PONV in patients undergoing craniotomy under general anesthesia.

Ethics and dissemination:

Ethics approval has been granted by the Bioethics Subcommittee of West China Hospital, Sichuan University: the approval number is 2018 (Number 231). Results will be expected to be published in peer-reviewed journals.

Trial registration: This study is registered with the Chinese Clinical Trial (ChiCTR1800017173)in July 2018, the registration status was prospective registration.

Keywords: intradermal thumbtack needle, Neiguan, nausea, vomiting, craniotomy.

strengths and limitations of this study

- ►A randomised controlled trial of 180 patients will be conducted to evaluate the effectiveness of intradermal thumbtack needle buried Neiguan (P6) point therapy in the prevention of PONV in patients undergoing craniotomy under general anesthesia. ► The feasibility of the trial has been examined by a pilot randomised trial of 30 patients. ► This trial will be conducted using rigorous methods, such as the blinding of data analyst and outcome assessors, and the implementation of interventions using clearly prespecified approaches. ► The control group lacked placebo effect.

Background

Postoperative nausea and vomiting (PONV), is one of the most commonly observed adverse reactions following anesthesia and surgery[1-3]. It increases the difficulty of medical care, delays the patient's recovery from anesthesia, extends their hospital stay and increases overall healthcare costs[4, 5]. Recently, clinical studies report that there is a high incidence, - about 30% - of patients experiencing PONV. This is much higher in patients who specifically undergo neurosurgery. The incidence in these cases can be as high as 73%. The studies also suggest that the occurrence of PONV can result in an increased risk of intracranial hematoma and hemorrhage[6, 7].

Pharmacological prophylaxis is widely used in clinical practice, and the most commonly used prophylactic antiemetics include serotonin (5-HT3) receptor antagonists, often in combination with either droperidol or

dexamethasone[8-10]. Recently, however, the US Food and Drug Administration (FDA), has reported that droperidol may cause death secondary to arrhythmia or QT prolongation, while other drugs have varying degrees of side effects[11]. At present, no therapy is categorically effective at preventing PONV.

Due to the limited efficacy and many side effects of drug therapy, various non-pharmacological techniques have been used in clinical practice. These therapies include acupuncture[12], acupressure[13], transcutaneous electrical nerve stimulation (TENS)[14, 15], and electro-acupuncture[16], among others[17]. In 2006, the American Society of Peri anesthesia Nurses (ASPAN), recommended pericardium 6 (P6; also known as Neiguan) acupoint stimulation (Class IIb, Grade A) and self-P6 acupoint compression before and after surgery (Grade C) as a complementary intervention for PONV prophylaxis. The 2014 American Anesthesia Outpatient Guide also recommended that acupuncture treatment may be used as an alternative or adjuvant therapy for prevention of PONV[18] . Many recent studies have supported the efficacy of P6 acupoint stimulation in preventing PONV[17, 19-21].

The existing acupuncture treatment is still mainly focused on electro-acupuncture or traditional needle operation. In our clinical practice, however, the limitations of these two acupuncture stimulation methods

(including fixed treatment and fixed treatment time, inconvenience of other medical operations during needle retention, etc.) have resulted in unstable efficacy.

A combination of traditional Chinese and Western medicine, including needle embedding therapy, was put forward in the 1950s. With the developments of acupuncture apparatus, intradermal thumbtack needle has emerged as a new kind of the embedding therapy. The Intradermal thumbtack needle (**Figure 1**), an improved subcutaneous needle, is a type of shallow needling method that reduces pain and prolongs the acupuncture effect via longer needle retention. Also, our previous clinical experience indicates that the time of nausea and vomiting in patients after surgery is uncertain[22-24]. As the Intradermal thumbtack needle has a 24-hour persistent stimulating effect, patients can self-press it at the P6 to relieve gastrointestinal discomfort when needed.

Therefore, we designed a single-center, prospective, single-blind, randomized controlled trial (RCT) to evaluate the efficacy of P6 acupoint stimulation by intradermal thumbtack needle as a non-pharmacological prophylaxis for PONV. This study incorporates the concept of fast tracksurgery, using a prospective randomized controlled method, inspired by the concept of a postoperative analgesia pump, to develop P6 acupoint stimulation treatment by intradermal thumbtack needle with long-term

stimulation characteristics（**Figure 2)**. The study is designed to evaluate the effectiveness and safety of P6 acupoint stimulation for the prevention of PONV in patients who undergo craniotomy under general anesthesia by intradermal thumbtack needle versus acupuncture filiform needles, and versus routine antiemetic. The objective is to compare the effect and safety using different methods.

Methods

Design:

This is a single-center, prospective, single-blind, parallel-group, RCT. The trial protocol strictly follows the principles of the Declaration of Helsinki (version Seoul, 2008) and approval has been obtained from the Sichuan University Ethics and Research Committee. Participants have been and will continue to be recruited from the West China Hospital of Sichuan University (WCHSU) from January 2018 to November 2019. All participants are required to give written informed consent. The study's flow chart is shown in **Figure 3**.

Patient population and setting:

A total of 180 Chinese patients undergoing craniotomy will be sequentially recruited at the WCHSU after fulfilling the eligibility criteria and signing the informed consent. A clinical assistant with institutional review board training will be in charge of patient enrolment.

Eligibility criteria

Inclusion criteria: Patients who fulfill the following conditions will be included: 1) scheduled for neurosurgery requiring opening of the cranium and dura; 2) aged between 18 and 70 years old; 3) American Society of Anesthesiologists (ASA) physical status classification of I or II; 4) undergoing general anesthesia; 5) no history of PONV or motion sickness; 6) no experience with acupuncture therapies; 7) no use of antiemetic 24 hours before surgery; 8) willingness to participate; and 9) having signed an informed consent form.

Exclusion criteria: Participants that meet any of the following criteria will be excluded: 1) nausea or vomiting 24 hours before surgery; 2) pregnant or lactating women; 3) menstruating phase of the menstrual cycle; 4) drug or alcohol abusers; 5) criminals; 6) recipients of chemotherapy or radiation therapy during the previous 7 days before surgery; 7) cardiac pacemaker; 8) refusal to accept acupuncture and TENS treatment; 9) mental disorder; 10) history of epilepsy and still taking an antiepileptic medicine; 11) unconscious before the surgery; 12) cannot normally communicate; 13) undergoing ventricle or brainstem surgery; 14) cerebral perfusion pressure (CPP) of greater than 150mmHg and signs of encephalopathy; 14) poorly controlled diabetes mellitus (fasting plasma glucose greater than 12 mmol/L); 15) bleeding disorders (hemophilia or

afibrinogenemia); and 16) serious systemic disease (AIDS or sepsis).

Dropout criteria: Participants who meet any of the following criteria are withdrawn from the study: 1) death; 2) waking up more than 2 hours after surgery; 3) trachea intubation; 4) persistent coma; 5) cognitive impairment; 6) further surgery or transfer to ICU if necessary for the aggravation of the disease, etc. Patients who are withdrawn are not replaced.

***Randomization and blinding*:**

A randomized grouping plan will be designed using the statistical software named Package for Encyclopedia Medical Statistics 3.1 (PEMS 3.1). Using this plan, the 180 patients will be randomly assigned to either an acupuncture, intradermal thumbtack needle, or control treatment group. The grouping scheme will be kept hidden in an envelope. The included participants will be randomly assigned to each group according to the distribution scheme in the envelope: 60 patients in each group. This study is a single-blind design, in order to keep patients unaware of which study group they will be randomly assigned to, and the efficacy evaluator and statistician are separated in this study.

Study investigators, acupuncturists and participants will be aware of the treatment allocation. Outcome assessors and data analysts will be blinded and participants will be asked not to reveal their allocation to assessors.

In addition, we will have blinded interpretation of the study results to minimise misleading data interpretation.

***Interventions*:**

The determination of the program and the point of acupuncture is based on previous research and The Name and Location of Acupoints (GB/T 12346-2006). All the practitioners performing the treatment must have an acupuncturist qualification certificate and have performed clinical treatment independently for more than 2 years. The acupuncturists are not replaced during the experiment.

All patients will receive the same anesthesia methods: general anesthesia with endotracheal intubation. Blood pressure, heart rate, pulse oximetry and end tidal CO_2 will be routinely monitored. Induction of anesthesia will be achieved with midazolam 0.05mg/kg, sufentanil 0.3μg/kg, atracurium 0.15mg/kg and propofol 2mg/kg. When endotracheal intubation and gastrointestinal decompression with either an orogastric or nasogastric tube are undertaken, the anesthesia will be maintained with 50% nitrous oxide and 3% sevoflurane, Actually, we adjusted the concentration of sevoflurane according to BIS and the vital signs, if the hypotension happened,and the BIS is low,we will decrease the sevoflurane. After the operation has commenced, participants will be given sufentanil 0.2μg/kg and atracurium 0.1mg/kg intermittently. 30 minutes before the end of the

operation, the patients will be treated with prophylactic antiemetic drugs: Ondansetron Hydrochloride Tablets 8mg according to the advice of doctors. After surgery, patients will be continually monitored in the post-anesthesia care unit (PACU) after anesthesia to continue the ventilator support. The tracheal tube will be removed after the patients awake. The time from the start of anesthesia induction to the time of removal of the tube will be recorded. Patients who then meet the criteria (Steward Rating Scale $\geqslant$4, and the blood gas index of special patients being normal as judged by the anesthetist) will be sent back to the ward.

For the acupuncture group (acupuncture is added at the base of basic treatment), bilateral Neiguan (P6, located on the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist) (**Figure 4**) will be selected.

The location of the acupoint refers to national standards of PRC published in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints"). After the patients are transported from the post-anesthesia care unit (PACU) to the common ward, the treatment will commence. After skin disinfection with a disposable disinfecting cotton swab, sterile and disposable stainless-steel needles (0.25 × 25 mm, Suzhou Hwato-med, Jiangsu, China) will be quickly and perpendicularly inserted into the skin at P6 acupoints bilaterally to a depth of 20mm. The duration of

reinforcing-reducing manipulation of twirling and rotating needle should be used for 1 minute to achieve de qi (a composite of sensations including soreness, numbness, distention, heaviness, and other sensations), which is recognized to be an essential component for acupuncture efficacy. The needles will be kept in place for 30 minutes and manipulated manually every 10 minutes to maintain the de qi. When the treatment is over, all needles will be carefully removed. The therapy includes 2 treatments, and the acupuncture will be administered immediately after and 24 hours after surgery.

For the group of thumbtack needle stimulation (press-needle is added at the base of conventional therapy), the bilateral P6 acupoint will be selected. The location of the acupoint refers to national standards of PRC published in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints"). Treatment will commence after the patients are transported from the post-anesthesia care unit (PACU) to the common ward. After skin cleansing with a 75% alcohol swab, Japanese SEIRIN PYONEX (0.2mm × 1.5 mm) will be quickly inserted into the skin and embedded at P6 acupoints bilaterally. Patients and their families will be asked to press the needle point when the patient feels nausea, experiences vomiting, bloating, pain and other discomfort. The needle will be replaced after 24 hours. The therapy is given twice as the thumbtack needle stimulation will

be given immediately after and 24 hours following surgery.

For the control treatment group of rapid rehabilitation surgery, the benefits, specific measures, prevention of complications, time and cost of hospitalization will be explained to patients and their families in detail using multimedia presentations and pamphlets prior to the operation. Preoperative measures also include fasting for 6 hours, fasting water for 2 hours and infusing water and carbohydrates 2 hours before surgery. Premedication will not be administered. Fluid volume management and temperature intervention, drainage system, urethral catheter and gastric tube will not be applied during the operation. The postoperative measures include multi-mode control of postoperative pain, early ambulation, early extubation (when tubes are applied), ADR monitoring and prognosis monitoring.

Outcome measures:

Main Outcome:

In this study, patients are monitored for 48 hours post-operatively. The observers will record any episodes of vomiting (criteria based on vomiting action or vomitus in the mouth) 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours following surgery. The incidence of PONV within 48 hours after craniotomy across the three groups is the main criteria to be measured.

Secondary Outcome:

The observers will evaluate the patients' degree of nausea using the WHO's PONV forth class rating scale: 0) no nausea at all; 1) mild nausea or abdominal discomfort without vomiting; 2) evident nausea without vomitus; 3) extreme nausea and vomitus containing gastric juice, which is uncontrolled by medicine. The pain score adopts a standard visual analogue scale (VAS) during 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after craniotomy under general anesthesia. The assessment of total rescue antiemetic dosage 0-48 hours after craniotomy under general anesthesia will be recorded. The length of stay in the hospital and patient satisfaction score with PONV management will also to recorded.

Adverse event reporting:

Adverse events will be recorded via voluntary reports by neurosurgeons, physical examination, laboratory examination, or other methods. All adverse events must be recorded on the CRF's adverse events page and the following information about adverse events should be provided: 1) severity degree (mild, moderate or severe); 2) the relationship with research therapy (definitely related, probably related, possibly related, probably irrelevant or definitely irrelevant); 3) duration (the start and end dates or if the adverse advent still exists at the last check); 4) serious

adverse event (SAE); 5) important medical events (if potentially harmful to patients medical or surgical intervention may be requested).

In order to ensure the safety of each patient, any serious adverse events that occur from the time the patient gives consent up to 30 days after completion of the study, whether or not associated with the treatment of this research, must be reported to the project director within 24 hours. Severe adverse events that occur 30 days after the cessation of the study do not need to be reported unless the researchers deem it relevant to the treatment. The recurrence, complication, or progression of previous reported serious adverse events must also be reported as first reported follow-up information, as soon as the first serious adverse event occurs. The researchers must report the events within 24 hours once receiving the follow-up information. If a serious adverse event is considered to be completely unrelated to the previously reported one, it should be reported as a new event.

***Sample size calculation and statistical analysis*:**

A German prospective observational study published in 2011 demonstrated an overall incidence of PONV in 47% of patients after craniotomy under general anesthesia. The sample size is determined by using PEMS 3.1 with α= 0.05 (two-sided) and β= 0.1 (90% power). The formula for calculation is as follows:

$$n = 2\lambda/(2sin^{-i}\sqrt{P_{max}} - 2sin^{-1}\sqrt{P_{min}})^2$$

In order to demonstrate a 30% absolute reduction in the incidence of PONV, the sample size will be 49 patients for each group. Considering the potential for loss and attrition (20%), 60 patients per group, or a total of 180 patients, should be reasonable. If a patient cannot complete the study due to death, reoperation, unconsciousness or cognitive impairment, that patient cannot be considered successfully treated and will be recorded as an episode of PONV for statistical purposes.

All data will be analyzed by a blinded statistician using PEMS 3.1 at a separate location from the WCHSU. The intention-to-treat principal will be used in the data analysis. Baseline data will be collected and compared first. Different statistics are presented differently, for example, continuous data is presented as mean (± standard deviation). Chi-square test is used to compare the incidence of postoperative vomiting, complete response rate, sex difference and other nominal data. Conversely, the Kruskal-Wallis test is used to compare the nausea score, satisfaction score and antiemetic dosage. Additionally, the Nemenyi test and Scheffé's method are used for multiple comparisons between groups. A *P* value <0.05 is considered statistically significant.

Patient and public involvement

The patients and public were not involved in planning and design of this

study.

The present trial was developed by acupuncturists based on previous clinical experience and literature. Patients were not involved in the design of the study. The outcomes were commonly used assessments of PONV in clinical practice. The cost of interventions and outcome measurements were mostly covered by the study funding so it was not thought to be a significant burden and were in line with patient preferences. The results will be disseminated to study participants via the website of our hospital.

Discussion

Our previous studies have shown the effectiveness and safety of acupuncture in the treatment of nausea and vomiting following craniotomy. In the clinic, however, we have found that, as the time of postoperative nausea and vomiting is not fixed, patients are eager to receive treatment when they experience nausea and vomiting. Often, however, acupuncture cannot be administered as there is no qualified practitioner available. In order to improve the availability of treatment, acupuncturists need to formulate new protocols. Seaband© and TENs are effective treatments for postoperative nausea and vomiting. They are easy to administer and non-invasive, though our previous studies have found that their efficacy is inferior to needle therapy. The intradermal thumbtack needle has a piercing effect and can be in place for 24 hours.

When the patient is nauseous, pressing the acupuncture point can achieve de-qi sensation. We therefore designed this randomized controlled study in order to demonstrate that intradermal thumbtack needle buried Neiguan point therapy can reduce the nausea and vomiting after craniotomy. It is conducive to clinical use and improved patient satisfaction.

Ethics and dissemination

Ethics approval has been granted by the Bioethics Subcommittee of West China Hospital, Sichuan University: the approval number is 2018 (Number 231). Results will be expected to be published in peer-reviewed journals.

The case report forms (CRFs) will be stored in a locked cabinet at the hospitals and accessible by the research team only. On completion of the trial and data checking, the CRFs will be transferred to be securely archived at Sichuan university for 5 years before being destroyed. The trial database will be anonymised, password protected and securely held. Patient identifiable data are shared only within the clinical team on a need-to-know basis to provide clinical care and ensure appropriate follow-up. The aggregated research findings will be presented at national and international scientific conferences and be submitted for publication in peer-reviewed journals.

Contributors

19

Jian-qin lv devised the study question and design. Yi yang and Yu li developed the idea into the full protocol and wrote the article draft.tian-hao xu reviewed the protocol. Ling-qi jian calculated the sample size and specified the statistical strategy. Chengwei wang is in charge of conducting all the procedures. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests

Patient consent

Obtained.

Ethics approval

This study protocol with the written informed consent forms has been peerreviewed and approved by Ethical approval of West China Hospital of Si-chuan University clinical trials and biomedical ethics committee 2018 (231) in July 2018.The approval number is 2018(231).

Availability of data and material:

The datasets used and/or analyzed after completing the current study will be available from the corresponding author by reasonable requests.

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Figure Legends

Figure 1: Intradermal thumbtack needle

Figure 2: Intradermal thumbtack needle being inserted into the Neiguan point (P6)

Figure 3: Trial flow chart

Figure 4: Location of P6 acupoint

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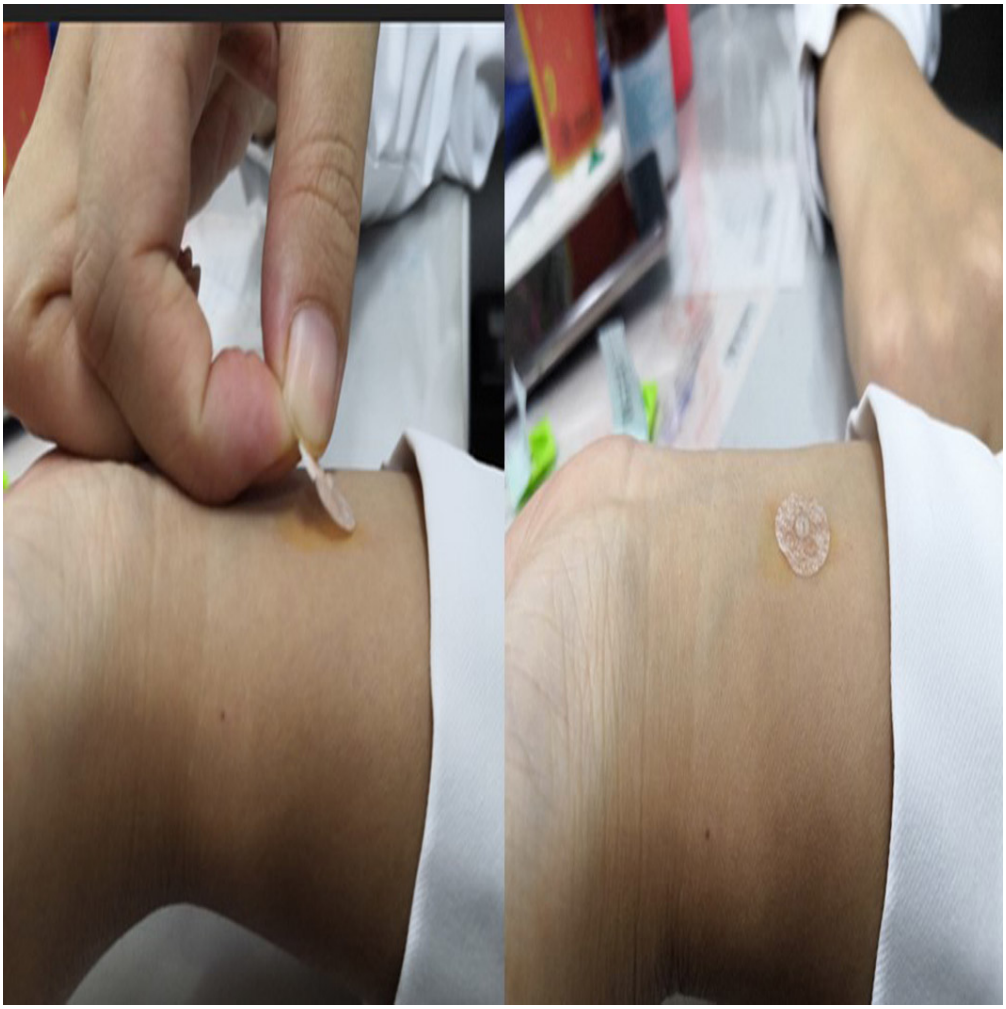

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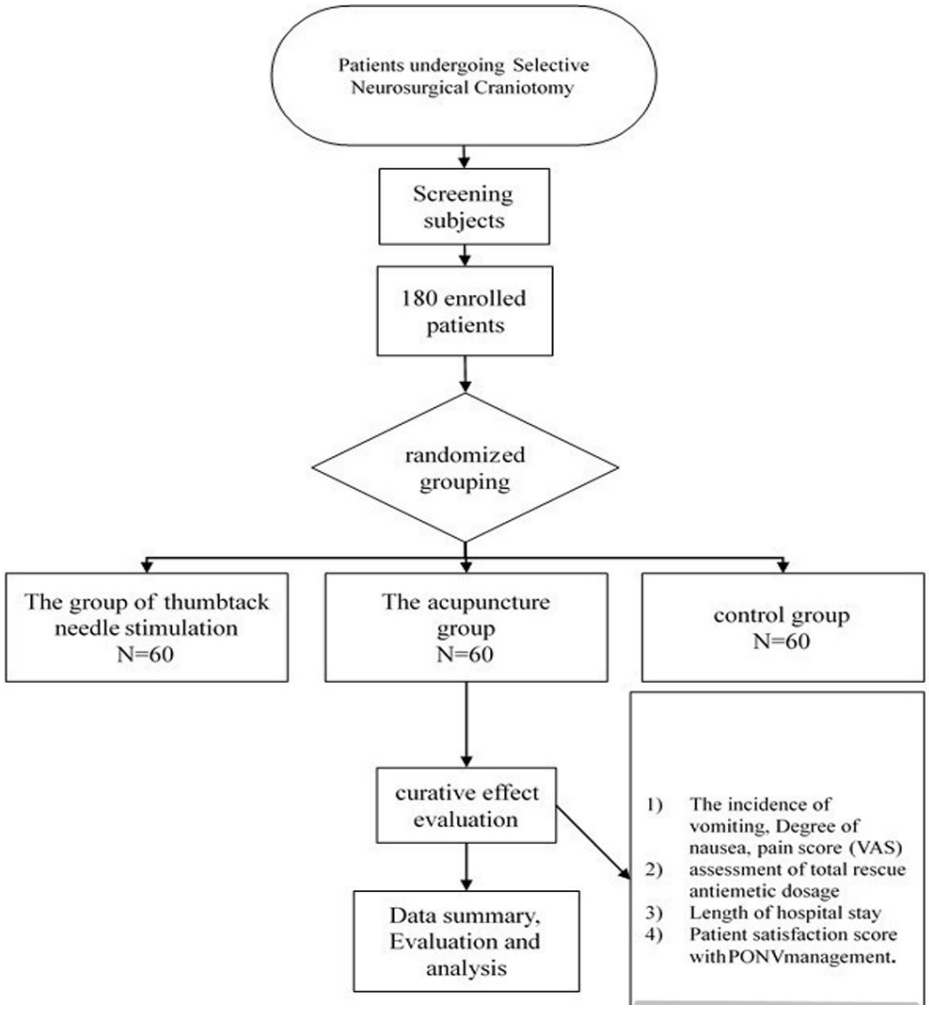

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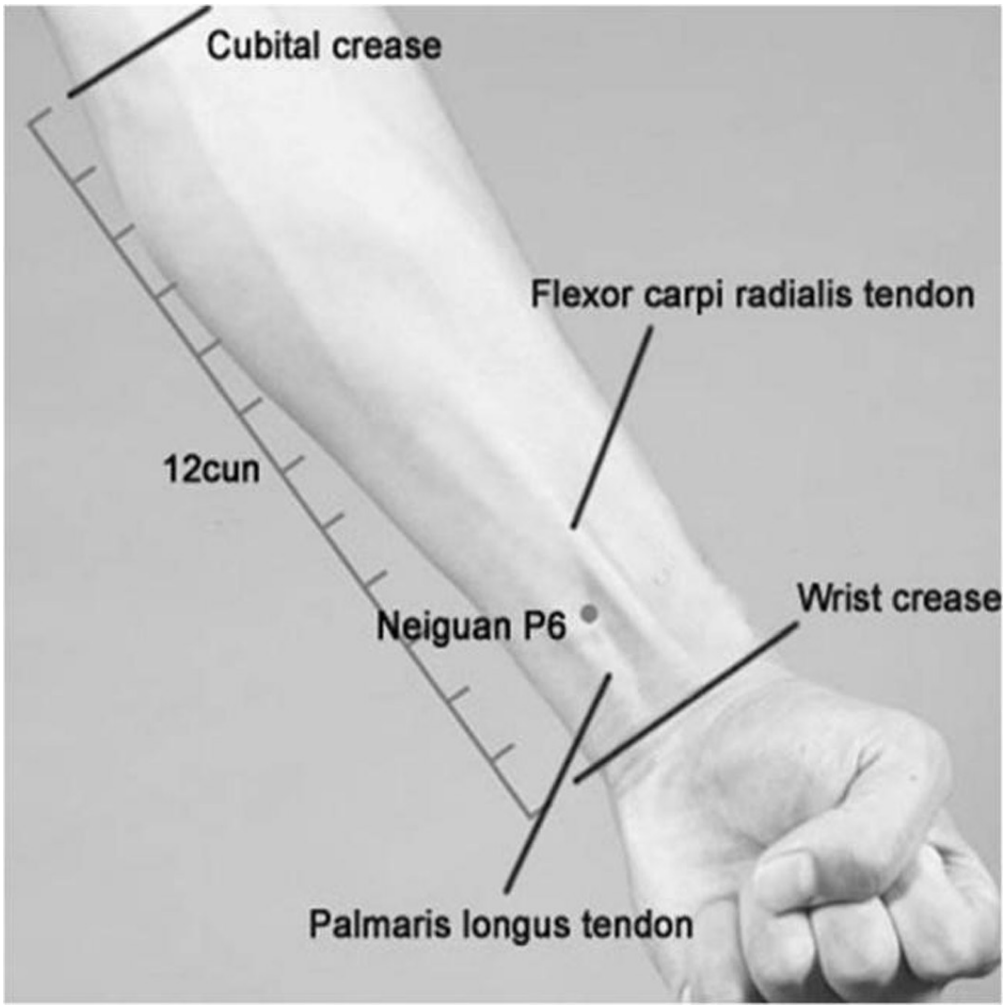

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	2
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A

	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Intradermal thumbtack needle buried Neiguan (P6) point for prevention of postoperative nausea and vomiting in patients undergoing craniotomy: study protocol for a randomized controlled trial

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Intradermal thumbtack needle buried Neiguan (P6) point for prevention of postoperative nausea and vomiting in patients undergoing craniotomy: study protocol for a randomized controlled trial

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Abstract

Introduction: Postoperative nausea and vomiting (PONV) is among the most common adverse reactions following anesthesia and surgery. Recent clinical studies have reported that the average incidence is about 30%, while in patients specifically undergoing neurosurgery the incidence can be as great as 73%. Studies also suggest that its occurrence increases the risk of intracranial hematoma and hemorrhage**.** The objective of this study is to evaluate the effectiveness of intradermal thumbtack needle buried Neiguan (P6) point therapy in the prevention of PONV in patients undergoing craniotomy under general anesthesia.

Methods and analysis: This is a single-center, three-arm, randomized controlled trial. 180 participants are randomly assigned to either an Acupuncture group, Intradermal thumbtack needle group or Control group in a 1:1:1 ratio. The P6 of the Acupuncture group is punctured at both sides perpendicularly to a depth of 20mm. Needles are retained for 30 minutes and stimulated every 10 minutes to maintain the de qi. The therapy includes 2 treatments; the acupuncture is administered immediately after and 24 hours after surgery. For the Intradermal thumbtack needle group, the intradermal thumbtack needle is quickly inserted into the skin and embedded at P6 acupoints bilaterally. Patients and their families are asked to press the needle point with the onset of

nausea, vomiting, bloating, pain and other reported discomfort. The needle is replaced after 24 hours. The therapy is administered immediately after and 24 hours after surgery. For the Control group, no intervention is carried out. The incidence of PONV within 48 hours after craniotomy across the three groups is observed. Other observations include: (1) assessment of nausea score (severity of nausea) and pain score （VAS) 0-2, 2-6, 6-24 and 24-48 hours after craniotomy under general anesthesia; (2) assessment of total rescue antiemetic dosage 0-48 hours after craniotomy under general anesthesia;（3）length of hospital stay; (4) patient satisfaction score with PONV management. We will perform all statistical analysis following the intention-to-treat principle.

Ethics and dissemination:

Ethics approval has been granted by the Bioethics Subcommittee of West China Hospital, Sichuan University: the approval number is 2018 (Number 231). Results will be expected to be published in peer-reviewed journals.

Trial registration: This study is registered with the Chinese Clinical Trial (ChiCTR1800017173)in July 2018, the registration status was prospective registration.

Keywords: intradermal thumbtack needle, Neiguan, nausea, vomiting, craniotomy.

strengths and limitations of this study

- ►A randomised controlled trial of 180 patients will be conducted to evaluate the effectiveness of intradermal thumbtack needle buried Neiguan (P6) point therapy in the prevention of PONV in patients undergoing craniotomy under general anesthesia. ► The feasibility of the trial has been examined by a pilot randomised trial of 30 patients. ► This trial will be conducted using rigorous methods, such as the blinding of data analyst and outcome assessors, and the implementation of interventions using clearly prespecified approaches. ► The control group lacked placebo effect.

Background

Postoperative nausea and vomiting (PONV), is one of the most commonly observed adverse reactions following anesthesia and surgery[1-3]. It increases the difficulty of medical care, delays the patient's recovery from anesthesia, extends their hospital stay and increases overall healthcare costs[4, 5]. Recently, clinical studies report that there is a high incidence, - about 30% - of patients experiencing PONV. This is much higher in patients who specifically undergo neurosurgery. The incidence in these cases can be as high as 73%. The studies also suggest that the occurrence of PONV can result in an increased risk of intracranial hematoma and hemorrhage[6, 7].

Pharmacological prophylaxis is widely used in clinical practice, and the most commonly used prophylactic antiemetics include serotonin (5-HT3) receptor antagonists, often in combination with either droperidol or

dexamethasone[8-10]. Recently, however, the US Food and Drug Administration (FDA), has reported that droperidol may cause death secondary to arrhythmia or QT prolongation, while other drugs have varying degrees of side effects[11]. At present, no therapy is categorically effective at preventing PONV.

Due to the limited efficacy and many side effects of drug therapy, various non-pharmacological techniques have been used in clinical practice. These therapies include acupuncture[12], acupressure[13], transcutaneous electrical nerve stimulation (TENS)[14, 15], and electro-acupuncture[16], among others[17]. In 2006, the American Society of Peri anesthesia Nurses (ASPAN), recommended pericardium 6 (P6; also known as Neiguan) acupoint stimulation (Class IIb, Grade A) and self-P6 acupoint compression before and after surgery (Grade C) as a complementary intervention for PONV prophylaxis. The 2014 American Anesthesia Outpatient Guide also recommended that acupuncture treatment may be used as an alternative or adjuvant therapy for prevention of PONV[18] . Many recent studies have supported the efficacy of P6 acupoint stimulation in preventing PONV[17, 19-21].

The existing acupuncture treatment is still mainly focused on electro-acupuncture or traditional needle operation. In our clinical practice, however, the limitations of these two acupuncture stimulation methods

(including fixed treatment and fixed treatment time, inconvenience of other medical operations during needle retention, etc.) have resulted in unstable efficacy.

A combination of traditional Chinese and Western medicine, including needle embedding therapy, was put forward in the 1950s. With the developments of acupuncture apparatus, intradermal thumbtack needle has emerged as a new kind of the embedding therapy. The Intradermal thumbtack needle (**Figure 1**), an improved subcutaneous needle, is a type of shallow needling method that reduces pain and prolongs the acupuncture effect via longer needle retention. Also, our previous clinical experience indicates that the time of nausea and vomiting in patients after surgery is uncertain[22-24]. As the Intradermal thumbtack needle has a 24-hour persistent stimulating effect, patients can self-press it at the P6 to relieve gastrointestinal discomfort when needed.

Therefore, we designed a single-center, prospective, single-blind, randomized controlled trial (RCT) to evaluate the efficacy of P6 acupoint stimulation by intradermal thumbtack needle as a non-pharmacological prophylaxis for PONV. This study incorporates the concept of fast tracksurgery, using a prospective randomized controlled method, inspired by the concept of a postoperative analgesia pump, to develop P6 acupoint stimulation treatment by intradermal thumbtack needle with long-term

stimulation characteristics（**Figure 2)**. The study is designed to evaluate the effectiveness and safety of P6 acupoint stimulation for the prevention of PONV in patients who undergo craniotomy under general anesthesia by intradermal thumbtack needle versus acupuncture filiform needles, and versus routine antiemetic. The objective is to compare the effect and safety using different methods.

Methods

Design:

This is a single-center, prospective, single-blind, parallel-group, RCT. The trial protocol strictly follows the principles of the Declaration of Helsinki (version Seoul, 2008) and approval has been obtained from the Sichuan University Ethics and Research Committee. Participants have been and will continue to be recruited from the West China Hospital of Sichuan University (WCHSU) from January 2018 to November 2019. All participants are required to give written informed consent. The study's flow chart is shown in **Figure 3**.

Patient population and setting:

A total of 180 Chinese patients undergoing craniotomy will be sequentially recruited at the WCHSU after fulfilling the eligibility criteria and signing the informed consent. A clinical assistant with institutional review board training will be in charge of patient enrolment.

Eligibility criteria

Inclusion criteria: Patients who fulfill the following conditions will be included: 1) scheduled for neurosurgery requiring opening of the cranium and dura; 2) aged between 18 and 70 years old; 3) American Society of Anesthesiologists (ASA) physical status classification of I or II; 4) undergoing general anesthesia; 5) no history of PONV or motion sickness; 6) no experience with acupuncture therapies; 7) no use of antiemetic 24 hours before surgery; 8) willingness to participate; and 9) having signed an informed consent form.

Exclusion criteria: Participants that meet any of the following criteria will be excluded: 1) nausea or vomiting 24 hours before surgery; 2) pregnant or lactating women; 3) menstruating phase of the menstrual cycle; 4) drug or alcohol abusers; 5) criminals; 6) recipients of chemotherapy or radiation therapy during the previous 7 days before surgery; 7) cardiac pacemaker; 8) refusal to accept acupuncture and TENS treatment; 9) mental disorder; 10) history of epilepsy and still taking an antiepileptic medicine; 11) unconscious before the surgery; 12) cannot normally communicate; 13) undergoing ventricle or brainstem surgery; 14) cerebral perfusion pressure (CPP) of greater than 150mmHg and signs of encephalopathy; 14) poorly controlled diabetes mellitus (fasting plasma glucose greater than 12 mmol/L); 15) bleeding disorders (hemophilia or

afibrinogenemia); and 16) serious systemic disease (AIDS or sepsis).

Dropout criteria: Participants who meet any of the following criteria are withdrawn from the study: 1) death; 2) waking up more than 2 hours after surgery; 3) trachea intubation; 4) persistent coma; 5) cognitive impairment; 6) further surgery or transfer to ICU if necessary for the aggravation of the disease, etc. Patients who are withdrawn are not replaced.

***Randomization and blinding*:**

A randomized grouping plan will be designed using the statistical software named Package for Encyclopedia Medical Statistics 3.1 (PEMS 3.1). Using this plan, the 180 patients will be randomly assigned to either an acupuncture, intradermal thumbtack needle, or control treatment group. The grouping scheme will be kept hidden in an envelope. The included participants will be randomly assigned to each group according to the distribution scheme in the envelope: 60 patients in each group. This study is a single-blind design, in order to keep patients unaware of which study group they will be randomly assigned to, and the efficacy evaluator and statistician are separated in this study.

Study investigators, acupuncturists and participants will be aware of the treatment allocation. Outcome assessors and data analysts will be blinded and participants will be asked not to reveal their allocation to assessors.

In addition, we will have blinded interpretation of the study results to minimise misleading data interpretation.

***Interventions*:**

The determination of the program and the point of acupuncture is based on previous research and The Name and Location of Acupoints (GB/T 12346-2006). All the practitioners performing the treatment must have an acupuncturist qualification certificate and have performed clinical treatment independently for more than 2 years. The acupuncturists are not replaced during the experiment.

All patients will receive the same anesthesia methods: general anesthesia with endotracheal intubation. Blood pressure, heart rate, pulse oximetry and end tidal CO_2 will be routinely monitored. Induction of anesthesia will be achieved with midazolam 0.05mg/kg, sufentanil 0.3μg/kg, atracurium 0.15mg/kg and propofol 2mg/kg. When endotracheal intubation and gastrointestinal decompression with either an orogastric or nasogastric tube are undertaken, the anesthesia will be maintained with 50% nitrous oxide and 3% sevoflurane.An attending anesthesiologist will adjust the concentration of sevoflurane according to BIS and the vital signs, if the hypotension happened and the BIS is low, he or she will decrease the sevolufrane. The target range of BIS was 40-60 during surgery.After the operation has commenced, participants will be given sufentanil 0.2μg/kg

and atracurium 0.1mg/kg intermittently. 30 minutes before the end of the operation, the patients will be treated with prophylactic antiemetic drugs: Ondansetron Hydrochloride Tablets 8mg according to the advice of doctors. After surgery, patients will be continually monitored in the post-anesthesia care unit (PACU) after anesthesia to continue the ventilator support. The tracheal tube will be removed after the patients awake. The time from the start of anesthesia induction to the time of removal of the tube will be recorded. Patients who then meet the criteria (Steward Rating Scale $\geqslant$4, and the blood gas index of special patients being normal as judged by the anesthetist) will be sent back to the ward.

For the acupuncture group (acupuncture is added at the base of basic treatment), bilateral Neiguan (P6, located on the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist) (**Figure 4**) will be selected.

The location of the acupoint refers to national standards of PRC published in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints"). After the patients are transported from the post-anesthesia care unit (PACU) to the common ward, the treatment will commence. After skin disinfection with a disposable disinfecting cotton swab, sterile and disposable stainless-steel needles (0.25 × 25 mm, Suzhou Hwato-med, Jiangsu, China) will be quickly and perpendicularly inserted into the skin

at P6 acupoints bilaterally to a depth of 20mm. The duration of reinforcing-reducing manipulation of twirling and rotating needle should be used for 1 minute to achieve de qi (a composite of sensations including soreness, numbness, distention, heaviness, and other sensations), which is recognized to be an essential component for acupuncture efficacy. The needles will be kept in place for 30 minutes and manipulated manually every 10 minutes to maintain the de qi. When the treatment is over, all needles will be carefully removed. The therapy includes 2 treatments, and the acupuncture will be administered immediately after and 24 hours after surgery.

For the group of thumbtack needle stimulation (press-needle is added at the base of conventional therapy), the bilateral P6 acupoint will be selected. The location of the acupoint refers to national standards of PRC published in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints"). Treatment will commence after the patients are transported from the post-anesthesia care unit (PACU) to the common ward. After skin cleansing with a 75% alcohol swab, Japanese SEIRIN PYONEX (0.2mm × 1.5 mm) will be quickly inserted into the skin and embedded at P6 acupoints bilaterally. Patients and their families will be asked to press the needle point when the patient feels nausea, experiences vomiting, bloating, pain and other discomfort. The needle will be replaced after 24

hours. The therapy is given twice as the thumbtack needle stimulation will be given immediately after and 24 hours following surgery.

For the control treatment group of rapid rehabilitation surgery, the benefits, specific measures, prevention of complications, time and cost of hospitalization will be explained to patients and their families in detail using multimedia presentations and pamphlets prior to the operation. Preoperative measures also include fasting for 6 hours, fasting water for 2 hours and infusing water and carbohydrates 2 hours before surgery. Premedication will not be administered. Fluid volume management and temperature intervention, drainage system, urethral catheter and gastric tube will not be applied during the operation. The postoperative measures include multi-mode control of postoperative pain, early ambulation, early extubation (when tubes are applied), ADR monitoring and prognosis monitoring.

Outcome measures:

Main Outcome:

In this study, patients are monitored for 48 hours post-operatively. The observers will record any episodes of vomiting (criteria based on vomiting action or vomitus in the mouth) 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours following surgery. The incidence of PONV within 48 hours after craniotomy across the three groups is the

main criteria to be measured.

Secondary Outcome:

The observers will evaluate the patients' degree of nausea using the WHO's PONV forth class rating scale: 0) no nausea at all; 1) mild nausea or abdominal discomfort without vomiting; 2) evident nausea without vomitus; 3) extreme nausea and vomitus containing gastric juice, which is uncontrolled by medicine. The pain score adopts a standard visual analogue scale (VAS) during 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12 to 24 hours and 24 to 48 hours after craniotomy under general anesthesia. The assessment of total rescue antiemetic dosage 0-48 hours after craniotomy under general anesthesia will be recorded. The length of stay in the hospital and patient satisfaction score with PONV management will also to recorded.

Adverse event reporting:

Adverse events will be recorded via voluntary reports by neurosurgeons, physical examination, laboratory examination, or other methods. All adverse events must be recorded on the CRF's adverse events page and the following information about adverse events should be provided: 1) severity degree (mild, moderate or severe); 2) the relationship with research therapy (definitely related, probably related, possibly related, probably irrelevant or definitely irrelevant); 3) duration (the start and end

dates or if the adverse advent still exists at the last check); 4) serious adverse event (SAE); 5) important medical events (if potentially harmful to patients medical or surgical intervention may be requested).

In order to ensure the safety of each patient, any serious adverse events that occur from the time the patient gives consent up to 30 days after completion of the study, whether or not associated with the treatment of this research, must be reported to the project director within 24 hours. Severe adverse events that occur 30 days after the cessation of the study do not need to be reported unless the researchers deem it relevant to the treatment. The recurrence, complication, or progression of previous reported serious adverse events must also be reported as first reported follow-up information, as soon as the first serious adverse event occurs. The researchers must report the events within 24 hours once receiving the follow-up information. If a serious adverse event is considered to be completely unrelated to the previously reported one, it should be reported as a new event.

***Sample size calculation and statistical analysis*:**

A German prospective observational study published in 2011 demonstrated an overall incidence of PONV in 47% of patients after craniotomy under general anesthesia. The sample size is determined by using PEMS 3.1 with α= 0.05 (two-sided) and β= 0.1 (90% power). The

formula for calculation is as follows:

$$\mathrm{n} = 2\lambda/(2sin^{-i}\sqrt{P_{max}} - 2sin^{-1}\sqrt{P_{min}})^2$$

In order to demonstrate a 30% absolute reduction in the incidence of PONV, the sample size will be 49 patients for each group. Considering the potential for loss and attrition (20%), 60 patients per group, or a total of 180 patients, should be reasonable. If a patient cannot complete the study due to death, reoperation, unconsciousness or cognitive impairment, that patient cannot be considered successfully treated and will be recorded as an episode of PONV for statistical purposes.

All data will be analyzed by a blinded statistician using PEMS 3.1 at a separate location from the WCHSU. The intention-to-treat principal will be used in the data analysis. Baseline data will be collected and compared first. Different statistics are presented differently, for example, continuous data is presented as mean (± standard deviation). Chi-square test is used to compare the incidence of postoperative vomiting, complete response rate, sex difference and other nominal data. Conversely, the Kruskal-Wallis test is used to compare the nausea score, satisfaction score and antiemetic dosage. Additionally, the Nemenyi test and Scheffé's method are used for multiple comparisons between groups. A *P* value <0.05 is considered statistically significant.

Patient and public involvement

The patients and public were not involved in planning and design of this study.

The present trial was developed by acupuncturists based on previous clinical experience and literature. Patients were not involved in the design of the study. The outcomes were commonly used assessments of PONV in clinical practice. The cost of interventions and outcome measurements were mostly covered by the study funding so it was not thought to be a significant burden and were in line with patient preferences. The results will be disseminated to study participants via the website of our hospital.

Discussion

Our previous studies have shown the effectiveness and safety of acupuncture in the treatment of nausea and vomiting following craniotomy. In the clinic, however, we have found that, as the time of postoperative nausea and vomiting is not fixed, patients are eager to receive treatment when they experience nausea and vomiting. Often, however, acupuncture cannot be administered as there is no qualified practitioner available. In order to improve the availability of treatment, acupuncturists need to formulate new protocols. Seaband© and TENs are effective treatments for postoperative nausea and vomiting. They are easy to administer and non-invasive, though our previous studies have found that their efficacy is inferior to needle therapy. The intradermal

thumbtack needle has a piercing effect and can be in place for 24 hours. When the patient is nauseous, pressing the acupuncture point can achieve de-qi sensation. We therefore designed this randomized controlled study in order to demonstrate that intradermal thumbtack needle buried Neiguan point therapy can reduce the nausea and vomiting after craniotomy. It is conducive to clinical use and improved patient satisfaction.

Ethics and dissemination

Ethics approval has been granted by the Bioethics Subcommittee of West China Hospital, Sichuan University: the approval number is 2018 (Number 231). Results will be expected to be published in peer-reviewed journals.

The case report forms (CRFs) will be stored in a locked cabinet at the hospitals and accessible by the research team only. On completion of the trial and data checking, the CRFs will be transferred to be securely archived at Sichuan university for 5 years before being destroyed. The trial database will be anonymised, password protected and securely held. Patient identifiable data are shared only within the clinical team on a need-to-know basis to provide clinical care and ensure appropriate follow-up. The aggregated research findings will be presented at national and international scientific conferences and be submitted for publication in peer-reviewed journals.

Contributors

Jian-qin lv devised the study question and design. Yi yang and Yu li developed the idea into the full protocol and wrote the article draft.tian-hao xu reviewed the protocol. Ling-qi jian calculated the sample size and specified the statistical strategy. Chengwei wang is in charge of conducting all the procedures. All authors read and approved the final manuscript.

Funding

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Competing interests

The authors declare that they have no competing interests

Patient consent

Obtained.

Ethics approval

This study protocol with the written informed consent forms has been peerreviewed and approved by Ethical approval of West China Hospital of Si-chuan University clinical trials and biomedical ethics committee 2018 (231) in July 2018.The approval number is 2018(231).

Availability of data and material:

The datasets used and/or analyzed after completing the current study will be available from the corresponding author by reasonable requests.

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Figure Legends

Figure 1: Intradermal thumbtack needle

Figure 2: Intradermal thumbtack needle being inserted into the Neiguan point (P6)

Figure 3: Trial flow chart

Figure 4: Location of P6 acupoint

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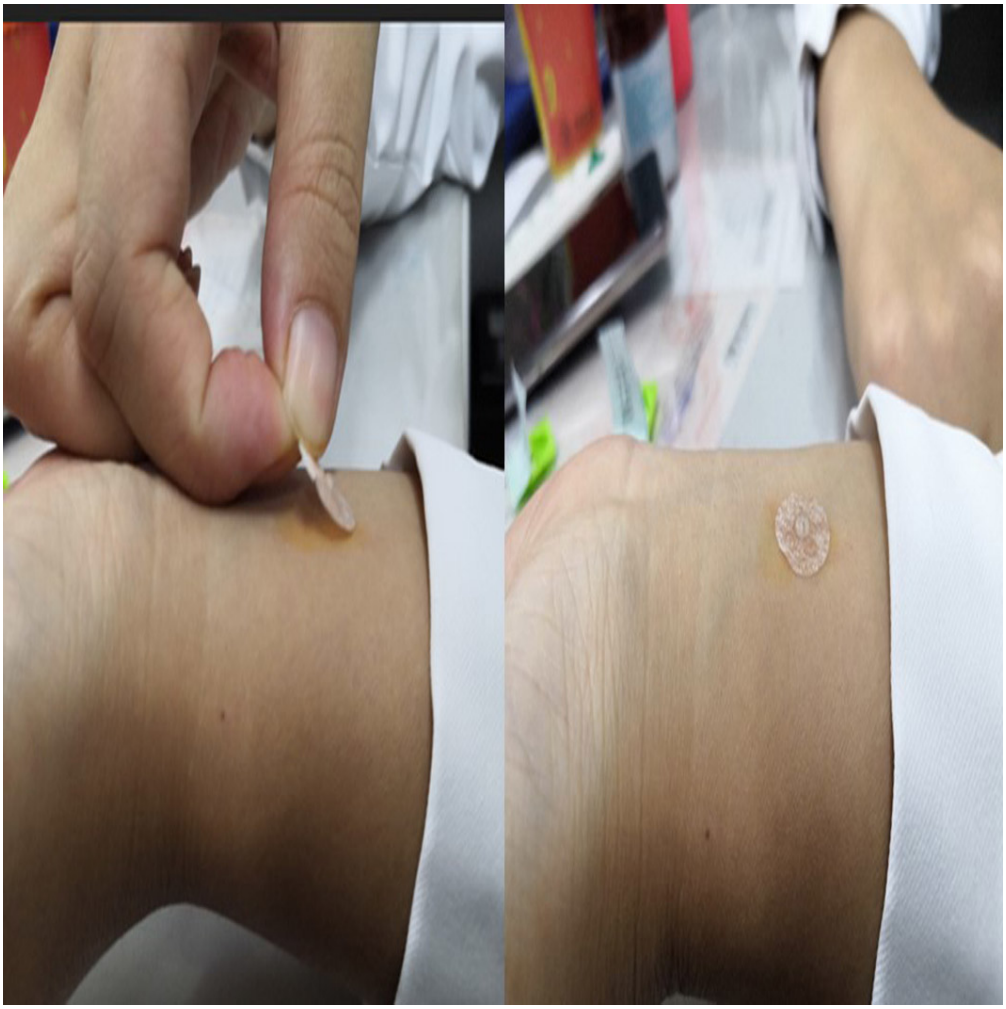

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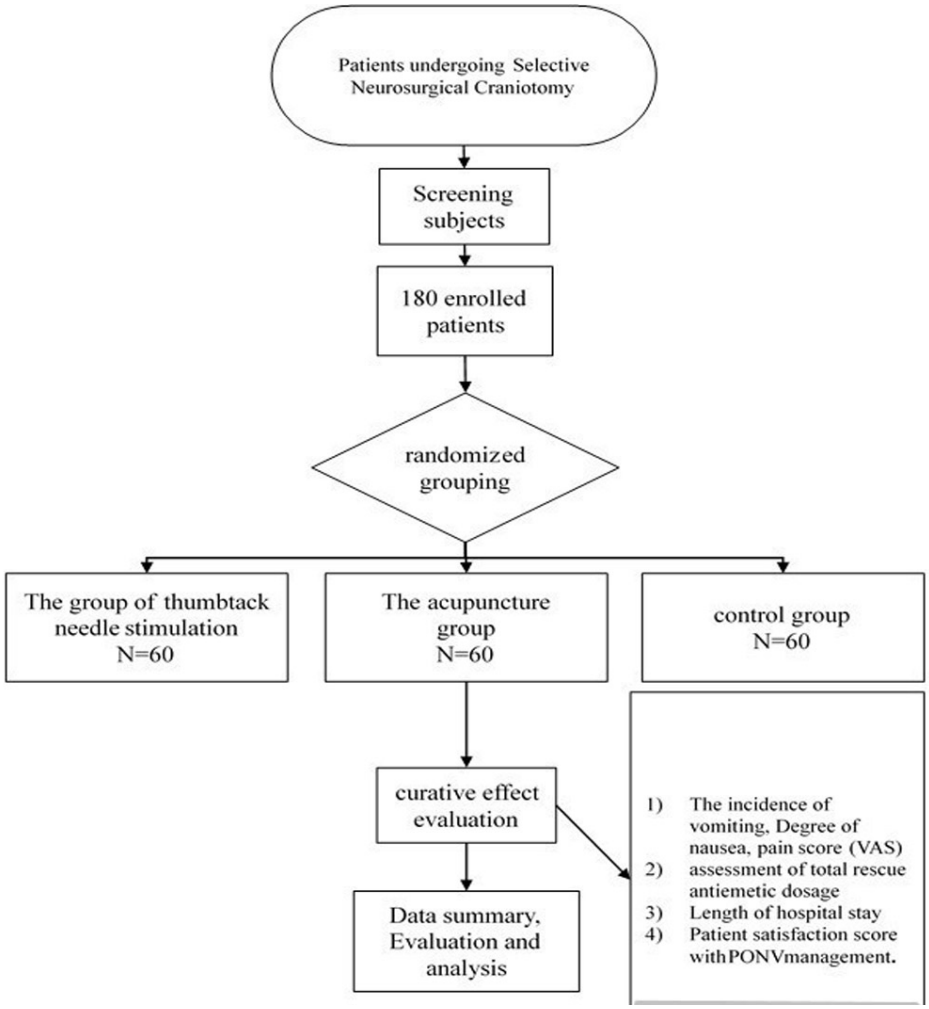

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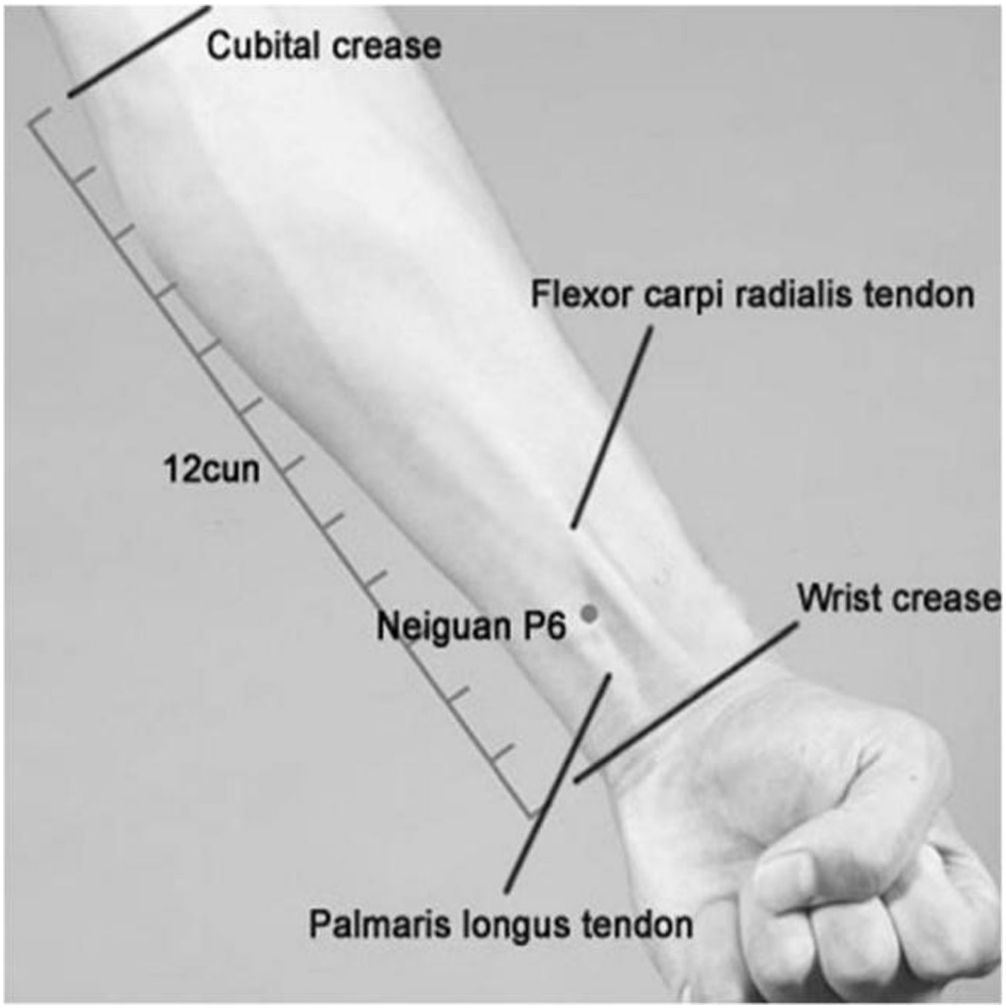

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	2
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A

	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.