

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032417
Article Type:	Protocol
Date Submitted by the Author:	21-Jun-2019
Complete List of Authors:	Lv, jian-qin; Sichuan University West China Hospital Wang, Chengwei; Sichuan University West China Hospital Yang, Yi; Sichuan University, West China School of Medicine Li, Yu; Sichuan University, West China School of Medicine Xu, Tian-hao; Sichuan University, West China School of Medicine Jian, Ling-qi; Sichuan University, West China School of Medicine
Keywords:	intradermal thumbtack needle, Neiguan (P6) , nausea, vomiting, craniotomy

SCHOLARONE™
Manuscripts

1
2
3
4 **Intradermal thumbtack needle buried Neiguan (P6) point for**
5 **prevention of postoperative nausea and vomiting in patients**
6 **undergoing craniotomy: study protocol for a randomized**
7 **controlled trial**
8
9
10
11
12
13
14

15 **Jian-qin Lv¹, Cheng-wei Wang^{1*}, Yi Yang², Yu Li², Tian hao Xu², Ling-qi**

16
17 **Jian²**

18
19
20 ¹ Integrated Traditional and Western Medicine Department, West China Hospital of
21 Sichuan University, Chengdu 610041, China
22

23
24 ² West China School of Medicine, Sichuan University, Chengdu 610041, China
25

26 jian-qin lv lvjianqin@wchscu.cn
27

28 *Correspondence Cheng-wei Wang wangchengwei@wchscu.cn
29

30 Yi Yang 2015181622057@stu.scu.edu.cn
31

32 Yu Li 2015181622024@stu.scu.edu.cn
33

34 Tian-hao Xu 2015181622054@stu.scu.edu.cn
35

36 Ling-qi Jian 2015181622018@stu.scu.edu.cn
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 nausea, vomiting, bloating, pain and other reported discomfort. The
5
6
7 needle is replaced after 24 hours. The therapy is administered
8
9 immediately after and 24 hours after surgery. For the Control group, no
10
11
12 intervention is carried out. The incidence of PONV within 48 hours after
13
14
15 craniotomy across the three groups is observed. Other observations
16
17
18 include: (1) assessment of nausea score (severity of nausea) and pain
19
20
21 score (VAS) 0-2, 2-6, 6-24 and 24-48 hours after craniotomy under
22
23
24 general anesthesia; (2) assessment of total rescue antiemetic dosage 0-48
25
26
27 hours after craniotomy under general anesthesia; (3) length of hospital
28
29
30 stay; (4) patient satisfaction score with PONV management. We will
31
32
33 perform all statistical analysis following the intention-to-treat principle.

Discussion: The results from this study may potentially confirm that the
34
35
36 therapy described can prevent PONV in patients undergoing craniotomy
37
38
39 under general anesthesia.

Ethics and dissemination:

40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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.

1
2
3
4 **Keywords:** intradermal thumbtack needle, Neiguan, nausea, vomiting,
5
6 craniotomy.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2
3
4 dexamethasone^[8-10]. Recently, however, the US Food and Drug
5
6 Administration (FDA), has reported that droperidol may cause death
7
8 secondary to arrhythmia or QT prolongation, while other drugs have
9
10 varying degrees of side effects^[11]. At present, no therapy is categorically
11
12 effective at preventing PONV.
13
14
15

16
17 Due to the limited efficacy and many side effects of drug therapy, various
18
19 non-pharmacological techniques have been used in clinical practice.
20
21 These therapies include acupuncture^[12], acupressure^[13], transcutaneous
22
23 electrical nerve stimulation (TENS)^[14, 15], and electro-acupuncture^[16],
24
25 among others^[17]. In 2006, the American Society of Peri anesthesia Nurses
26
27 (ASPAN), recommended pericardium 6 (P6; also known as Neiguan)
28
29 acupoint stimulation (Class IIb, Grade A) and self-P6 acupoint
30
31 compression before and after surgery (Grade C) as a complementary
32
33 intervention for PONV prophylaxis. The 2014 American Anesthesia
34
35 Outpatient Guide also recommended that acupuncture treatment may be
36
37 used as an alternative or adjuvant therapy for prevention of PONV^[18] .
38
39 Many recent studies have supported the efficacy of P6 acupoint
40
41 stimulation in preventing PONV^[17, 19-21].
42
43
44
45
46
47
48
49
50

51
52 The existing acupuncture treatment is still mainly focused on electro-
53
54 acupuncture or traditional needle operation. In our clinical practice,
55
56 however, the limitations of these two acupuncture stimulation methods
57
58
59
60

1
2
3
4 (including fixed treatment and fixed treatment time, inconvenience of
5
6 other medical operations during needle retention, etc.) have resulted in
7
8 unstable efficacy.
9

10
11
12 A combination of traditional Chinese and Western medicine, including
13
14 needle embedding therapy, was put forward in the 1950s. With the
15
16 developments of acupuncture apparatus, intradermal thumbtack needle
17
18 has emerged as a new kind of the embedding therapy. The Intradermal
19
20 thumbtack needle (**Figure 1**), an improved subcutaneous needle, is a type
21
22 of shallow needling method that reduces pain and prolongs the
23
24 acupuncture effect via longer needle retention. Also, our previous clinical
25
26 experience indicates that the time of nausea and vomiting in patients
27
28 after surgery is uncertain^[22-24]. As the Intradermal thumbtack needle has
29
30 a 24-hour persistent stimulating effect, patients can self-press it at the P6
31
32 to relieve gastrointestinal discomfort when needed.
33
34
35
36
37
38
39
40

41
42 Therefore, we designed a single-center, prospective, double-blind,
43
44 randomized controlled trial (RCT) to evaluate the efficacy of P6 acupoint
45
46 stimulation by intradermal thumbtack needle as a non-pharmacological
47
48 prophylaxis for PONV. This study incorporates the concept of fast
49
50 tracksurgery, using a prospective randomized controlled method, inspired
51
52 by the concept of a postoperative analgesia pump, to develop P6 acupoint
53
54 stimulation treatment by intradermal thumbtack needle with long-term
55
56
57
58
59
60

1
2
3
4 stimulation characteristics (**Figure 2**). The study is designed to evaluate
5
6 the effectiveness and safety of P6 acupoint stimulation for the prevention
7
8 of PONV in patients who undergo craniotomy under general anesthesia
9
10 by intradermal thumbtack needle versus acupuncture filiform needles,
11
12 and versus routine antiemetic. The objective is to compare the effect and
13
14 safety using different methods.
15
16
17
18
19

20 **Methods**

21 ***Design:***

22
23 This is a single-center, prospective, single-blind, parallel-group, RCT. The
24
25 trial protocol strictly follows the principles of the Declaration of Helsinki
26
27 (version Seoul, 2008) and approval has been obtained from the Sichuan
28
29 University Ethics and Research Committee. Participants have been and
30
31 will continue to be recruited from the West China Hospital of Sichuan
32
33 University (WCHSU) from January 2018 to November 2019. All
34
35 participants are required to give written informed consent. The study's
36
37 flow chart is shown in **Figure 3**.
38
39
40
41
42
43
44
45
46
47

48 ***Patient population and setting:***

49
50 A total of 180 Chinese patients undergoing craniotomy will be
51
52 sequentially recruited at the WCHSU after fulfilling the eligibility criteria
53
54 and signing the informed consent. A clinical assistant with institutional
55
56 review board training will be in charge of patient enrolment.
57
58
59
60

8

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

1
2
3
4 afibrinogenemia); and 16) serious systemic disease (AIDS or sepsis).
5
6

7 *Dropout criteria:* Participants who meet any of the following criteria are
8
9
10 withdrawn from the study: 1) death; 2) waking up more than 2 hours
11
12 after surgery; 3) trachea intubation; 4) persistent coma; 5) cognitive
13
14 impairment; 6) further surgery or transfer to ICU if necessary for the
15
16 aggravation of the disease, etc. Patients who are withdrawn are not
17
18 replaced.
19
20
21
22

23 ***Randomization and blinding:***

24
25
26 A randomized grouping plan will be designed using the statistical software
27
28 named Package for Encyclopedia Medical Statistics 3.1 (PEMS 3.1). Using
29
30 this plan, the 180 patients will be randomly assigned to either an
31
32 acupuncture, intradermal thumbtack needle, or control treatment group.
33
34 The grouping scheme will be kept hidden in an envelope. The included
35
36 participants will be randomly assigned to each group according to the
37
38 distribution scheme in the envelope: 60 patients in each group. This study
39
40 is a single-blind design, mainly for patient unawareness, and the efficacy
41
42 evaluator and statistician are separated in this study.
43
44
45
46
47
48
49

50
51 Study investigators, acupuncturists and participants will be aware of the
52
53 treatment allocation. Outcome assessors and data analysts will be blinded
54
55 and participants will be asked not to reveal their allocation to assessors.
56
57

58 In addition, we will have blinded interpretation of the study results to
59
60

10

1
2
3
4 minimise misleading data interpretation.
5
6

7 ***Interventions:***
8
9

10 The determination of the program and the point of acupuncture is based
11 on previous research and The Name and Location of Acupoints (GB/T
12 12346-2006). All the practitioners performing the treatment must have
13 an acupuncturist qualification certificate and have performed clinical
14 treatment independently for more than 2 years. The acupuncturists are
15 not replaced during the experiment.
16
17
18
19
20
21
22
23
24

25 All patients will receive the same anesthesia methods: general anesthesia
26 with endotracheal intubation. Blood pressure, heart rate, pulse oximetry
27 and end tidal CO₂ will be routinely monitored. Induction of anesthesia will
28 be achieved with midazolam 0.05mg/kg, sufentanil 0.3µg/kg, atracurium
29 0.15mg/kg and propofol 2mg/kg. When endotracheal intubation and
30 gastrointestinal decompression with either an orogastric or nasogastric
31 tube are undertaken, the anesthesia will be maintained with 50% nitrous
32 oxide and 3% sevoflurane. After the operation has commenced,
33 participants will be given sufentanil 0.2µg/kg and atracurium 0.1mg/kg
34 intermittently. 30 minutes before the end of the operation, the patients
35 will be treated with prophylactic antiemetic drugs: Ondansetron
36 Hydrochloride Tablets 8mg according to the advice of doctors. After
37 surgery, patients will be continually monitored in the post-anesthesia care
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

11

1
2
3
4 unit (PACU) after anesthesia to continue the ventilator support. The
5
6 tracheal tube will be removed after the patients awake. The time from the
7
8 start of anesthesia induction to the time of removal of the tube will be
9
10 recorded. Patients who then meet the criteria (Steward Rating Scale ≥ 4 ,
11
12 and the blood gas index of special patients being normal as judged by the
13
14 anesthetist) will be sent back to the ward.
15
16
17
18
19

20 For the acupuncture group (acupuncture is added at the base of basic
21
22 treatment), bilateral Neiguan (P6, located on the line joining Daling and
23
24 Quze, between the tendons of palmaris longus and flexor carpi radialis, 2
25
26 cun above the transverse crease of the wrist) (**Figure 4**) will be selected.
27
28
29

30
31 The location of the acupoint refers to national standards of PRC published
32
33 in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints").
34
35 After the patients are transported from the post-anesthesia care unit
36
37 (PACU) to the common ward, the treatment will commence. After skin
38
39 disinfection with a disposable disinfecting cotton swab, sterile and
40
41 disposable stainless-steel needles (0.25 × 25 mm, Suzhou Hwato-med,
42
43 Jiangsu, China) will be quickly and perpendicularly inserted into the skin
44
45 at P6 acupoints bilaterally to a depth of 20mm. The duration of
46
47 reinforcing-reducing manipulation of twirling and rotating needle should
48
49 be used for 1 minute to achieve de qi (a composite of sensations including
50
51 soreness, numbness, distention, heaviness, and other sensations), which
52
53
54
55
56
57
58
59
60

1
2
3
4 is recognized to be an essential component for acupuncture efficacy. The
5
6 needles will be kept in place for 30 minutes and manipulated manually
7
8 every 10 minutes to maintain the de qi. When the treatment is over, all
9
10 needles will be carefully removed. The therapy includes 2 treatments, and
11
12 the acupuncture will be administered immediately after and 24 hours
13
14 after surgery.
15
16
17
18
19

20 For the group of thumbtack needle stimulation (press-needle is added at
21
22 the base of conventional therapy), the bilateral P6 acupoint will be
23
24 selected. The location of the acupoint refers to national standards of PRC
25
26 published in 2006 (GB/T 12346-2006) ("The Name and Positioning of
27
28 Acupoints"). Treatment will commence after the patients are transported
29
30 from the post-anesthesia care unit (PACU) to the common ward. After
31
32 skin cleansing with a 75% alcohol swab, Japanese SEIRIN PYONEX (0.2mm
33
34 × 1.5 mm) will be quickly inserted into the skin and embedded at P6
35
36 acupoints bilaterally. Patients and their families will be asked to press the
37
38 needle point when the patient feels nausea, experiences vomiting,
39
40 bloating, pain and other discomfort. The needle will be replaced after 24
41
42 hours. The therapy is given twice as the thumbtack needle stimulation will
43
44 be given immediately after and 24 hours following surgery.
45
46
47
48
49
50
51
52
53

54 For the control treatment group of rapid rehabilitation surgery, the
55
56 benefits, specific measures, prevention of complications, time and cost of
57
58
59

1
2
3
4 hospitalization will be explained to patients and their families in detail
5
6 using multimedia presentations and pamphlets prior to the operation.
7
8
9 Preoperative measures also include fasting for 6 hours, fasting water for
10
11 2 hours and infusing water and carbohydrates 2 hours before surgery.
12
13
14 Premedication will not be administered. Fluid volume management and
15
16 temperature intervention, drainage system, urethral catheter and gastric
17
18 tube will not be applied during the operation. The postoperative
19
20 measures include multi-mode control of postoperative pain, early
21
22 ambulation, early extubation (when tubes are applied), ADR monitoring
23
24 and prognosis monitoring.
25
26
27
28

29
30
31 **Outcome measures:**

32
33 *Main Outcome:*

34
35
36 In this study, patients are monitored for 48 hours post-operatively. The
37
38 observers will record any episodes of vomiting (criteria based on vomiting
39
40 action or vomitus in the mouth) 0 to 2 hours, 2 to 6 hours, 6 to 12 hours,
41
42 12 to 24 hours and 24 to 48 hours following surgery. The incidence of
43
44 PONV within 48 hours after craniotomy across the three groups is the
45
46 main criteria to be measured.
47
48
49
50

51
52
53 *Secondary Outcome:*

54
55
56 The observers will evaluate the patients' degree of nausea using the
57
58 WHO's PONV forth class rating scale: 0) no nausea at all; 1) mild nausea
59
60

1
2
3
4 or abdominal discomfort without vomiting; 2) evident nausea without
5
6 vomitus; 3) extreme nausea and vomitus containing gastric juice, which is
7
8 uncontrolled by medicine. The pain score adopts a standard visual
9
10 analogue scale (VAS) during 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12
11
12 to 24 hours and 24 to 48 hours after craniotomy under general anesthesia.
13
14
15 The assessment of total rescue antiemetic dosage 0-48 hours after
16
17 craniotomy under general anesthesia will be recorded. The length of stay
18
19 in the hospital and patient satisfaction score with PONV management will
20
21 also to recorded.
22
23
24
25
26
27

28 *Adverse event reporting:*
29

30
31 Adverse events will be recorded via voluntary reports by neurosurgeons,
32
33 physical examination, laboratory examination, or other methods. All
34
35 adverse events must be recorded on the CRF's adverse events page and
36
37 the following information about adverse events should be provided: 1)
38
39 severity degree (mild, moderate or severe); 2) the relationship with
40
41 research therapy (definitely related, probably related, possibly related,
42
43 probably irrelevant or definitely irrelevant); 3) duration (the start and end
44
45 dates or if the adverse advent still exists at the last check); 4) serious
46
47 adverse event (SAE); 5) important medical events (if potentially harmful
48
49 to patients medical or surgical intervention may be requested).
50
51
52
53
54
55
56
57

58 In order to ensure the safety of each patient, any serious adverse events
59
60

1
2
3
4 that occur from the time the patient gives consent up to 30 days after
5
6 completion of the study, whether or not associated with the treatment of
7
8 this research, must be reported to the project director within 24 hours.
9
10 Severe adverse events that occur 30 days after the cessation of the study
11
12 do not need to be reported unless the researchers deem it relevant to the
13
14 treatment. The recurrence, complication, or progression of previous
15
16 reported serious adverse events must also be reported as first reported
17
18 follow-up information, as soon as the first serious adverse event occurs.
19
20 The researchers must report the events within 24 hours once receiving
21
22 the follow-up information. If a serious adverse event is considered to be
23
24 completely unrelated to the previously reported one, it should be
25
26 reported as a new event.
27
28
29
30
31
32
33
34
35

36 ***Sample size calculation and statistical analysis:***
37
38

39 A German prospective observational study published in 2011
40
41 demonstrated an overall incidence of PONV in 47% of patients after
42
43 craniotomy under general anesthesia. The sample size is determined by
44
45 using PEMS 3.1 with $\alpha= 0.05$ (two-sided) and $\beta= 0.1$ (90% power). The
46
47 formula for calculation is as follows:
48
49
50
51

$$52 \quad n = 2\lambda / (2\sin^{-1}\sqrt{P_{max}} - 2\sin^{-1}\sqrt{P_{min}})^2$$

53
54
55

56 In order to demonstrate a 30% absolute reduction in the incidence of
57
58 PONV, the sample size will be 49 patients for each group. Considering the
59
60

1
2
3
4 potential for loss and attrition (20%), 60 patients per group, or a total of
5
6 180 patients, should be reasonable. If a patient cannot complete the study
7
8 due to death, reoperation, unconsciousness or cognitive impairment, the
9
10 patient will be recorded as an episode of PONV.
11
12

13
14
15 All data will be analyzed by a blinded statistician using PEMS 3.1 at a
16
17 separate location from the WCHSU. The intention-to-treat principal will
18
19 be used in the data analysis. Baseline data will be collected and compared
20
21 first. Different statistics are presented differently, for example,
22
23 continuous data is presented as mean (\pm standard deviation). Chi-square
24
25 test is used to compare the incidence of postoperative vomiting,
26
27 complete response rate, sex difference and other nominal data.
28
29 Conversely, the Kruskal-Wallis test is used to compare the nausea score,
30
31 satisfaction score and antiemetic dosage. Additionally, the Nemenyi test
32
33 and Scheffé's method are used for multiple comparisons between groups.
34
35
36
37
38
39
40
41 A *P* value <0.05 is considered statistically significant.
42
43

44 **Patient and public involvement**

45
46
47 The patients and public were not involved in planning and design of this
48
49 study.
50
51

52
53 The present trial was developed by acupuncturists based on previous
54
55 clinical experience and literature. Patients were not involved in the design
56
57 of the study. The outcomes were commonly used assessments of PONV
58
59
60

1
2
3
4 in clinical practice. The cost of interventions and outcome measurements
5
6 were mostly covered by the study funding so it was not thought to be a
7
8 significant burden and were in line with patient preferences. The results
9
10 will be disseminated to study participants via the website of our hospital.
11
12
13

14 **Discussion**

15
16
17 Our previous studies have shown the effectiveness and safety of
18
19 acupuncture in the treatment of nausea and vomiting following
20
21 craniotomy. In the clinic, however, we have found that, as the time of
22
23 postoperative nausea and vomiting is not fixed, patients are eager to
24
25 receive treatment when they experience nausea and vomiting. Often,
26
27 however, acupuncture cannot be administered as there is no qualified
28
29 practitioner available. In order to improve the availability of treatment,
30
31 acupuncturists need to formulate new protocols. Seaband© and TENs are
32
33 effective treatments for postoperative nausea and vomiting. They are
34
35 easy to administer and non-invasive, though our previous studies have
36
37 found that their efficacy is inferior to needle therapy. The intradermal
38
39 thumbtack needle has a piercing effect and can be in place for 24 hours.
40
41 When the patient is nauseous, pressing the acupuncture point can
42
43 achieve de-qi sensation. We therefore designed this randomized
44
45 controlled study in order to demonstrate that intradermal thumbtack
46
47 needle buried Neiguan point therapy can reduce the nausea and vomiting
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 after craniotomy. It is conducive to clinical use and improved patient
5
6 satisfaction.
7
8

9 10 **Ethics and dissemination**

11
12
13 Ethics approval has been granted by the Bioethics Subcommittee of West
14
15 China Hospital, Sichuan University: the approval number is 2018 (Number
16
17 231). Results will be expected to be published in peer-reviewed journals.
18
19

20
21 The case report forms (CRFs) will be stored in a locked cabinet at the
22
23 hospitals and accessible by the research team only. On completion of the
24
25 trial and data checking, the CRFs will be transferred to be securely
26
27 archived at Sichuan university for 5 years before being destroyed. The trial
28
29 database will be anonymised, password protected and securely held.
30
31 Patient identifiable data are shared only within the clinical team on a
32
33 need-to-know basis to provide clinical care and ensure appropriate
34
35 follow-up. The aggregated research findings will be presented at national
36
37 and international scientific conferences and be submitted for publication
38
39 in peer-reviewed journals.
40
41
42
43
44
45
46
47

48 **Contributors**

49
50 Jian-qin lv devised the study question and design. Yi yang developed the idea into the
51
52 full protocol and wrote the article draft. tianhao xu reviewed the protocol. Lingqi jian
53
54 calculated the sample size and specified the statistical strategy. Chengwei wang is in
55
56 charge of conducting all the procedures. All authors read and approved the final
57
58 manuscript. All authors read and approved the final manuscript.
59
60

Funding

This research is supported by sichuan provincial administration of traditional Chinese medicine research fund support (2018QN037) , National College Students' innovation and entrepreneurship training program (C2018102074) ,The funding bodies do not play roles in study design, data collection, analysis, interpretation of results, and the manuscript.

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.

References

- [1] Frey UH, Funk M, Löhlein C, Peters J. Effect of P6 acustimulation on post-operative nausea and vomiting in patients undergoing a laparoscopic cholecystectomy. *Acta Anaesthesiol Scand*. 2009. 53(10): 1341-7.
- [2] Golembiewski J, Chernin E, Chopra T. Prevention and treatment of postoperative nausea and vomiting. *Am J Health Syst Pharm*. 2005. 62(12): 1247-60; quiz 1261-2.
- [3] Unit P C. Causes of Postoperative Complications of 9 136 Patients in the Post-anaesthesia Care Unit[J]. *Journal of China Medical University*, 2011, 40(4):349-351.
- [4] Sato K, Sai S, Adachi T. Is microvascular decompression surgery a high risk for postoperative nausea and vomiting in patients undergoing craniotomy. *J Anesth*. 2013. 27(5): 725-30.
- [5] Rahimi SY, Alleyne CH, Vernier E, Witcher MR, Vender JR. Postoperative pain management with tramadol after craniotomy: evaluation and cost analysis. *J Neurosurg*. 2010. 112(2): 268-72.
- [6] Guang-Qiang C, Qian W, Yi Z. Preventive Medication for Postoperative Vomiting in Patients Undergoing Neurosurgery Craniotomy:A Retrospect Study[J]. *Evaluation and Analysis of Drug-Use in Hospitals of China*, 2009. 9(5): 375-376.
- [7] Misra S, Parthasarathi G, Vilanilam GC. The effect of gabapentin premedication on postoperative nausea, vomiting, and pain in patients on preoperative dexamethasone undergoing craniotomy for intracranial tumors. *J Neurosurg Anesthesiol*. 2013. 25(4): 386-91.
- [8] Ryu JH, Lee JE, Lim YJ, et al. A prospective, randomized, double-blind, and multicenter trial of prophylactic effects of ramosetron postoperative nausea and vomiting (PONV) after craniotomy: comparison with ondansetron. *BMC Anesthesiol*. 2014. 14: 63.
- [9] Fabling JM, Gan TJ, El-Moalem HE, Warner DS, Borel CO. A randomized, double-blind comparison of ondansetron versus placebo for prevention of nausea and vomiting after infratentorial craniotomy. *J Neurosurg Anesthesiol*. 2002. 14(2): 102-7.
- [10] Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. *Can J Anaesth*. 2004. 51(4): 326-41.
- [11] Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs*. 2000. 59(2): 213-43.
- [12] Alizadeh R, Esmacili S, Shoar S, Bagheri-Hariri S, Shoar N. Acupuncture in preventing postoperative nausea and vomiting: efficacy of two acupuncture points versus a single one. *J Acupunct Meridian Stud*. 2014. 7(2): 71-5.
- [13] Ling J, Bailiang Y, Jinfu T. Neiguan Massaged to Prevent Ache and Nausea and Vomit after Laparoscopic Cholecystectomy—A Randomized Controlled Clinical Trial[J]. *Journal of Zhejiang University of Traditional Chinese Medicine*, 2010. 34(5): 745-746.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
- [14] Nilsson I, Karlsson A, Lindgren L, Bergenheim T, Koskinen LO, Nilsson U. The efficacy of P6 acupressure with sea-band in reducing postoperative nausea and vomiting in patients undergoing craniotomy: a randomized, double-blinded, placebo-controlled study. *J Neurosurg Anesthesiol.* 2015. 27(1): 42-50.
- [15] Liu X, Li S, Wang B, An L, Ren X, Wu H. Intraoperative and postoperative anaesthetic and analgesic effect of multipoint transcutaneous electrical acupuncture stimulation combined with sufentanil anaesthesia in patients undergoing supratentorial craniotomy. *Acupunct Med.* 2015. 33(4): 270-6.
- [16] An LX, Chen X, Ren XJ, Wu HF. Electro-acupuncture decreases postoperative pain and improves recovery in patients undergoing a supratentorial craniotomy. *Am J Chin Med.* 2014. 42(5): 1099-109.
- [17] Asmussen S, Maybauer DM, Chen JD, et al. Effects of Acupuncture in Anesthesia for Craniotomy: A Meta-Analysis. *J Neurosurg Anesthesiol.* 2017. 29(3): 219-227.
- [18] Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014. 118(1): 85-113.
- [19] Cheong KB, Zhang JP, Huang Y, Zhang ZJ. The effectiveness of acupuncture in prevention and treatment of postoperative nausea and vomiting--a systematic review and meta-analysis. *PLoS One.* 2013. 8(12): e82474.
- [20] Lu Z, Dong H, Wang Q, Xiong L. Perioperative acupuncture modulation: more than anaesthesia. *Br J Anaesth.* 2015. 115(2): 183-93.
- [21] Zhang JQ, Xue FS, Meng FM, Li RP. Assessing the anaesthetic and analgesic effects of electroacupuncture in patients undergoing craniotomy. *Acupunct Med.* 2016. 34(1): 69-70.
- [22] Jian-Qin L, Hui P, Ning L I. Acupuncture in the Treatment of Postoperative Nausea and Vomiting: A Report of One Case and Review of Related Literature[J]. *West China Medical Journal*, 2013. (11): 1726-1730.
- [23] Lü JQ, Feng R Z, Pan H, et al. [A randomized controlled clinical trial for acupuncture stimulation of Neiguan (PC 6) to prevent postoperative nausea and vomiting]. [J]. *Acupuncture Research*, 2013, 38(3):245.
- [24] Lv JQ, Feng RZ, Li N. P6 acupoint stimulation for prevention of postoperative nausea and vomiting in patients undergoing craniotomy: study protocol for a randomized controlled trial. *Trials.* 2013. 14: 153.

Figure Legends

48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

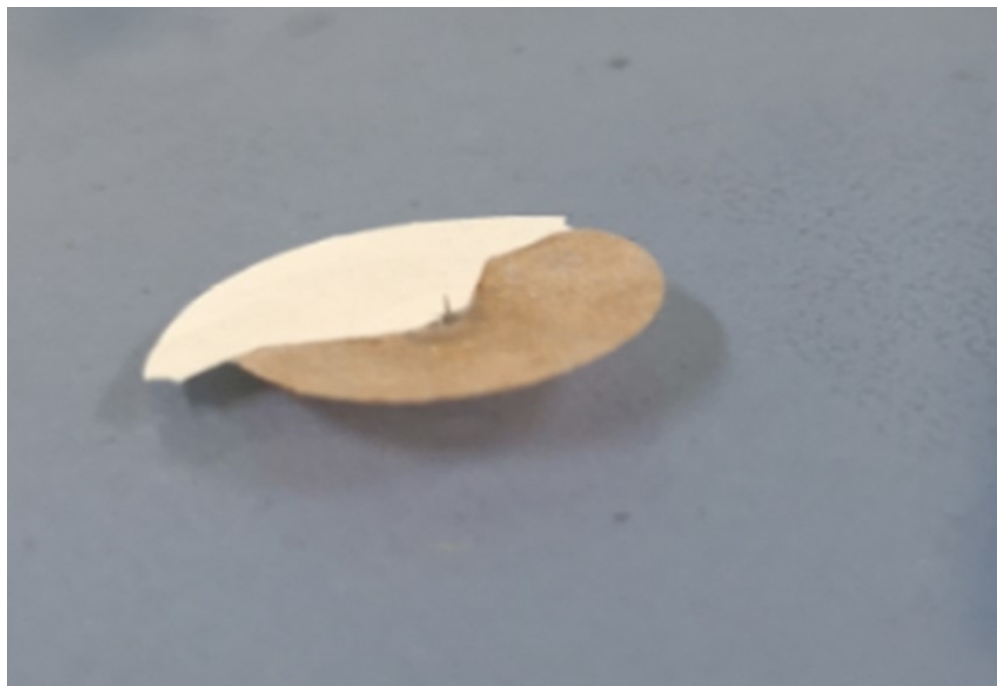


Figure 1 Intradermal thumbtack needle

144x98mm (150 x 150 DPI)

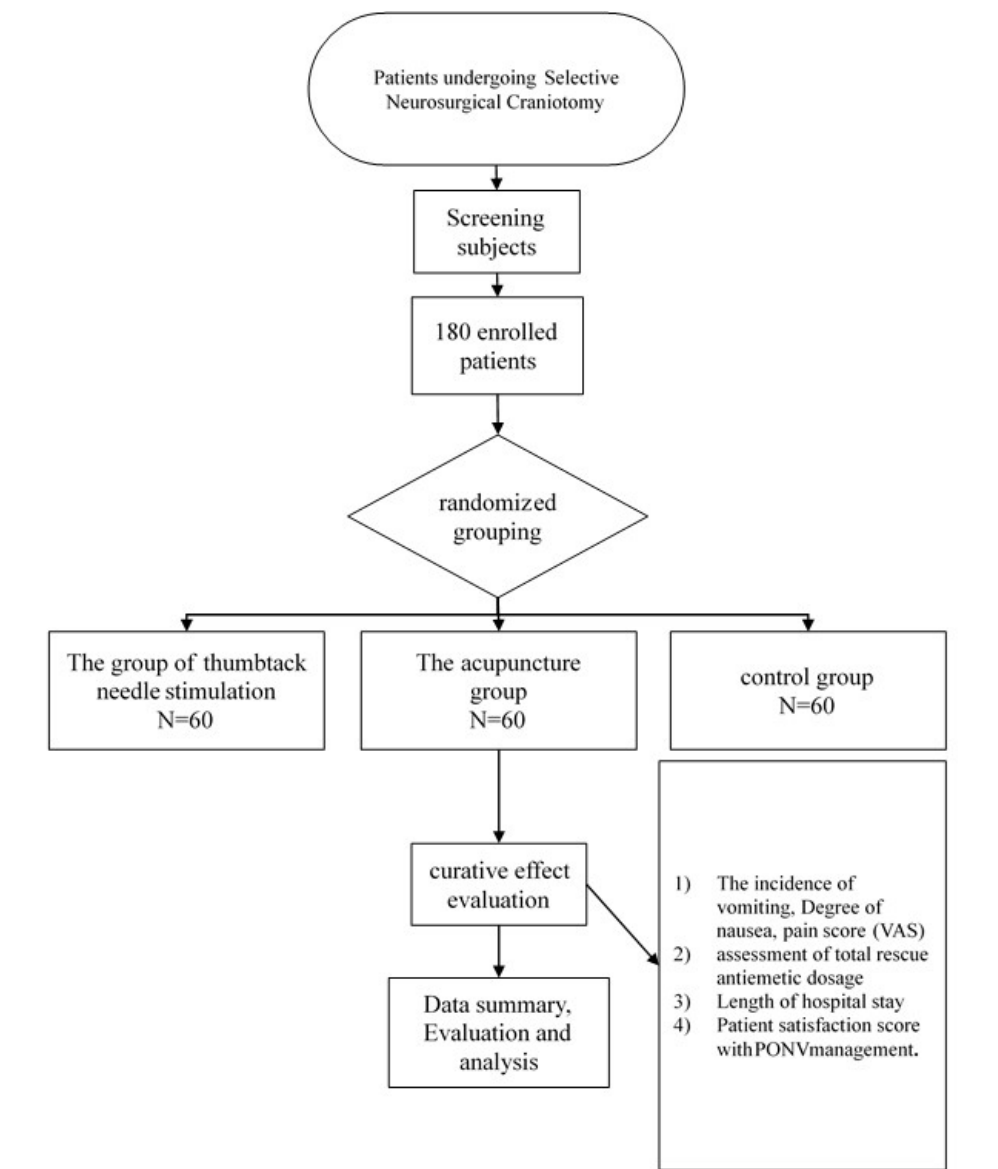
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



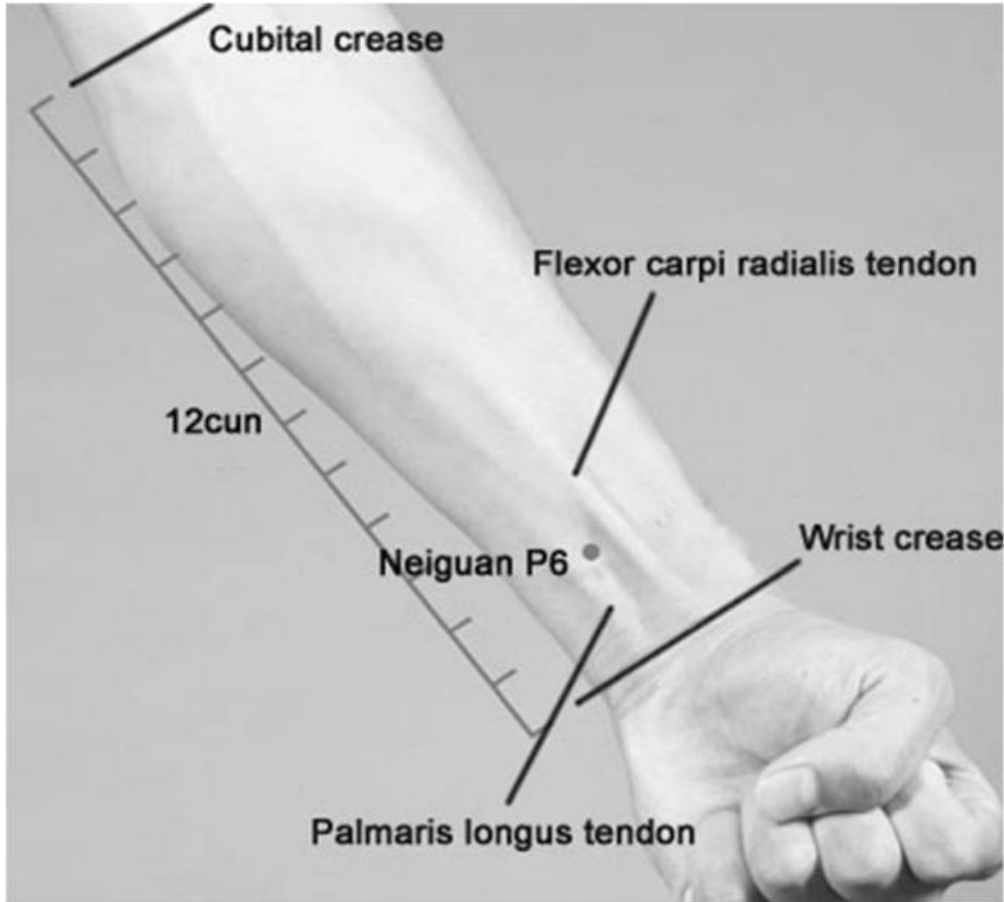
Intradermal thumbtack needle being inserted into the Neiguan point (P6)

165x75mm (150 x 150 DPI)



Trial flow chart

171x200mm (96 x 96 DPI)



Location of P6 acupoint

75x68mm (220 x 220 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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			

1 2 3 4 5 6 7 8 9 10 11	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
12 13 14 15 16 17		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
18 19 20 21 22 23 24 25	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
26 27 28 29 30 31	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
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
35 36 37 38 39 40		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
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	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
53 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032417.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Oct-2019
Complete List of Authors:	Lv, jian-qin; Sichuan University West China Hospital Wang, Chengwei; Sichuan University West China Hospital Yang, Yi; Sichuan University, West China School of Medicine Li, Yu; Sichuan University, West China School of Medicine Xu, Tian-hao; Sichuan University, West China School of Medicine Jian, Ling-qi; Sichuan University, West China School of Medicine
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	intradermal thumbtack needle, Neiguan (P6) , nausea, vomiting, craniotomy

SCHOLARONE™
Manuscripts

1
2
3
4 **Intradermal thumbtack needle buried Neiguan (P6) point for**
5 **prevention of postoperative nausea and vomiting in patients**
6 **undergoing craniotomy: study protocol for a randomized**
7 **controlled trial**
8
9
10
11
12
13
14

15 **Jian-qin Lv¹, Cheng-wei Wang^{1*}, Yi Yang², Yu Li², Tian hao Xu², Ling-qi**

16
17 **Jian²**

18
19
20 ¹ Integrated Traditional and Western Medicine Department, West China Hospital of
21 Sichuan University, Chengdu 610041, China
22

23
24 ² West China School of Medicine, Sichuan University, Chengdu 610041, China
25

26 jian-qin lv lvjianqin@wchscu.cn
27

28 *Correspondence Cheng-wei Wang wangchengwei@wchscu.cn
29

30 Yi Yang 2015181622057@stu.scu.edu.cn
31

32 Yu Li 2015181622024@stu.scu.edu.cn
33

34 Tian-hao Xu 2015181622054@stu.scu.edu.cn
35

36 Ling-qi Jian 2015181622018@stu.scu.edu.cn
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 nausea, vomiting, bloating, pain and other reported discomfort. The
5
6
7 needle is replaced after 24 hours. The therapy is administered
8
9 immediately after and 24 hours after surgery. For the Control group, no
10
11
12 intervention is carried out. The incidence of PONV within 48 hours after
13
14
15 craniotomy across the three groups is observed. Other observations
16
17
18 include: (1) assessment of nausea score (severity of nausea) and pain
19
20
21 score (VAS) 0-2, 2-6, 6-24 and 24-48 hours after craniotomy under
22
23
24 general anesthesia; (2) assessment of total rescue antiemetic dosage 0-48
25
26
27 hours after craniotomy under general anesthesia; (3) length of hospital
28
29
30 stay; (4) patient satisfaction score with PONV management. We will
31
32
33 perform all statistical analysis following the intention-to-treat principle.

34
35
36 **Discussion:** The results from this study may potentially confirm that the
37
38
39 therapy described can prevent PONV in patients undergoing craniotomy
40
41
42 under general anesthesia.

43 44 45 **Ethics and dissemination:**

46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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.

1
2
3
4 **Keywords:** intradermal thumbtack needle, Neiguan, nausea, vomiting,
5
6 craniotomy.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2
3
4 dexamethasone^[8-10]. Recently, however, the US Food and Drug
5
6 Administration (FDA), has reported that droperidol may cause death
7
8 secondary to arrhythmia or QT prolongation, while other drugs have
9
10 varying degrees of side effects^[11]. At present, no therapy is categorically
11
12 effective at preventing PONV.
13
14
15

16
17 Due to the limited efficacy and many side effects of drug therapy, various
18
19 non-pharmacological techniques have been used in clinical practice.
20
21 These therapies include acupuncture^[12], acupressure^[13], transcutaneous
22
23 electrical nerve stimulation (TENS)^[14, 15], and electro-acupuncture^[16],
24
25 among others^[17]. In 2006, the American Society of Peri anesthesia Nurses
26
27 (ASPAN), recommended pericardium 6 (P6; also known as Neiguan)
28
29 acupoint stimulation (Class IIb, Grade A) and self-P6 acupoint
30
31 compression before and after surgery (Grade C) as a complementary
32
33 intervention for PONV prophylaxis. The 2014 American Anesthesia
34
35 Outpatient Guide also recommended that acupuncture treatment may be
36
37 used as an alternative or adjuvant therapy for prevention of PONV^[18] .
38
39 Many recent studies have supported the efficacy of P6 acupoint
40
41 stimulation in preventing PONV^[17, 19-21].
42
43
44
45
46
47
48
49
50

51
52 The existing acupuncture treatment is still mainly focused on electro-
53
54 acupuncture or traditional needle operation. In our clinical practice,
55
56 however, the limitations of these two acupuncture stimulation methods
57
58
59
60

1
2
3
4 (including fixed treatment and fixed treatment time, inconvenience of
5
6 other medical operations during needle retention, etc.) have resulted in
7
8 unstable efficacy.
9

10
11
12 A combination of traditional Chinese and Western medicine, including
13
14 needle embedding therapy, was put forward in the 1950s. With the
15
16 developments of acupuncture apparatus, intradermal thumbtack needle
17
18 has emerged as a new kind of the embedding therapy. The Intradermal
19
20 thumbtack needle (**Figure 1**), an improved subcutaneous needle, is a type
21
22 of shallow needling method that reduces pain and prolongs the
23
24 acupuncture effect via longer needle retention. Also, our previous clinical
25
26 experience indicates that the time of nausea and vomiting in patients
27
28 after surgery is uncertain^[22-24]. As the Intradermal thumbtack needle has
29
30 a 24-hour persistent stimulating effect, patients can self-press it at the P6
31
32 to relieve gastrointestinal discomfort when needed.
33
34
35
36
37
38
39
40

41
42 Therefore, we designed a single-center, prospective, single-blind,
43
44 randomized controlled trial (RCT) to evaluate the efficacy of P6 acupoint
45
46 stimulation by intradermal thumbtack needle as a non-pharmacological
47
48 prophylaxis for PONV. This study incorporates the concept of fast
49
50 tracksurgery, using a prospective randomized controlled method, inspired
51
52 by the concept of a postoperative analgesia pump, to develop P6 acupoint
53
54 stimulation treatment by intradermal thumbtack needle with long-term
55
56
57
58
59
60

1
2
3
4 stimulation characteristics (**Figure 2**). The study is designed to evaluate
5
6 the effectiveness and safety of P6 acupoint stimulation for the prevention
7
8 of PONV in patients who undergo craniotomy under general anesthesia
9
10 by intradermal thumbtack needle versus acupuncture filiform needles,
11
12 and versus routine antiemetic. The objective is to compare the effect and
13
14 safety using different methods.
15
16
17
18
19

20 **Methods**

21 ***Design:***

22
23 This is a single-center, prospective, single-blind, parallel-group, RCT. The
24
25 trial protocol strictly follows the principles of the Declaration of Helsinki
26
27 (version Seoul, 2008) and approval has been obtained from the Sichuan
28
29 University Ethics and Research Committee. Participants have been and
30
31 will continue to be recruited from the West China Hospital of Sichuan
32
33 University (WCHSU) from January 2018 to November 2019. All
34
35 participants are required to give written informed consent. The study's
36
37 flow chart is shown in **Figure 3**.
38
39
40
41
42
43
44
45
46
47

48 ***Patient population and setting:***

49
50 A total of 180 Chinese patients undergoing craniotomy will be
51
52 sequentially recruited at the WCHSU after fulfilling the eligibility criteria
53
54 and signing the informed consent. A clinical assistant with institutional
55
56 review board training will be in charge of patient enrolment.
57
58
59
60

8

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

1
2
3
4 afibrinogenemia); and 16) serious systemic disease (AIDS or sepsis).
5
6

7 *Dropout criteria:* Participants who meet any of the following criteria are
8
9
10 withdrawn from the study: 1) death; 2) waking up more than 2 hours
11
12 after surgery; 3) trachea intubation; 4) persistent coma; 5) cognitive
13
14 impairment; 6) further surgery or transfer to ICU if necessary for the
15
16 aggravation of the disease, etc. Patients who are withdrawn are not
17
18 replaced.
19
20
21
22

23 ***Randomization and blinding:***

24
25
26 A randomized grouping plan will be designed using the statistical software
27
28 named Package for Encyclopedia Medical Statistics 3.1 (PEMS 3.1). Using
29
30 this plan, the 180 patients will be randomly assigned to either an
31
32 acupuncture, intradermal thumbtack needle, or control treatment group.
33
34 The grouping scheme will be kept hidden in an envelope. The included
35
36 participants will be randomly assigned to each group according to the
37
38 distribution scheme in the envelope: 60 patients in each group. This study
39
40 is a single-blind design, in order to keep patients unaware of which study
41
42 group they will be randomly assigned to, and the efficacy evaluator and
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
10
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.

1
2
3
4 In addition, we will have blinded interpretation of the study results to
5
6 minimise misleading data interpretation.
7
8

9
10 ***Interventions:***
11

12
13 The determination of the program and the point of acupuncture is based
14
15 on previous research and The Name and Location of Acupoints (GB/T
16
17 12346-2006). All the practitioners performing the treatment must have
18
19 an acupuncturist qualification certificate and have performed clinical
20
21 treatment independently for more than 2 years. The acupuncturists are
22
23 not replaced during the experiment.
24
25
26
27

28
29 All patients will receive the same anesthesia methods: general anesthesia
30
31 with endotracheal intubation. Blood pressure, heart rate, pulse oximetry
32
33 and end tidal CO₂ will be routinely monitored. Induction of anesthesia will
34
35 be achieved with midazolam 0.05mg/kg, sufentanil 0.3µg/kg, atracurium
36
37 0.15mg/kg and propofol 2mg/kg. When endotracheal intubation and
38
39 gastrointestinal decompression with either an orogastric or nasogastric
40
41 tube are undertaken, the anesthesia will be maintained with 50% nitrous
42
43 oxide and 3% sevoflurane, Actually, we adjusted the concentration of
44
45 sevoflurane according to BIS and the vital signs, if the hypotension
46
47 happened, and the BIS is low, we will decrease the sevoflurane. After the
48
49 operation has commenced, participants will be given sufentanil 0.2µg/kg
50
51 and atracurium 0.1mg/kg intermittently. 30 minutes before the end of the
52
53
54
55
56
57
58
59
60

1
2
3
4 operation, the patients will be treated with prophylactic antiemetic drugs:
5
6 Ondansetron Hydrochloride Tablets 8mg according to the advice of
7
8 doctors. After surgery, patients will be continually monitored in the post-
9
10 anesthesia care unit (PACU) after anesthesia to continue the ventilator
11
12 support. The tracheal tube will be removed after the patients awake. The
13
14 time from the start of anesthesia induction to the time of removal of the
15
16 tube will be recorded. Patients who then meet the criteria (Steward
17
18 Rating Scale ≥ 4 , and the blood gas index of special patients being normal
19
20 as judged by the anesthetist) will be sent back to the ward.
21
22
23
24
25
26
27

28 For the acupuncture group (acupuncture is added at the base of basic
29
30 treatment), bilateral Neiguan (P6, located on the line joining Daling and
31
32 Quze, between the tendons of palmaris longus and flexor carpi radialis, 2
33
34 cun above the transverse crease of the wrist) (**Figure 4**) will be selected.
35
36
37
38

39 The location of the acupoint refers to national standards of PRC published
40
41 in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints").
42
43 After the patients are transported from the post-anesthesia care unit
44
45 (PACU) to the common ward, the treatment will commence. After skin
46
47 disinfection with a disposable disinfecting cotton swab, sterile and
48
49 disposable stainless-steel needles (0.25 × 25 mm, Suzhou Hwato-med,
50
51 Jiangsu, China) will be quickly and perpendicularly inserted into the skin
52
53 at P6 acupoints bilaterally to a depth of 20mm. The duration of
54
55
56
57
58
59
60

1
2
3
4 reinforcing-reducing manipulation of twirling and rotating needle should
5
6 be used for 1 minute to achieve de qi (a composite of sensations including
7
8 soreness, numbness, distention, heaviness, and other sensations), which
9
10 is recognized to be an essential component for acupuncture efficacy. The
11
12 needles will be kept in place for 30 minutes and manipulated manually
13
14 every 10 minutes to maintain the de qi. When the treatment is over, all
15
16 needles will be carefully removed. The therapy includes 2 treatments, and
17
18 the acupuncture will be administered immediately after and 24 hours
19
20 after surgery.
21
22
23
24
25
26
27

28 For the group of thumbtack needle stimulation (press-needle is added at
29
30 the base of conventional therapy), the bilateral P6 acupoint will be
31
32 selected. The location of the acupoint refers to national standards of PRC
33
34 published in 2006 (GB/T 12346-2006) (“The Name and Positioning of
35
36 Acupoints”). Treatment will commence after the patients are transported
37
38 from the post-anesthesia care unit (PACU) to the common ward. After
39
40 skin cleansing with a 75% alcohol swab, Japanese SEIRIN PYONEX (0.2mm
41
42 × 1.5 mm) will be quickly inserted into the skin and embedded at P6
43
44 acupoints bilaterally. Patients and their families will be asked to press the
45
46 needle point when the patient feels nausea, experiences vomiting,
47
48 bloating, pain and other discomfort. The needle will be replaced after 24
49
50 hours. The therapy is given twice as the thumbtack needle stimulation will
51
52
53
54
55
56
57
58
59
60

1
2
3
4 be given immediately after and 24 hours following surgery.
5
6

7 For the control treatment group of rapid rehabilitation surgery, the
8 benefits, specific measures, prevention of complications, time and cost of
9 hospitalization will be explained to patients and their families in detail
10 using multimedia presentations and pamphlets prior to the operation.
11
12 Preoperative measures also include fasting for 6 hours, fasting water for
13 2 hours and infusing water and carbohydrates 2 hours before surgery.
14
15 Premedication will not be administered. Fluid volume management and
16 temperature intervention, drainage system, urethral catheter and gastric
17 tube will not be applied during the operation. The postoperative
18 measures include multi-mode control of postoperative pain, early
19 ambulation, early extubation (when tubes are applied), ADR monitoring
20 and prognosis monitoring.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 **Outcome measures:**

40
41 *Main Outcome:*

42
43
44
45 In this study, patients are monitored for 48 hours post-operatively. The
46 observers will record any episodes of vomiting (criteria based on vomiting
47 action or vomitus in the mouth) 0 to 2 hours, 2 to 6 hours, 6 to 12 hours,
48 12 to 24 hours and 24 to 48 hours following surgery. The incidence of
49 PONV within 48 hours after craniotomy across the three groups is the
50 main criteria to be measured.
51
52
53
54
55
56
57
58
59
60

1
2
3
4 *Secondary Outcome:*
5
6

7 The observers will evaluate the patients' degree of nausea using the
8 WHO's PONV forth class rating scale: 0) no nausea at all; 1) mild nausea
9 or abdominal discomfort without vomiting; 2) evident nausea without
10 vomitus; 3) extreme nausea and vomitus containing gastric juice, which is
11 uncontrolled by medicine. The pain score adopts a standard visual
12 analogue scale (VAS) during 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12
13 to 24 hours and 24 to 48 hours after craniotomy under general anesthesia.
14 The assessment of total rescue antiemetic dosage 0-48 hours after
15 craniotomy under general anesthesia will be recorded. The length of stay
16 in the hospital and patient satisfaction score with PONV management will
17 also to recorded.
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 *Adverse event reporting:*
37
38

39 Adverse events will be recorded via voluntary reports by neurosurgeons,
40 physical examination, laboratory examination, or other methods. All
41 adverse events must be recorded on the CRF's adverse events page and
42 the following information about adverse events should be provided: 1)
43 severity degree (mild, moderate or severe); 2) the relationship with
44 research therapy (definitely related, probably related, possibly related,
45 probably irrelevant or definitely irrelevant); 3) duration (the start and end
46 dates or if the adverse advent still exists at the last check); 4) serious
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 adverse event (SAE); 5) important medical events (if potentially harmful
5
6 to patients medical or surgical intervention may be requested).
7
8

9
10 In order to ensure the safety of each patient, any serious adverse events
11 that occur from the time the patient gives consent up to 30 days after
12 completion of the study, whether or not associated with the treatment of
13 this research, must be reported to the project director within 24 hours.
14
15 Severe adverse events that occur 30 days after the cessation of the study
16 do not need to be reported unless the researchers deem it relevant to the
17 treatment. The recurrence, complication, or progression of previous
18 reported serious adverse events must also be reported as first reported
19 follow-up information, as soon as the first serious adverse event occurs.
20
21 The researchers must report the events within 24 hours once receiving
22 the follow-up information. If a serious adverse event is considered to be
23 completely unrelated to the previously reported one, it should be
24 reported as a new event.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

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

45
46
47 A German prospective observational study published in 2011
48 demonstrated an overall incidence of PONV in 47% of patients after
49 craniotomy under general anesthesia. The sample size is determined by
50 using PEMS 3.1 with $\alpha= 0.05$ (two-sided) and $\beta= 0.1$ (90% power). The
51 formula for calculation is as follows:
52
53
54
55
56
57
58
59
60

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

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 (\pm 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

1
2
3
4 study.
5
6

7 The present trial was developed by acupuncturists based on previous
8 clinical experience and literature. Patients were not involved in the design
9 of the study. The outcomes were commonly used assessments of PONV
10 in clinical practice. The cost of interventions and outcome measurements
11 were mostly covered by the study funding so it was not thought to be a
12 significant burden and were in line with patient preferences. The results
13 will be disseminated to study participants via the website of our hospital.
14
15
16
17
18
19
20
21
22
23
24
25

26 **Discussion**

27
28 Our previous studies have shown the effectiveness and safety of
29 acupuncture in the treatment of nausea and vomiting following
30 craniotomy. In the clinic, however, we have found that, as the time of
31 postoperative nausea and vomiting is not fixed, patients are eager to
32 receive treatment when they experience nausea and vomiting. Often,
33 however, acupuncture cannot be administered as there is no qualified
34 practitioner available. In order to improve the availability of treatment,
35 acupuncturists need to formulate new protocols. Seaband© and TENs are
36 effective treatments for postoperative nausea and vomiting. They are
37 easy to administer and non-invasive, though our previous studies have
38 found that their efficacy is inferior to needle therapy. The intradermal
39 thumbtack needle has a piercing effect and can be in place for 24 hours.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 When the patient is nauseous, pressing the acupuncture point can
5
6 achieve de-qi sensation. We therefore designed this randomized
7
8 controlled study in order to demonstrate that intradermal thumbtack
9
10 needle buried Neiguan point therapy can reduce the nausea and vomiting
11
12 after craniotomy. It is conducive to clinical use and improved patient
13
14 satisfaction.
15
16
17
18
19

20 **Ethics and dissemination**

21
22
23 Ethics approval has been granted by the Bioethics Subcommittee of West
24
25 China Hospital, Sichuan University: the approval number is 2018 (Number
26
27 231). Results will be expected to be published in peer-reviewed journals.
28
29

30
31
32 The case report forms (CRFs) will be stored in a locked cabinet at the
33
34 hospitals and accessible by the research team only. On completion of the
35
36 trial and data checking, the CRFs will be transferred to be securely
37
38 archived at Sichuan university for 5 years before being destroyed. The trial
39
40 database will be anonymised, password protected and securely held.
41
42 Patient identifiable data are shared only within the clinical team on a
43
44 need-to-know basis to provide clinical care and ensure appropriate
45
46 follow-up. The aggregated research findings will be presented at national
47
48 and international scientific conferences and be submitted for publication
49
50 in peer-reviewed journals.
51
52
53
54
55
56

57 **Contributors**

58
59
60 19

1
2
3
4 Jian-qin lv devised the study question and design. Yi yang and Yu li developed the idea
5 into the full protocol and wrote the article draft.tian-hao xu reviewed the protocol.
6
7 Ling-qi jian calculated the sample size and specified the statistical strategy. Chengwei
8 wang is in charge of conducting all the procedures. All authors read and approved the
9
10 final manuscript.
11
12

13 14 **Funding**

15
16 This research is supported by sichuan provincial administration of traditional Chinese
17 medicine research fund support (2018QN037) , National College Students'
18 innovation and entrepreneurship training program (C2018102074) ,The funding
19 bodies do not play roles in study design, data collection, analysis, interpretation of
20 results, and the manuscript.
21
22
23
24
25
26

27 **Competing interests**

28
29 The authors declare that they have no competing interests
30
31

32 **Patient consent**

33
34
35 Obtained.
36

37 **Ethics approval**

38
39 This study protocol with the written informed consent forms has been peerreviewed
40 and approved by Ethical approval of West China Hospital of Si-chuan University clinical
41 trials and biomedical ethics committee 2018 (231) in July 2018.The approval number
42 is 2018(231).
43
44
45

46 **Availability of data and material:**

47
48
49 The datasets used and/or analyzed after completing the current study will be available
50 from the corresponding author by reasonable requests.
51
52
53
54
55
56
57
58
59
60

References

- [1] Frey UH, Funk M, Löhlein C, Peters J. Effect of P6 acustimulation on post-operative nausea and vomiting in patients undergoing a laparoscopic cholecystectomy. *Acta Anaesthesiol Scand*. 2009. 53(10): 1341-7.
- [2] Golembiewski J, Chernin E, Chopra T. Prevention and treatment of postoperative nausea and vomiting. *Am J Health Syst Pharm*. 2005. 62(12): 1247-60; quiz 1261-2.
- [3] Unit P C. Causes of Postoperative Complications of 9 136 Patients in the Post-anaesthesia Care Unit[J]. *Journal of China Medical University*, 2011, 40(4):349-351.
- [4] Sato K, Sai S, Adachi T. Is microvascular decompression surgery a high risk for postoperative nausea and vomiting in patients undergoing craniotomy. *J Anesth*. 2013. 27(5): 725-30.
- [5] Rahimi SY, Alleyne CH, Vernier E, Witcher MR, Vender JR. Postoperative pain management with tramadol after craniotomy: evaluation and cost analysis. *J Neurosurg*. 2010. 112(2): 268-72.
- [6] Guang-Qiang C, Qian W, Yi Z. Preventive Medication for Postoperative Vomiting in Patients Undergoing Neurosurgery Craniotomy:A Retrospect Study[J]. *Evaluation and Analysis of Drug-Use in Hospitals of China*, 2009. 9(5): 375-376.
- [7] Misra S, Parthasarathi G, Vilanilam GC. The effect of gabapentin premedication on postoperative nausea, vomiting, and pain in patients on preoperative dexamethasone undergoing craniotomy for intracranial tumors. *J Neurosurg Anesthesiol*. 2013. 25(4): 386-91.
- [8] Ryu JH, Lee JE, Lim YJ, et al. A prospective, randomized, double-blind, and multicenter trial of prophylactic effects of ramosetron postoperative nausea and vomiting (PONV) after craniotomy: comparison with ondansetron. *BMC Anesthesiol*. 2014. 14: 63.
- [9] Fabling JM, Gan TJ, El-Moalem HE, Warner DS, Borel CO. A randomized, double-blind comparison of ondansetron versus placebo for prevention of nausea and vomiting after infratentorial craniotomy. *J Neurosurg Anesthesiol*. 2002. 14(2): 102-7.
- [10] Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. *Can J Anaesth*. 2004. 51(4): 326-41.
- [11] Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs*. 2000. 59(2): 213-43.
- [12] Alizadeh R, Esmacili S, Shoar S, Bagheri-Hariri S, Shoar N. Acupuncture in preventing postoperative nausea and vomiting: efficacy of two acupuncture points versus a single one. *J Acupunct Meridian Stud*. 2014. 7(2): 71-5.
- [13] Ling J, Bailiang Y, Jinfu T. Neiguan Massaged to Prevent Ache and Nausea and Vomit after Laparoscopic Cholecystectomy—A Randomized Controlled Clinical Trial[J]. *Journal of Zhejiang University of Traditional Chinese Medicine*, 2010. 34(5): 745-746.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
- [14] Nilsson I, Karlsson A, Lindgren L, Bergenheim T, Koskinen LO, Nilsson U. The efficacy of P6 acupressure with sea-band in reducing postoperative nausea and vomiting in patients undergoing craniotomy: a randomized, double-blinded, placebo-controlled study. *J Neurosurg Anesthesiol.* 2015. 27(1): 42-50.
- [15] Liu X, Li S, Wang B, An L, Ren X, Wu H. Intraoperative and postoperative anaesthetic and analgesic effect of multipoint transcutaneous electrical acupuncture stimulation combined with sufentanil anaesthesia in patients undergoing supratentorial craniotomy. *Acupunct Med.* 2015. 33(4): 270-6.
- [16] An LX, Chen X, Ren XJ, Wu HF. Electro-acupuncture decreases postoperative pain and improves recovery in patients undergoing a supratentorial craniotomy. *Am J Chin Med.* 2014. 42(5): 1099-109.
- [17] Asmussen S, Maybauer DM, Chen JD, et al. Effects of Acupuncture in Anesthesia for Craniotomy: A Meta-Analysis. *J Neurosurg Anesthesiol.* 2017. 29(3): 219-227.
- [18] Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014. 118(1): 85-113.
- [19] Cheong KB, Zhang JP, Huang Y, Zhang ZJ. The effectiveness of acupuncture in prevention and treatment of postoperative nausea and vomiting--a systematic review and meta-analysis. *PLoS One.* 2013. 8(12): e82474.
- [20] Lu Z, Dong H, Wang Q, Xiong L. Perioperative acupuncture modulation: more than anaesthesia. *Br J Anaesth.* 2015. 115(2): 183-93.
- [21] Zhang JQ, Xue FS, Meng FM, Li RP. Assessing the anaesthetic and analgesic effects of electroacupuncture in patients undergoing craniotomy. *Acupunct Med.* 2016. 34(1): 69-70.
- [22] Jian-Qin L, Hui P, Ning L I. Acupuncture in the Treatment of Postoperative Nausea and Vomiting: A Report of One Case and Review of Related Literature[J]. *West China Medical Journal*, 2013. (11): 1726-1730.
- [23] Lü JQ, Feng R Z, Pan H, et al. [A randomized controlled clinical trial for acupuncture stimulation of Neiguan (PC 6) to prevent postoperative nausea and vomiting]. [J]. *Acupuncture Research*, 2013, 38(3):245.
- [24] Lv JQ, Feng RZ, Li N. P6 acupoint stimulation for prevention of postoperative nausea and vomiting in patients undergoing craniotomy: study protocol for a randomized controlled trial. *Trials.* 2013. 14: 153.

Figure Legends

48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



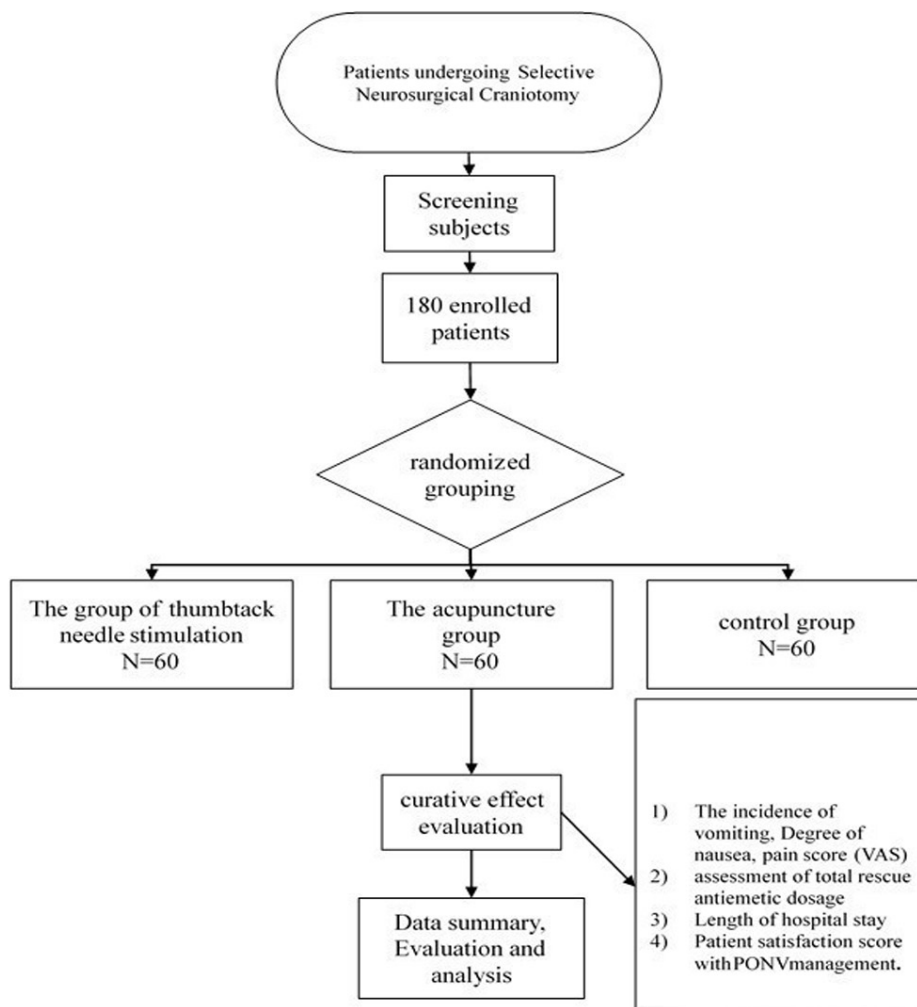
90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



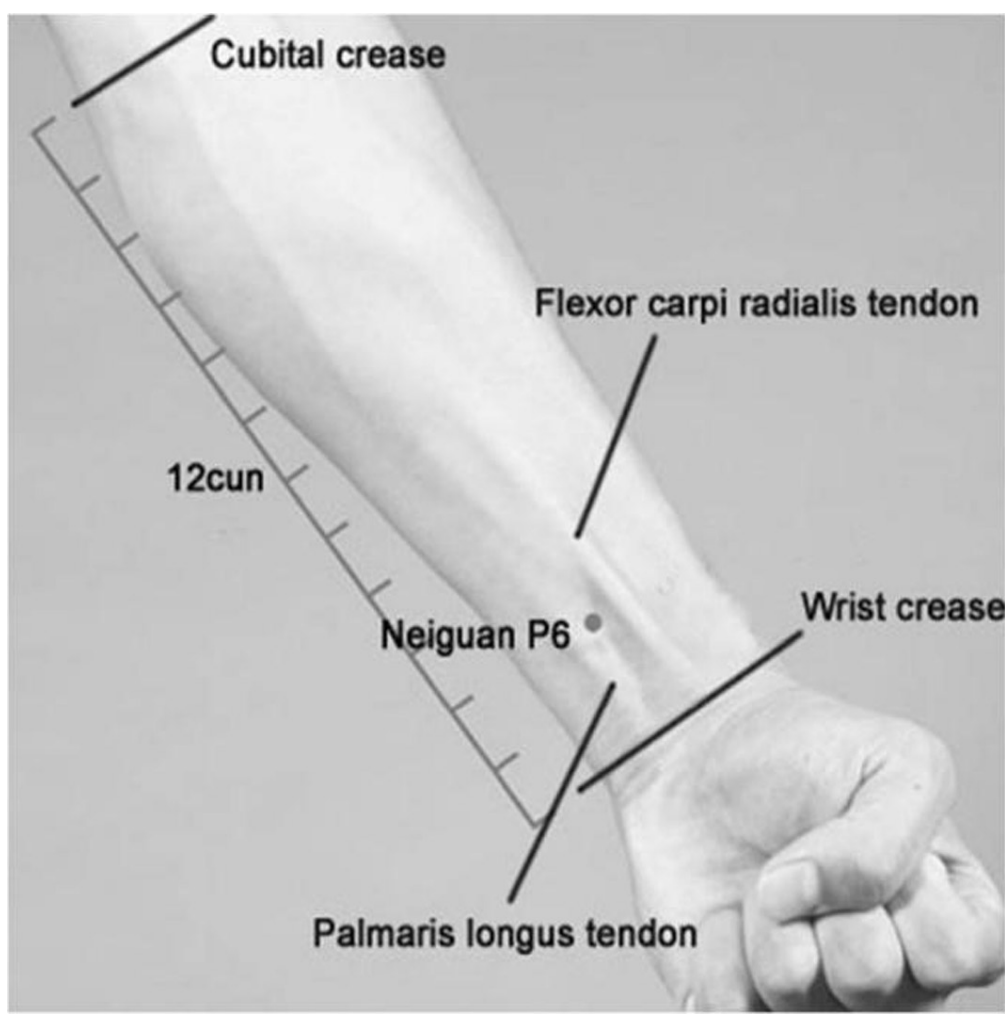
90x90mm (300 x 300 DPI)



90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



90x90mm (300 x 300 DPI)



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			

1 2 3 4 5 6 7 8 9 10 11	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
12 13 14 15 16 17		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
18 19 20 21 22 23 24 25	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
26 27 28 29 30 31	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
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
35 36 37 38 39 40		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
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	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
53 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032417.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Oct-2019
Complete List of Authors:	Lv, jian-qin; Sichuan University West China Hospital Wang, Chengwei; Sichuan University West China Hospital Yang, Yi; Sichuan University, West China School of Medicine Li, Yu; Sichuan University, West China School of Medicine Xu, Tian-hao; Sichuan University, West China School of Medicine Jian, Ling-qi; Sichuan University, West China School of Medicine
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	intradermal thumbtack needle, Neiguan (P6) , nausea, vomiting, craniotomy

SCHOLARONE™
Manuscripts

1
2
3
4 **Intradermal thumbtack needle buried Neiguan (P6) point for**
5 **prevention of postoperative nausea and vomiting in patients**
6 **undergoing craniotomy: study protocol for a randomized**
7 **controlled trial**
8
9
10
11
12
13
14

15 **Jian-qin Lv¹, Cheng-wei Wang^{1*}, Yi Yang², Yu Li², Tian hao Xu², Ling-qi**

16
17 **Jian²**

18
19
20 ¹ Integrated Traditional and Western Medicine Department, West China Hospital of
21 Sichuan University, Chengdu 610041, China
22

23
24 ² West China School of Medicine, Sichuan University, Chengdu 610041, China
25

26 jian-qin lv lvjianqin@wchscu.cn
27

28 *Correspondence Cheng-wei Wang wangchengwei@wchscu.cn
29

30 Yi Yang 2015181622057@stu.scu.edu.cn
31

32 Yu Li 2015181622024@stu.scu.edu.cn
33

34 Tian-hao Xu 2015181622054@stu.scu.edu.cn
35

36 Ling-qi Jian 2015181622018@stu.scu.edu.cn
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 nausea, vomiting, bloating, pain and other reported discomfort. The
5
6 needle is replaced after 24 hours. The therapy is administered
7
8 immediately after and 24 hours after surgery. For the Control group, no
9
10 intervention is carried out. The incidence of PONV within 48 hours after
11
12 craniotomy across the three groups is observed. Other observations
13
14 include: (1) assessment of nausea score (severity of nausea) and pain
15
16 score (VAS) 0-2, 2-6, 6-24 and 24-48 hours after craniotomy under
17
18 general anesthesia; (2) assessment of total rescue antiemetic dosage 0-48
19
20 hours after craniotomy under general anesthesia; (3) length of hospital
21
22 stay; (4) patient satisfaction score with PONV management. We will
23
24 perform all statistical analysis following the intention-to-treat principle.
25
26
27
28
29
30
31
32

33 **Ethics and dissemination:**

34
35
36 Ethics approval has been granted by the Bioethics Subcommittee of West
37
38 China Hospital, Sichuan University: the approval number is 2018 (Number
39
40 231). Results will be expected to be published in peer-reviewed journals.
41
42
43

44 **Trial registration:** This study is registered with the Chinese Clinical Trial
45
46 (ChiCTR1800017173) in July 2018, the registration status was prospective
47
48 registration.
49
50

51
52 **Keywords:** intradermal thumbtack needle, Neiguan, nausea, vomiting,
53
54 craniotomy.
55
56
57
58
59
60

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

1
2
3
4 dexamethasone^[8-10]. Recently, however, the US Food and Drug
5
6 Administration (FDA), has reported that droperidol may cause death
7
8 secondary to arrhythmia or QT prolongation, while other drugs have
9
10 varying degrees of side effects^[11]. At present, no therapy is categorically
11
12 effective at preventing PONV.
13
14

15
16
17 Due to the limited efficacy and many side effects of drug therapy, various
18
19 non-pharmacological techniques have been used in clinical practice.
20
21 These therapies include acupuncture^[12], acupressure^[13], transcutaneous
22
23 electrical nerve stimulation (TENS)^[14, 15], and electro-acupuncture^[16],
24
25 among others^[17]. In 2006, the American Society of Peri anesthesia Nurses
26
27 (ASPAN), recommended pericardium 6 (P6; also known as Neiguan)
28
29 acupoint stimulation (Class IIb, Grade A) and self-P6 acupoint
30
31 compression before and after surgery (Grade C) as a complementary
32
33 intervention for PONV prophylaxis. The 2014 American Anesthesia
34
35 Outpatient Guide also recommended that acupuncture treatment may be
36
37 used as an alternative or adjuvant therapy for prevention of PONV^[18].
38
39 Many recent studies have supported the efficacy of P6 acupoint
40
41 stimulation in preventing PONV^[17, 19-21].
42
43
44
45
46
47
48
49
50

51
52 The existing acupuncture treatment is still mainly focused on electro-
53
54 acupuncture or traditional needle operation. In our clinical practice,
55
56 however, the limitations of these two acupuncture stimulation methods
57
58
59
60

1
2
3
4 (including fixed treatment and fixed treatment time, inconvenience of
5
6 other medical operations during needle retention, etc.) have resulted in
7
8 unstable efficacy.
9

10
11
12 A combination of traditional Chinese and Western medicine, including
13
14 needle embedding therapy, was put forward in the 1950s. With the
15
16 developments of acupuncture apparatus, intradermal thumbtack needle
17
18 has emerged as a new kind of the embedding therapy. The Intradermal
19
20 thumbtack needle (**Figure 1**), an improved subcutaneous needle, is a type
21
22 of shallow needling method that reduces pain and prolongs the
23
24 acupuncture effect via longer needle retention. Also, our previous clinical
25
26 experience indicates that the time of nausea and vomiting in patients
27
28 after surgery is uncertain^[22-24]. As the Intradermal thumbtack needle has
29
30 a 24-hour persistent stimulating effect, patients can self-press it at the P6
31
32 to relieve gastrointestinal discomfort when needed.
33
34
35
36
37
38
39
40

41
42 Therefore, we designed a single-center, prospective, single-blind,
43
44 randomized controlled trial (RCT) to evaluate the efficacy of P6 acupoint
45
46 stimulation by intradermal thumbtack needle as a non-pharmacological
47
48 prophylaxis for PONV. This study incorporates the concept of fast
49
50 tracksurgery, using a prospective randomized controlled method, inspired
51
52 by the concept of a postoperative analgesia pump, to develop P6 acupoint
53
54 stimulation treatment by intradermal thumbtack needle with long-term
55
56
57
58
59
60

1
2
3
4 stimulation characteristics (**Figure 2**). The study is designed to evaluate
5
6 the effectiveness and safety of P6 acupoint stimulation for the prevention
7
8 of PONV in patients who undergo craniotomy under general anesthesia
9
10 by intradermal thumbtack needle versus acupuncture filiform needles,
11
12 and versus routine antiemetic. The objective is to compare the effect and
13
14 safety using different methods.
15
16
17
18
19

20 **Methods**

21 ***Design:***

22
23 This is a single-center, prospective, single-blind, parallel-group, RCT. The
24
25 trial protocol strictly follows the principles of the Declaration of Helsinki
26
27 (version Seoul, 2008) and approval has been obtained from the Sichuan
28
29 University Ethics and Research Committee. Participants have been and
30
31 will continue to be recruited from the West China Hospital of Sichuan
32
33 University (WCHSU) from January 2018 to November 2019. All
34
35 participants are required to give written informed consent. The study's
36
37 flow chart is shown in **Figure 3**.
38
39
40
41
42
43
44
45
46
47

48 ***Patient population and setting:***

49
50 A total of 180 Chinese patients undergoing craniotomy will be
51
52 sequentially recruited at the WCHSU after fulfilling the eligibility criteria
53
54 and signing the informed consent. A clinical assistant with institutional
55
56 review board training will be in charge of patient enrolment.
57
58
59
60

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

1
2
3
4 afibrinogenemia); and 16) serious systemic disease (AIDS or sepsis).
5
6

7 *Dropout criteria:* Participants who meet any of the following criteria are
8
9
10 withdrawn from the study: 1) death; 2) waking up more than 2 hours
11
12 after surgery; 3) trachea intubation; 4) persistent coma; 5) cognitive
13
14 impairment; 6) further surgery or transfer to ICU if necessary for the
15
16 aggravation of the disease, etc. Patients who are withdrawn are not
17
18 replaced.
19
20
21
22

23 ***Randomization and blinding:***
24

25
26 A randomized grouping plan will be designed using the statistical software
27
28 named Package for Encyclopedia Medical Statistics 3.1 (PEMS 3.1). Using
29
30 this plan, the 180 patients will be randomly assigned to either an
31
32 acupuncture, intradermal thumbtack needle, or control treatment group.
33
34 The grouping scheme will be kept hidden in an envelope. The included
35
36 participants will be randomly assigned to each group according to the
37
38 distribution scheme in the envelope: 60 patients in each group. This study
39
40 is a single-blind design, in order to keep patients unaware of which study
41
42 group they will be randomly assigned to, and the efficacy evaluator and
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

9

1
2
3
4 In addition, we will have blinded interpretation of the study results to
5
6 minimise misleading data interpretation.
7
8

9
10 ***Interventions:***
11

12
13 The determination of the program and the point of acupuncture is based
14
15 on previous research and The Name and Location of Acupoints (GB/T
16
17 12346-2006). All the practitioners performing the treatment must have
18
19 an acupuncturist qualification certificate and have performed clinical
20
21 treatment independently for more than 2 years. The acupuncturists are
22
23 not replaced during the experiment.
24
25
26
27

28
29 All patients will receive the same anesthesia methods: general anesthesia
30
31 with endotracheal intubation. Blood pressure, heart rate, pulse oximetry
32
33 and end tidal CO₂ will be routinely monitored. Induction of anesthesia will
34
35 be achieved with midazolam 0.05mg/kg, sufentanil 0.3µg/kg, atracurium
36
37 0.15mg/kg and propofol 2mg/kg. When endotracheal intubation and
38
39 gastrointestinal decompression with either an orogastric or nasogastric
40
41 tube are undertaken, the anesthesia will be maintained with 50% nitrous
42
43 oxide and 3% sevoflurane. An attending anesthesiologist will adjust the
44
45 concentration of sevoflurane according to BIS and the vital signs, if the
46
47 hypotension happened and the BIS is low, he or she will decrease the
48
49 sevoflurane. The target range of BIS was 40-60 during surgery. After the
50
51 operation has commenced, participants will be given sufentanil 0.2µg/kg
52
53
54
55
56
57
58
59
60

10

1
2
3
4 and atracurium 0.1mg/kg intermittently. 30 minutes before the end of the
5
6 operation, the patients will be treated with prophylactic antiemetic drugs:
7
8 Ondansetron Hydrochloride Tablets 8mg according to the advice of
9
10 doctors. After surgery, patients will be continually monitored in the post-
11
12 anesthesia care unit (PACU) after anesthesia to continue the ventilator
13
14 support. The tracheal tube will be removed after the patients awake. The
15
16 time from the start of anesthesia induction to the time of removal of the
17
18 tube will be recorded. Patients who then meet the criteria (Steward
19
20 Rating Scale ≥ 4 , and the blood gas index of special patients being normal
21
22 as judged by the anesthetist) will be sent back to the ward.
23
24
25
26
27
28
29

30 For the acupuncture group (acupuncture is added at the base of basic
31
32 treatment), bilateral Neiguan (P6, located on the line joining Daling and
33
34 Quze, between the tendons of palmaris longus and flexor carpi radialis, 2
35
36 cun above the transverse crease of the wrist) (**Figure 4**) will be selected.
37
38
39

40
41 The location of the acupoint refers to national standards of PRC published
42
43 in 2006 (GB/T 12346-2006) ("The Name and Positioning of Acupoints").
44
45 After the patients are transported from the post-anesthesia care unit
46
47 (PACU) to the common ward, the treatment will commence. After skin
48
49 disinfection with a disposable disinfecting cotton swab, sterile and
50
51 disposable stainless-steel needles (0.25 × 25 mm, Suzhou Hwato-med,
52
53 Jiangsu, China) will be quickly and perpendicularly inserted into the skin
54
55
56
57
58
59
60

1
2
3
4 at P6 acupoints bilaterally to a depth of 20mm. The duration of
5
6 reinforcing-reducing manipulation of twirling and rotating needle should
7
8 be used for 1 minute to achieve de qi (a composite of sensations including
9
10 soreness, numbness, distention, heaviness, and other sensations), which
11
12 is recognized to be an essential component for acupuncture efficacy. The
13
14 needles will be kept in place for 30 minutes and manipulated manually
15
16 every 10 minutes to maintain the de qi. When the treatment is over, all
17
18 needles will be carefully removed. The therapy includes 2 treatments, and
19
20 the acupuncture will be administered immediately after and 24 hours
21
22 after surgery.
23
24
25
26
27
28
29

30 For the group of thumbtack needle stimulation (press-needle is added at
31
32 the base of conventional therapy), the bilateral P6 acupoint will be
33
34 selected. The location of the acupoint refers to national standards of PRC
35
36 published in 2006 (GB/T 12346-2006) (“The Name and Positioning of
37
38 Acupoints”). Treatment will commence after the patients are transported
39
40 from the post-anesthesia care unit (PACU) to the common ward. After
41
42 skin cleansing with a 75% alcohol swab, Japanese SEIRIN PYONEX (0.2mm
43
44 × 1.5 mm) will be quickly inserted into the skin and embedded at P6
45
46 acupoints bilaterally. Patients and their families will be asked to press the
47
48 needle point when the patient feels nausea, experiences vomiting,
49
50 bloating, pain and other discomfort. The needle will be replaced after 24
51
52
53
54
55
56
57
58
59
60

1
2
3
4 hours. The therapy is given twice as the thumbtack needle stimulation will
5
6 be given immediately after and 24 hours following surgery.
7
8

9
10 For the control treatment group of rapid rehabilitation surgery, the
11 benefits, specific measures, prevention of complications, time and cost of
12 hospitalization will be explained to patients and their families in detail
13 using multimedia presentations and pamphlets prior to the operation.
14
15 Preoperative measures also include fasting for 6 hours, fasting water for
16 2 hours and infusing water and carbohydrates 2 hours before surgery.
17
18 Premedication will not be administered. Fluid volume management and
19 temperature intervention, drainage system, urethral catheter and gastric
20 tube will not be applied during the operation. The postoperative
21 measures include multi-mode control of postoperative pain, early
22 ambulation, early extubation (when tubes are applied), ADR monitoring
23 and prognosis monitoring.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 **Outcome measures:**

42 *Main Outcome:*

43
44
45 In this study, patients are monitored for 48 hours post-operatively. The
46 observers will record any episodes of vomiting (criteria based on vomiting
47 action or vomitus in the mouth) 0 to 2 hours, 2 to 6 hours, 6 to 12 hours,
48
49 12 to 24 hours and 24 to 48 hours following surgery. The incidence of
50
51 PONV within 48 hours after craniotomy across the three groups is the
52
53
54
55
56
57
58
59
60

1
2
3
4 main criteria to be measured.
5
6

7 *Secondary Outcome:*
8
9

10 The observers will evaluate the patients' degree of nausea using the
11 WHO's PONV forth class rating scale: 0) no nausea at all; 1) mild nausea
12 or abdominal discomfort without vomiting; 2) evident nausea without
13 vomitus; 3) extreme nausea and vomitus containing gastric juice, which is
14 uncontrolled by medicine. The pain score adopts a standard visual
15 analogue scale (VAS) during 0 to 2 hours, 2 to 6 hours, 6 to 12 hours, 12
16 to 24 hours and 24 to 48 hours after craniotomy under general anesthesia.
17 The assessment of total rescue antiemetic dosage 0-48 hours after
18 craniotomy under general anesthesia will be recorded. The length of stay
19 in the hospital and patient satisfaction score with PONV management will
20 also to recorded.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39

40 *Adverse event reporting:*
41
42

43 Adverse events will be recorded via voluntary reports by neurosurgeons,
44 physical examination, laboratory examination, or other methods. All
45 adverse events must be recorded on the CRF's adverse events page and
46 the following information about adverse events should be provided: 1)
47 severity degree (mild, moderate or severe); 2) the relationship with
48 research therapy (definitely related, probably related, possibly related,
49 probably irrelevant or definitely irrelevant); 3) duration (the start and end
50
51
52
53
54
55
56
57
58
59
60

14

1
2
3
4 dates or if the adverse event still exists at the last check); 4) serious
5
6 adverse event (SAE); 5) important medical events (if potentially harmful
7
8 to patients medical or surgical intervention may be requested).
9

10
11
12 In order to ensure the safety of each patient, any serious adverse events
13
14 that occur from the time the patient gives consent up to 30 days after
15
16 completion of the study, whether or not associated with the treatment of
17
18 this research, must be reported to the project director within 24 hours.
19
20 Severe adverse events that occur 30 days after the cessation of the study
21
22 do not need to be reported unless the researchers deem it relevant to the
23
24 treatment. The recurrence, complication, or progression of previous
25
26 reported serious adverse events must also be reported as first reported
27
28 follow-up information, as soon as the first serious adverse event occurs.
29
30 The researchers must report the events within 24 hours once receiving
31
32 the follow-up information. If a serious adverse event is considered to be
33
34 completely unrelated to the previously reported one, it should be
35
36 reported as a new event.
37
38
39
40
41
42
43
44
45
46

47 ***Sample size calculation and statistical analysis:***
48

49
50 A German prospective observational study published in 2011
51
52 demonstrated an overall incidence of PONV in 47% of patients after
53
54 craniotomy under general anesthesia. The sample size is determined by
55
56 using PEMS 3.1 with $\alpha= 0.05$ (two-sided) and $\beta= 0.1$ (90% power). The
57
58
59
60

formula for calculation is as follows:

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

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 (\pm 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

16

1
2
3
4 The patients and public were not involved in planning and design of this
5
6 study.
7
8

9
10 The present trial was developed by acupuncturists based on previous
11
12 clinical experience and literature. Patients were not involved in the design
13
14 of the study. The outcomes were commonly used assessments of PONV
15
16 in clinical practice. The cost of interventions and outcome measurements
17
18 were mostly covered by the study funding so it was not thought to be a
19
20 significant burden and were in line with patient preferences. The results
21
22 will be disseminated to study participants via the website of our hospital.
23
24
25
26
27

28 **Discussion**

29
30
31 Our previous studies have shown the effectiveness and safety of
32
33 acupuncture in the treatment of nausea and vomiting following
34
35 craniotomy. In the clinic, however, we have found that, as the time of
36
37 postoperative nausea and vomiting is not fixed, patients are eager to
38
39 receive treatment when they experience nausea and vomiting. Often,
40
41 however, acupuncture cannot be administered as there is no qualified
42
43 practitioner available. In order to improve the availability of treatment,
44
45 acupuncturists need to formulate new protocols. Seaband© and TENs are
46
47 effective treatments for postoperative nausea and vomiting. They are
48
49 easy to administer and non-invasive, though our previous studies have
50
51 found that their efficacy is inferior to needle therapy. The intradermal
52
53
54
55
56
57
58
59
60

1
2
3
4 thumbtack needle has a piercing effect and can be in place for 24 hours.
5
6
7 When the patient is nauseous, pressing the acupuncture point can
8
9 achieve de-qi sensation. We therefore designed this randomized
10
11 controlled study in order to demonstrate that intradermal thumbtack
12
13 needle buried Neiguan point therapy can reduce the nausea and vomiting
14
15 after craniotomy. It is conducive to clinical use and improved patient
16
17 satisfaction.
18
19
20
21

22 23 **Ethics and dissemination**

24
25
26 Ethics approval has been granted by the Bioethics Subcommittee of West
27
28 China Hospital, Sichuan University: the approval number is 2018 (Number
29
30 231). Results will be expected to be published in peer-reviewed journals.
31
32

33
34 The case report forms (CRFs) will be stored in a locked cabinet at the
35
36 hospitals and accessible by the research team only. On completion of the
37
38 trial and data checking, the CRFs will be transferred to be securely
39
40 archived at Sichuan university for 5 years before being destroyed. The trial
41
42 database will be anonymised, password protected and securely held.
43
44 Patient identifiable data are shared only within the clinical team on a
45
46 need-to-know basis to provide clinical care and ensure appropriate
47
48 follow-up. The aggregated research findings will be presented at national
49
50 and international scientific conferences and be submitted for publication
51
52 in peer-reviewed journals.
53
54
55
56
57
58
59
60

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

This research is supported by sichuan provincial administration of traditional Chinese medicine research fund support (2018QN037) , National College Students' innovation and entrepreneurship training program (C2018102074) ,The funding bodies do not play roles in study design, data collection, analysis, interpretation of results, and the manuscript.

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.

References

- [1] Frey UH, Funk M, Löhlein C, Peters J. Effect of P6 acustimulation on post-operative nausea and vomiting in patients undergoing a laparoscopic cholecystectomy. *Acta Anaesthesiol Scand*. 2009. 53(10): 1341-7.
- [2] Golembiewski J, Chernin E, Chopra T. Prevention and treatment of postoperative nausea and vomiting. *Am J Health Syst Pharm*. 2005. 62(12): 1247-60; quiz 1261-2.
- [3] Unit P C. Causes of Postoperative Complications of 9 136 Patients in the Post-anaesthesia Care Unit[J]. *Journal of China Medical University*, 2011, 40(4):349-351.
- [4] Sato K, Sai S, Adachi T. Is microvascular decompression surgery a high risk for postoperative nausea and vomiting in patients undergoing craniotomy. *J Anesth*. 2013. 27(5): 725-30.
- [5] Rahimi SY, Alleyne CH, Vernier E, Witcher MR, Vender JR. Postoperative pain management with tramadol after craniotomy: evaluation and cost analysis. *J Neurosurg*. 2010. 112(2): 268-72.
- [6] Guang-Qiang C, Qian W, Yi Z. Preventive Medication for Postoperative Vomiting in Patients Undergoing Neurosurgery Craniotomy:A Retrospect Study[J]. *Evaluation and Analysis of Drug-Use in Hospitals of China*, 2009. 9(5): 375-376.
- [7] Misra S, Parthasarathi G, Vilanilam GC. The effect of gabapentin premedication on postoperative nausea, vomiting, and pain in patients on preoperative dexamethasone undergoing craniotomy for intracranial tumors. *J Neurosurg Anesthesiol*. 2013. 25(4): 386-91.
- [8] Ryu JH, Lee JE, Lim YJ, et al. A prospective, randomized, double-blind, and multicenter trial of prophylactic effects of ramosetron postoperative nausea and vomiting (PONV) after craniotomy: comparison with ondansetron. *BMC Anesthesiol*. 2014. 14: 63.
- [9] Fabling JM, Gan TJ, El-Moalem HE, Warner DS, Borel CO. A randomized, double-blind comparison of ondansetron versus placebo for prevention of nausea and vomiting after infratentorial craniotomy. *J Neurosurg Anesthesiol*. 2002. 14(2): 102-7.
- [10] Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. *Can J Anaesth*. 2004. 51(4): 326-41.
- [11] Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs*. 2000. 59(2): 213-43.
- [12] Alizadeh R, Esmacili S, Shoar S, Bagheri-Hariri S, Shoar N. Acupuncture in preventing postoperative nausea and vomiting: efficacy of two acupuncture points versus a single one. *J Acupunct Meridian Stud*. 2014. 7(2): 71-5.
- [13] Ling J, Bailiang Y, Jinfu T. Neiguan Massaged to Prevent Ache and Nausea and Vomit after Laparoscopic Cholecystectomy—A Randomized Controlled Clinical Trial[J]. *Journal of Zhejiang University of Traditional Chinese Medicine*, 2010. 34(5): 745-746.

20

- 1
2
3
4 [14] Nilsson I, Karlsson A, Lindgren L, Bergenheim T, Koskinen LO, Nilsson U. The efficacy of P6 acupressure
5 with sea-band in reducing postoperative nausea and vomiting in patients undergoing craniotomy: a
6 randomized, double-blinded, placebo-controlled study. *J Neurosurg Anesthesiol.* 2015. 27(1): 42-50.
7
- 8 [15] Liu X, Li S, Wang B, An L, Ren X, Wu H. Intraoperative and postoperative anaesthetic and analgesic effect
9 of multipoint transcutaneous electrical acupuncture stimulation combined with sufentanil anaesthesia in
10 patients undergoing supratentorial craniotomy. *Acupunct Med.* 2015. 33(4): 270-6.
11
- 12 [16] An LX, Chen X, Ren XJ, Wu HF. Electro-acupuncture decreases postoperative pain and improves recovery
13 in patients undergoing a supratentorial craniotomy. *Am J Chin Med.* 2014. 42(5): 1099-109.
14
- 15 [17] Asmussen S, Maybauer DM, Chen JD, et al. Effects of Acupuncture in Anesthesia for Craniotomy: A Meta-
16 Analysis. *J Neurosurg Anesthesiol.* 2017. 29(3): 219-227.
17
- 18 [18] Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea
19 and vomiting. *Anesth Analg.* 2014. 118(1): 85-113.
20
- 21 [19] Cheong KB, Zhang JP, Huang Y, Zhang ZJ. The effectiveness of acupuncture in prevention and treatment
22 of postoperative nausea and vomiting--a systematic review and meta-analysis. *PLoS One.* 2013. 8(12):
23 e82474.
24
- 25 [20] Lu Z, Dong H, Wang Q, Xiong L. Perioperative acupuncture modulation: more than anaesthesia. *Br J*
26 *Anaesth.* 2015. 115(2): 183-93.
27
- 28 [21] Zhang JQ, Xue FS, Meng FM, Li RP. Assessing the anaesthetic and analgesic effects of electroacupuncture
29 in patients undergoing craniotomy. *Acupunct Med.* 2016. 34(1): 69-70.
30
- 31 [22] Jian-Qin L, Hui P, Ning L I. Acupuncture in the Treatment of Postoperative Nausea and Vomiting: A Report
32 of One Case and Review of Related Literature[J]. *West China Medical Journal*, 2013. (11): 1726-1730.
33
- 34 [23] Lü JQ, Feng R Z, Pan H, et al. [A randomized controlled clinical trial for acupuncture stimulation of Neiguan
35 (PC 6) to prevent postoperative nausea and vomiting]. [J]. *Acupuncture Research*, 2013, 38(3):245.
36
- 37 [24] Lv JQ, Feng RZ, Li N. P6 acupoint stimulation for prevention of postoperative nausea and vomiting in
38 patients undergoing craniotomy: study protocol for a randomized controlled trial. *Trials.* 2013. 14: 153.
39
40
41
42
43
44
45
46
47

Figure Legends

48 Figure 1: Intradermal thumbtack needle

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

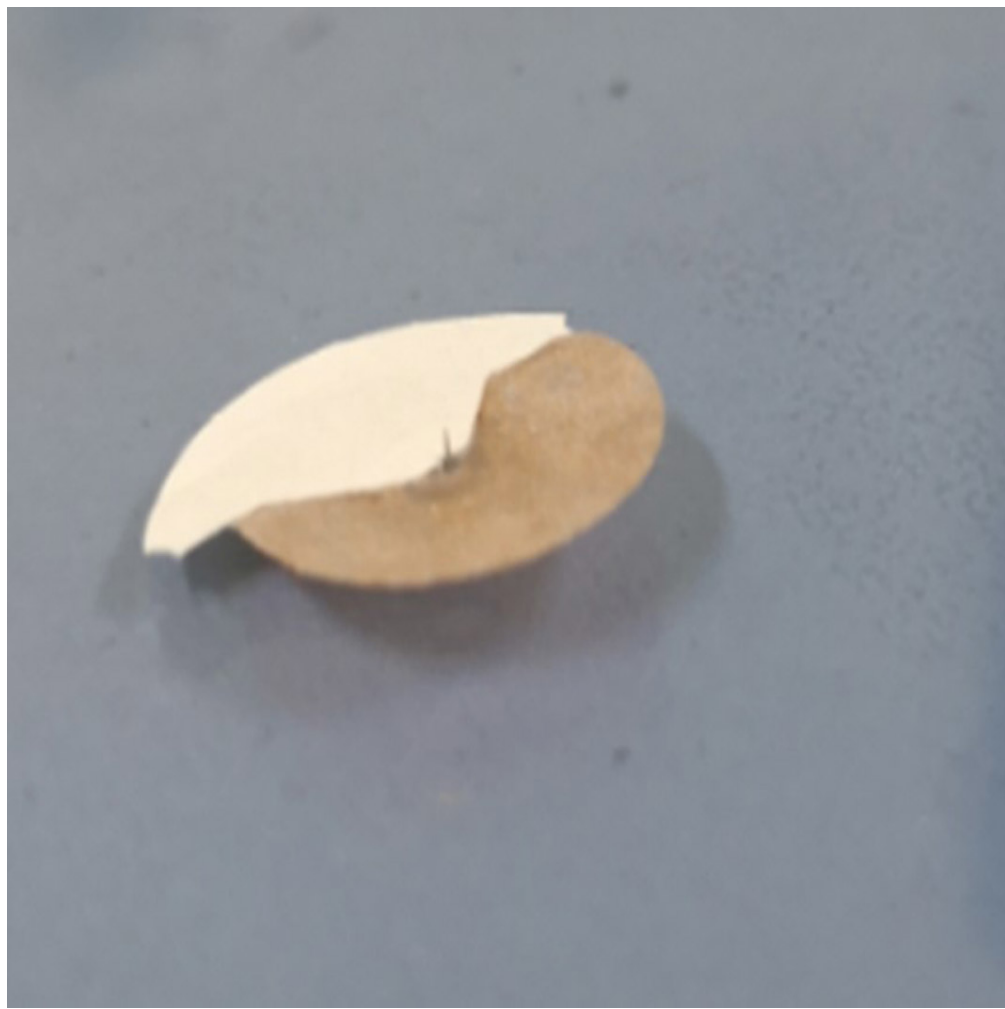
50 Figure 3: Trial flow chart

51 Figure 4: Location of P6 acupoint

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



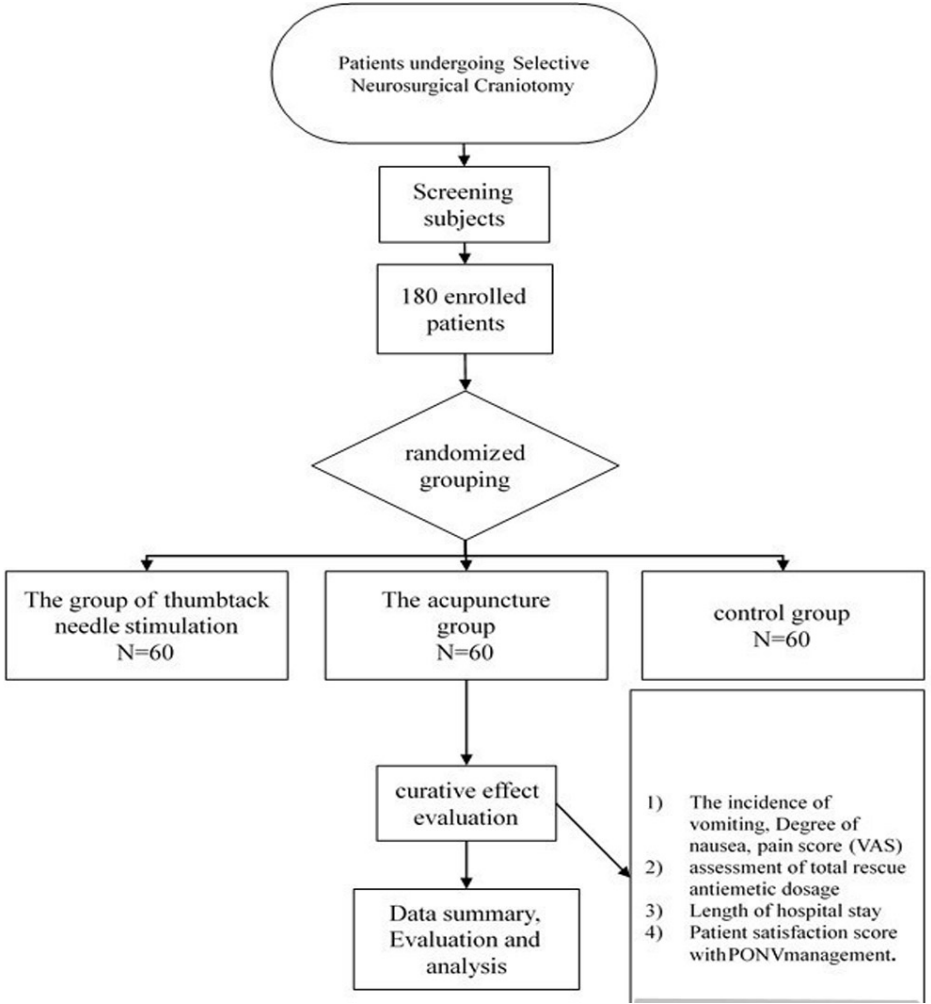
90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



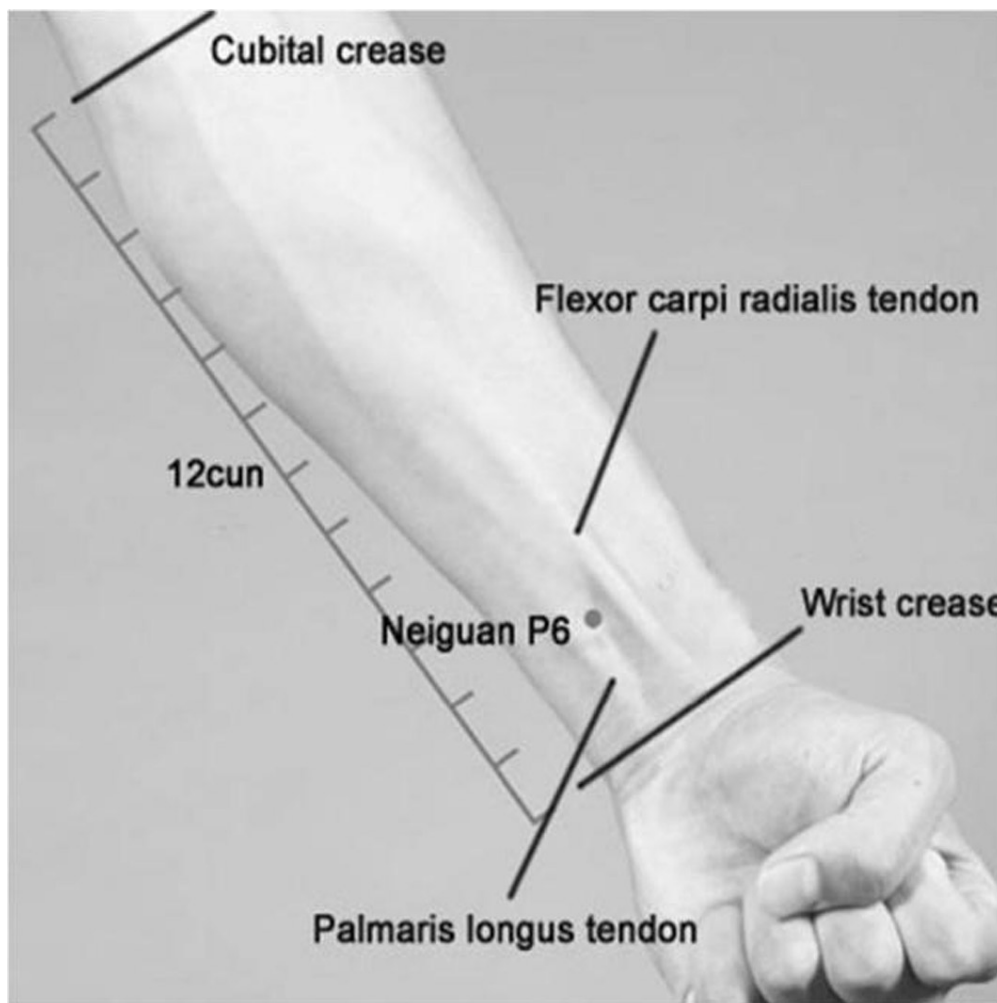
90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



90x90mm (300 x 300 DPI)



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			

1 2 3 4 5 6 7 8 9 10 11	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
12 13 14 15 16 17		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
18 19 20 21 22 23 24 25	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
26 27 28 29 30 31	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
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
35 36 37 38 39 40		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
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	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
53 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.