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Safety of different acupuncture manipulations for posterior circulation ischemia with vertigo

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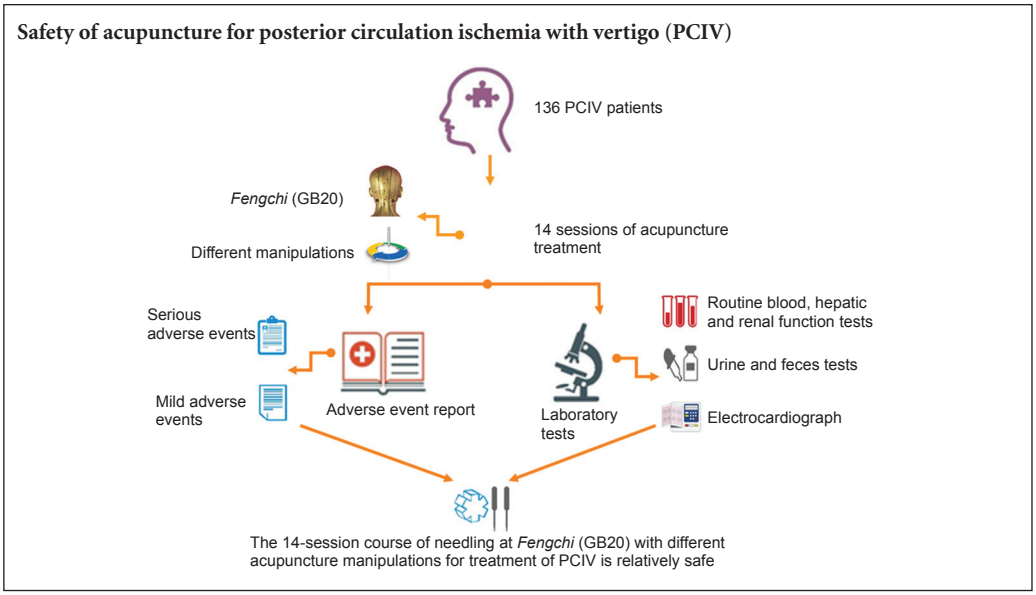
Graphical Abstract



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Abstract

Acupuncture at *Fengchi* (GB20) in the posterior neck improves vertigo. However, subarachnoid hemorrhage and spinal epidural hematoma have been reported to occur after acupuncture in the posterior neck. Therefore, in the present study, we assessed the safety of acupuncture at *Fengchi*. Laboratory tests and adverse event reports were used to evaluate the safety of different acupuncture manipulations for the treatment of posterior circulation ischemia with vertigo. A total of 136 patients were randomly assigned to four groups. Verum acupuncture was conducted with different needle insertion directions (contralateral paropia or prominentia laryngea) and different needle twisting frequencies (60 or 120 times/minute) at *Fengchi* and matching acupoints (for example, *Zhongwan* [CV12], *Qihai* [CV6], *Zusanli* [ST36], and *Fenglong* [ST40]). The patients received 14 treatments over 3–4 weeks. Routine blood analysis, hepatic and renal function tests, urine and feces tests and electrocardiography were performed before the first treatment session and after the final session. Adverse events were recorded after every session. Of the 136 patients, 120 completed the study. There were no significant differences between pretreatment and posttreatment test results in any of the groups. Only five patients suffered from minor adverse events (needling pain, slight hematoma and transient chest tightness). No serious adverse events were found. Our results indicate that a 14-session course of needling at *Fengchi* is relatively safe for treating posterior circulation ischemia with vertigo.

Key Words: *nerve regeneration; posterior circulation ischemia; vertigo; acupuncture; direction; twisting frequency; Fengchi (GB20); adverse event; safety; neural regeneration*

Introduction

Frequent symptoms of posterior circulation ischemia (PCI) include vertigo, nystagmus, coma and ataxia. Vertigo is the main symptom of PCI (Searls et al., 2012). Acupuncture treatment improves symptoms of vertigo resulting from PCI (Zhao et al., 1997). The *Fengchi* (GB20) acupoint is commonly used in the treatment of vertigo, and promotes blood flow.

Acupuncture has been used in China for thousands of years and its use is growing in many other countries such

as the USA, UK, Australia, Canada, Denmark and Norway (Hanssen et al., 2005; MacPherson et al., 2006; Xue et al., 2008; Zhang et al., 2012). The greater acceptance of acupuncture worldwide has led to increasing demands for evidence of its effectiveness and safety, important for both patients and acupuncture practitioners. Serious adverse events associated with acupuncture, including viral hepatitis, pneumothorax, and nerve injury, have been documented, mostly in case reports and retrospective surveys (Yamashita et al., 2001; Ernst and Sherman, 2003; Lao et al., 2003). However, these serious adverse events or complications have rarely been found in prospective studies addressing acupuncture safety, although mild and transient adverse events such as needling pain, bleeding or hematoma are common (White et al., 2001; Endres et al., 2004; MacPherson et al., 2004; Witt et al., 2009). Together, this evidence suggests that acupuncture is a relatively safe procedure.

The safety of acupuncture is an important issue and deserves careful attention. A recent systematic review of Chinese literature about acupuncture-related adverse events (Zhang et al., 2010) revealed that the acupoints most frequently involved in cases of subarachnoid hemorrhage and spinal epidural hematoma are located on the posterior neck, for example at *Fengchi*, the main acupoint in the present study. In addition to the acupoint location, needling manipulations such as the direction and depth of insertion (Lin et al., 2013) might also be associated with acupuncture-related adverse events. Therefore, in the present study, we used standard laboratory tests and adverse event reporting to evaluate the safety of needling at *Fengchi* as a treatment for PCI with vertigo (PCIV) using different acupuncture manipulations (direction and twisting frequency).

Subjects and Methods

Study design

We performed a randomized prospective controlled trial in patients with PCIV. This study was performed in the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine in China, which is known as the National Clinical Research Center of Acupuncture and Moxibustion, China. With the approval of the regional ethics review boards of Tianjin University of Traditional Chinese Medicine, 250 patients were screened between 1 February 2012 and 1 December 2013.

Subjects

Electronic bulletin boards and notices on printed recruitment posters were placed in the Outpatient Department at the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, China. Interested patients were referred to the study investigators, and screening evaluations were conducted by experienced clinicians. Patients were screened for participation if they fulfilled the following diagnostic criteria proposed by the World Health Organization (WHO Task Force on Stroke and other Cerebrovascular Disorders, 1989): (1) dizziness or vertigo; (2) vertebrobasilar insufficiency revealed by transcranial Doppler/magnetic resonance imaging; (3) major symptoms possibly accompanied by unsteadiness or ataxia; unilateral or bilateral visual, motor or sensory disturbances; double vision; dysarthria or swallowing impairment; acute impairment of consciousness or acute confusion.

Inclusion criteria: Male or female patients meeting all of the following criteria were considered for admission to the trial:

(1) Diagnosed with vertebrobasilar insufficiency; (2) aged between 40 and 75 years; (3) volunteered to undergo acupuncture treatment and able to cooperate with the inspection; (4) provided signed informed consent.

Exclusion criteria: Patients presenting with one of the following conditions were excluded from the trial:

(1) Cerebral hemorrhage and bulbar paralysis; (2) aural or ocular vertigo; (3) systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 120 mmHg; (4) Glasgow coma scale score of < 15 or Hasegawa's dementia scale score of < 27.5; (5) serious heart, liver or kidney disease; (6) critical illness requiring surgery; (7) pregnancy or lactation; (8) severe mental illness; (9) currently participating, or participated in the past 3 months, in other clinical research.

All patients who met the inclusion criteria were given ample time to decide whether they would participate in the study. All patients who wanted to enter the study signed the informed consent form. This trial was registered at the Chinese Clinical Trial Registry (ChiCTR-RTRCC-12002675) and performed according to the principles of the *Declaration of Helsinki*. The trial protocol was approved by the Medical Ethics Committee, Tianjin University of Traditional Chinese Medicine, China (approval No. TJUTCM-EC20110005). **Figure 1** shows the study flow chart.

Randomization and group assignment

All subjects were randomly assigned to one of four verum acupuncture groups according to a randomization list generated in Excel 2003 and using numbered, opaque, sealed envelopes. Groups and main acupuncture points are defined in **Figure 2**. The outcome assessors and statistician were blinded to the experimental grouping.

Acupuncture administration

We used sterile disposable stainless steel needles (length: 40 mm, diameter: 0.25 mm; Hwatuo, Suzhou Medical Supplies Factory Co., Ltd., Suzhou, Jiangsu Province, China). Patients underwent 14 treatment sessions over 3–4 weeks. Each session lasted 20 minutes. *Fengchi* (inferior to the occipital bone, in the depression between the origins of the sternocleidomastoid and trapezius muscles) was selected as the main acupoint, and matching acupoints were added based on individualized pattern diagnoses: *Zhongwan* (CV12, on the anterior midline, 4 cun above the umbilicus); *Qihai* (CV6, on the anterior midline, 1.5 cun below the umbilicus); *Zusanli* (ST36, three cun directly below *Dubi* (ST35) and one finger-breadth lateral to the anterior border of the tibia); *Fenglong* (ST40, one finger-breadth lateral to *Tiaokou* (ST38) and at the midpoint of the line joining *Dubi* and the

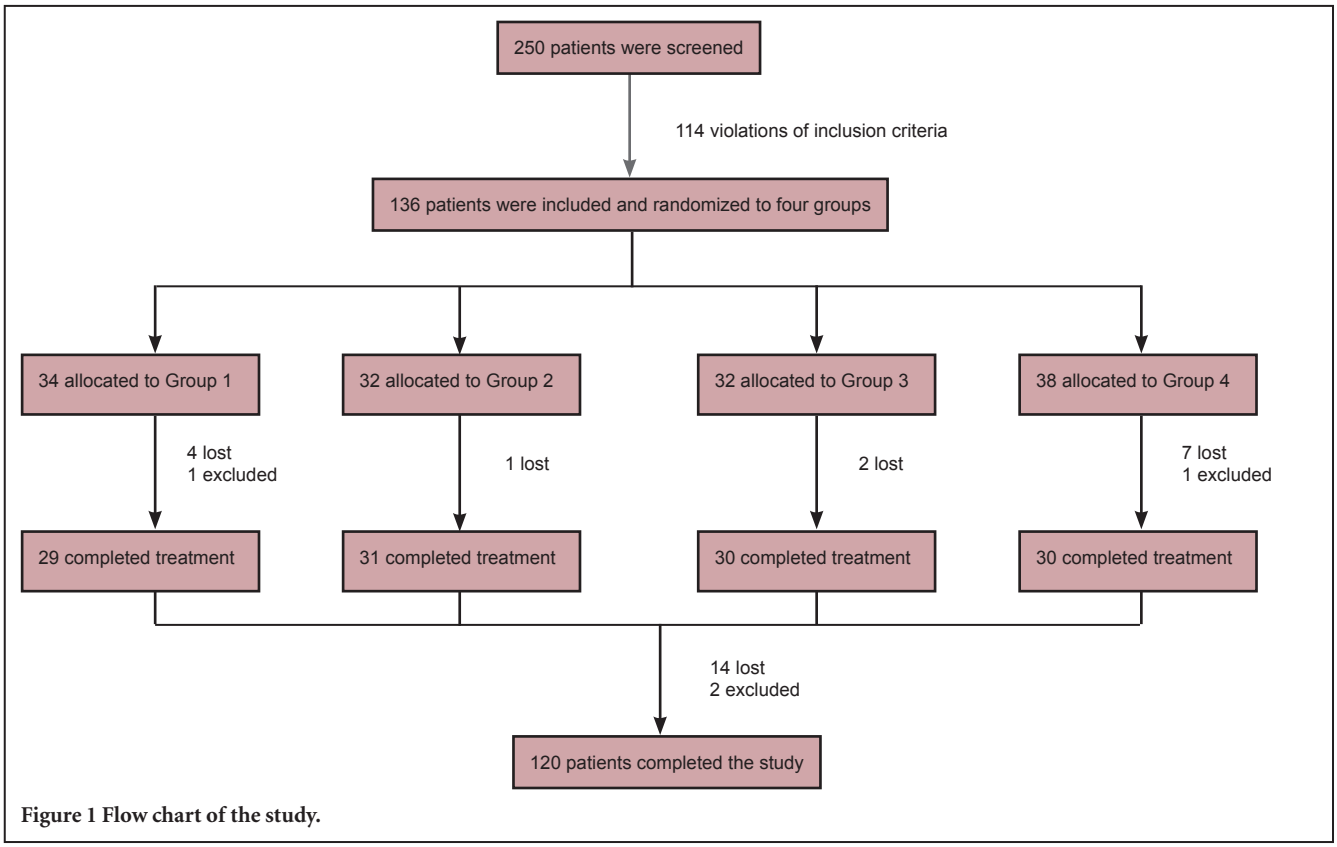
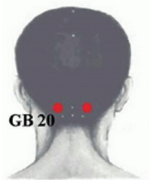


Figure 1 Flow chart of the study.



	Direction	Frequency
Group 1	Contralateral paropia	60 times per minute
Group 2	Prominentia laryngea	60 times per minute
Group 3	Contralateral paropia	120 times per minute
Group 4	Prominentia larygea	120 times per minute

Figure 2 Main needling point and manipulations in the four groups.
GB20: *Fengchi* acupoint.

tip of the external malleolus); *Taixi* (KI3, in the depression between the tip of the medial malleolus and the Achilles tendon); *Zhaohai* (KI6, in the depression directly below the tip of the medial malleolus); *Neiguan* (PC6, on the line joining *Daling* (PC7) and *Quze* (PC3), between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist); *Laogong* (PC8, on the radial aspect of the third metacarpal bone, at the tip of the middle finger when a fist is made and the finger is flexed). The angle, depth, and manipulation of matching acupoints conformed to typical prescriptions. Needling manipulations were performed manually by one experienced acupuncturist who had been practicing for more than 20 years.

Needling at the main acupoint *Fengchi* was performed with the patient sitting. For needle retention, the patient lay prone. The needle was manually inserted deeply (0.5–0.8 cun) in either the contralateral paropia or prominentia laryngea direction, and twisted 60 or 120 times for 1 minute. After *Deqi* (a sensation of numbness, distension, or electrical tingling at the needling site, which might radiate along the corresponding meridian), the needles were retained in place for 20 minutes.

Outcome measures

Laboratory tests were performed before the first acupuncture session and after the final session. Adverse events, including pain, hematoma, perforation, bleeding, fainting, local infection, abscess, or breakage or retention of the needle after treatment, were recorded after every session.

The laboratory tests comprised routine blood analysis, hepatic and renal function measurement, urine and feces tests and electrocardiography (ECG).

Routine blood analysis included hemoglobin level and counts of leukocytes, erythrocytes, neutrophilic granulocytes and lymphocytes.

Hepatic and renal function tests comprised measurement of carbamide, creatinine, total protein, albumin, globulin, alanine aminotransferase and aspartate transaminase.

Urine tests included measurement of excreted protein and glucose, and counts of leucocytes and erythrocytes. The fecal occult blood test was also conducted.

Twelve-lead ECGs were performed with patients in the supine position. Heart rate and rhythm, durations of P-wave, QRS interval and QT(c) interval, and QRS axis were evaluated. ECG variables were analyzed with standard ECG nomenclature and definitions.

Blood, urine and feces samples were collected at 8:00 a.m. on the day before the first treatment and the day after the final treatment. Normal values for all laboratory tests were provided by the Clinical Laboratory in the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, China.

Table 1 Demographic and clinical characteristics at baseline

	Group 1	Group 2	Group 3	Group 4	Total	*P*
n	29	31	30	30	120	
Age (mean±SD, year)	58.76±7.17	59.97±6.95	61.69±6.88	57.14±7.16	59.36±7.43	0.096[a]
Sex (male/female, *n*)	5/24	9/22	15/15	7/23	36/84	0.035[b]
Body mass index (mean±SD, kg/m^2)	24.52±4.31	23.69±3.04	25.16±3.02	24.07±3.09	24.36±3.37	0.360[a]
Full-time education (mean±SD, year)	11.97±2.88	11.87±2.54	13.29±3.32	12.47±2.62	12.41±2.88	0.197[a]
Age of onset of vertigo (mean±SD, year)	53.17±8.43	54.48±9.31	57.83±10.09	51.80±8.84	54.33±9.35	0.075[a]
Medication (*n*[%])						
Antihypertensive	5(17.24)	3(9.68)	8(26.67)	5(16.67)	21(17.5)	0.380[b]
Lipid-modulating	4(13.79)	3(9.68)	3(10.00)	3(10.00)	13(10.83)	1.000[b]
Antidiabetic	0	3(9.68)	2(6.67)	0	5(4.17)	0.145[b]

[a]Analysis of covariance; [b]chi-square test.

Table 2 Routine blood test results

	Normal values	Group 1 (*n* = 29)	Group 2 (*n* = 31)	Group 3 (*n* = 30)	Group 4 (*n* = 30)
Leukocytes ($\times 10^9$)					
Pretreatment	4.3–10.8	5.92±1.12	5.64±1.28	6.13±1.65	5.63±1.22
Posttreatment		5.95±1.59	5.34±1.36	6.03±1.67	5.41±1.06
Erythrocytes ($\times 10^{12}$)					
Pretreatment	4.2–5.9	4.42±0.29	4.49±0.32	4.61±0.40	4.42±0.40
Posttreatment		4.34±0.27	4.47±0.36	4.62±0.37	4.38±0.38
Hemoglobin (g/L)					
Pretreatment	120–180	132.88±8.58	135.83±11.06	137.07±13.61	134.91±11.28
Posttreatment		131.21±8.84	135.70±13.05	138.46±13.18	133.63±10.09
Neutrophils (%)					
Pretreatment	50–70	56.22±6.50	55.82±9.09	58.94±8.38	59.76±8.03
Posttreatment		58.33±8.29	54.82±10.23	59.53±6.59	57.32±7.26*
Lymphocyte (%)					
Pretreatment	20–40	34.74±6.74	34.36±8.93	31.71±7.70	31.64±7.87
Posttreatment		32.72±7.79*	35.12±10.69	30.89±6.25	34.65±9.76

Values are presented as the mean ± SD. *$P < 0.05$, *vs.* pretreatment (paired *t*-test).

Sample size

We estimated the sample size with the formula used in previous relevant literature. We planned to enroll 144 participants (36 per group), allowing for a 15% dropout rate.

Statistical analysis

All data, expressed as the mean ± SD, were statistically analyzed using SPSS v19.0 (IBM, Armonk, NY, USA). Data were analyzed by study personnel and a statistician blinded to experimental grouping. Analysis of covariance and paired *t*-test were used to analyze measurement data. The chi-square test was used for enumerated data.

Results

Quantitative analysis of patients

Two hundred and fifty patients were screened. Of these, 136 with PCIV met the inclusion criteria, gave signed consent, and were randomly assigned to four verum acupuncture groups. Of those enrolled, 14 were lost during the treatment course, because they had difficulties in keeping to the schedule, and two were excluded. Altogether, 120 patients completed the study (29 in group 1, 31 in group 2, 30 in group 3 and 30 in group 4). The demographic characteristics for participants are shown in **Table 1**. There were no significant differences between the groups in mean age, body mass index, age of vertigo onset, or commonly used drugs (all $P > 0.05$); a significant difference was found in sex ratio between the groups ($P < 0.05$).

Routine blood analysis

Neutrophil percentage in group 4 and lymphocyte percentage in group 1 were significantly greater after acupuncture treatment than before (both $P < 0.05$). All other within-group comparisons were non-significant ($P > 0.05$). All pretreatment and posttreatment blood test results were in the normal range (**Table 2**).

Hepatic and renal function

Aspartate transaminase levels were statistically greater after treatment than before in groups 3 and 4 ($P < 0.05$). For albumin, the pretreatment value was significantly higher than the posttreatment value in group 4 only ($P < 0.05$). Alanine aminotransferase level in group 1 was significantly higher after treatment than before ($P < 0.05$). All other within-group comparisons were nonsignificant ($P > 0.05$). Despite these differences, all measures of hepatic and renal function in the

Table 3 Hepatic and renal function test results

	Normal values	Group 1 (n = 29)	Group 2 (n = 31)	Group 3 (n = 30)	Group 4 (n = 30)
Carbamide (mM)					
Pretreatment	2.5–6.4	5.15±1.36	5.56±1.82	5.38±1.51	5.06±1.56
Posttreatment		4.83±1.23	5.10±1.11	5.34±1.12	4.98±1.43
Creatinine (μM)					
Pretreatment	44–133	53.25±8.68	61.56±12.92	62.80±15.74	54.29±16.48
Posttreatment		52.25±6.00	58.83±11.95	63.84±16.99	54.63±13.76
Total protein (g/L)					
Pretreatment	67–81	73.02±4.04	71.27±8.29	71.19±5.03	70.01±11.61
Posttreatment		70.77±7.83	72.66±6.73	72.27±3.51	71.20±5.51
Albumin (g/L)					
Pretreatment	40–55	43.70±3.65	42.70±4.19	44.06±3.33	43.01±3.66
Posttreatment		43.25±3.66	42.47±4.43	44.70±6.77	41.54±3.95*
Globulin (g/L)					
Pretreatment	25–35	29.31±4.89	29.67±6.11	27.65±4.63	29.69±6.81
Posttreatment		28.80±5.19	30.01±7.43	28.60±3.63	29.45±6.49
Alanine aminotransferase (IU/L)					
Pretreatment	4–46	22.40±9.96	21.30±9.44	21.61±12.35	22.57±14.58
Posttreatment		20.02±8.95*	20.35±8.64	21.86±10.86	22.12±13.89
Aspartate transaminase (IU/L)					
Pretreatment	5–40	20.43±4.46	22.13±6.28	20.00±6.44	20.18±6.40
Posttreatment		19.79±4.33	21.95±4.72	22.26±6.80*	21.69±6.23*

Values are presented as the mean ± SD. *P < 0.05, *vs.* pretreatment (paired t-test).

Table 4 Results of urine and feces tests and electrocardiograph

	Group 1 (n = 29)	Group 2 (n = 31)	Group 3 (n = 30)	Group 4 (n = 30)
Urine test				
Leucocytes in urine				
Pretreatment	3(10.3)	2(6.5)	5(16.7)	5(16.7)
Posttreatment	1(3.4)	2(6.5)	1(3.3)	2(6.7)
Urine protein				
Pretreatment	0	1(3.2)	1(3.3)	0
Posttreatment	0	0	0	0
Erythrocytes in urine				
Pretreatment	1(3.4)	3(9.7)	1(3.3)	2(6.7)
Posttreatment	0	0	0	2(6.7)
Urine glucose				
Pretreatment	1(3.4)	1(3.2)	0	0
Posttreatment	1(3.4)	1(3.2)	0	0
Feces test				
Pretreatment	0	0	0	0
Posttreatment	0	0	0	0
Electrocardiograph test				
Pretreatment	5(17.2)	14(45.2)	10(33.3)	11(36.7)
Posttreatment	5(17.2)	9(29.0)	10(33.3)	9(30.0)

Number (percentage) of subjects with abnormal results.

four groups were in the normal range before and after treatment (**Table 3**).

Urine and feces tests and ECG

No significant differences were found in urine and feces tests or ECG after treatment compared to baseline (P > 0.05). Moreover, the number of patients with values outside the normal rage did not increase after 14 treatments (**Table 4**).

Adverse events

No serious adverse events were reported. Several mild adverse events occurred during the study. One patient in group 4 had a mild hematoma at the acupuncture site shortly after treatment. No patients were terminated from the study because of pain, but two patients (one in group 1 and one in group 4) did complain that acupuncture was very painful and one patient in group 3 felt mild pain at the acupuncture site more than one hour after treatment. One patient in group 2 suffered from chest tightness from the supine position, but this symptom disappeared when the patient changed position to sitting.

Discussion

Our results demonstrate that the protocol of needling at *Fengchi* in two different directions (contralateral paropia or prominentia laryngea) and twisting frequencies (60 or 120 per minute) is relatively safe for patients with PCIV. This will be valuable in the design of randomized clinical trials addressing the role of acupuncture in PCIV or other diseases.

The laboratory tests we chose to investigate acupuncture safety (blood analysis, hepatic and renal function measurements, urine and feces tests, and ECG) are commonly used as screening tests to investigate drug safety. Changes in certain biochemical indexes are considered sensitive markers for certain diseases. For example, elevated albumin excretion and abnormal levels of proteinuria are indicative of chronic kidney disease (Keane and Eknoyan, 1999; Levey et al.,

2003), and leukocyte and neutrophil numbers are markers of the inflammatory reaction. Dufour et al. (2000) indicated that aspartate transaminase, alanine aminotransferase, total protein, and albumin should be used to evaluate patients with known or suspected liver disease; of these, alanine aminotransferase is the most important test for identifying acute and chronic hepatic disease. Liver diseases such as hepatitis and bacterial and viral infections have been repeatedly associated with acupuncture (MacPherson et al., 2004; Karmochkine et al., 2006; Nguyen et al., 2007; Ernst et al., 2011). There has been some reduction in the number of reports addressing hepatic disease and infection resulting from acupuncture in recent years (White, 2004); however, as acupuncture gains an increasingly important role in today's multidisciplinary clinics, its complications, although infrequent, cannot be overlooked.

To the best of our knowledge, the present study is the first to use laboratory tests to explore the influence of acupuncture on hematological and biochemical indexes. The lack of difference between pre- and posttreatment values in the present study provides measurable evidence for the clinical safety of acupuncture and may be useful in pursuing further studies on its safety using different manipulations.

We found no serious adverse events in the present study. This result is consistent with several prospective surveys of acupuncture safety from the UK (MacPherson et al., 2001; White et al., 2001). Two other surveys, conducted in Germany—one comprising more than 2 million consecutive acupuncture treatments in 229,230 patients (Witt et al., 2009) and the other more than 760,000 acupuncture treatments (Melchart et al., 2004)—reported only a few serious adverse events; these included pneumothorax and nerve damage. Serious acupuncture-related adverse events may be classified into two categories: traumatic and infectious. The majority of the traumatic injuries could have been avoided if the acupuncturists had better anatomical knowledge and received professional training (Peuker and Grönemeyer, 2001). In our study, needling manipulations were performed by an experienced acupuncturist who had been practicing for more than 20 years. Furthermore, the acupuncturist received professional training before our trial to ensure accuracy of needle manipulation. The qualified acupuncturist plays an important role in avoiding serious adverse events, and acupuncture can be considered safe in the hands of competent practitioners (Vincent, 2001).

Another common type of adverse event is infection. Hepatitis, human immunodeficiency virus and subacute bacterial endocarditis represent the three most serious infectious complications resulting from acupuncture (Ernst and White, 1997). Infections result primarily from poor aseptic procedure and insufficient knowledge of practitioners, who often disinfect reusable acupuncture needles with alcohol instead of sterilizing them (Zhang et al., 2010). Our study used sterile disposable stainless steel needles. To avoid cross-contamination, each patient had their own needles and the acupuncturist adopted strict sterilization procedures. The use of disposable sterile acupuncture needles is strongly recommended (World Health Organization, 1999) and is mandatory in some western countries, but may not be fully established in non-western countries, especially in rural areas (Sun et al., 1999; Sanchez et al., 2000; Shin et al., 2000). The use of disposable needles is important to ensure the safety of acupuncture. Based on the above, we propose that if acupuncture is used according to established safety rules and carefully at appropriate anatomic regions by a qualified acupuncturist, it is a relatively safe treatment method.

In contrast to serious complications, mild adverse reactions to acupuncture are common. However, despite previous literature showing a strong association between needling pain, slight hemorrhage and hematoma with acupuncture (Ernst and Sherman, 2003; Nguyen et al., 2007; Witt et al., 2009; Capili et al., 2010), few adverse events were observed in our study. Only five patients reported adverse events throughout the treatment period; of these, three experienced needling pain, one had a minor hematoma and one reported transient chest tightness. A previous study demonstrated that men and elderly individuals experienced most adverse events (Zhao et al., 2011). In the present study, the average age was 59.36 years and 70% of subjects were female; this, combined with the high tolerance for acupuncture treatment in China, may contribute to the low incidence of adverse events we observed.

Our study has several limitations. First, a relatively brief treatment period was chosen, so the study demonstrates that a 14-session acupuncture protocol is safe for people with PCIV, but longer durations of treatment should be investigated. The second limitation was the small sample size. We know that the best evidence of treatment safety is a large-scale prospective study or meta-analysis. If the samples were larger, this would provide a better evaluation of acupuncture safety.

In summary, we used laboratory tests and adverse event reporting to assess the safety of different acupuncture manipulations in patients with PCIV. Laboratory data from 120 subjects showed no clinical differences between pre- and posttreatment values; no serious adverse events were associated with acupuncture and only five patients suffered any adverse events throughout the treatment period. Our data indicate that needling at *Fengchi* to treat PCIV, in different directions (towards the contralateral paropia or prominentia laryngea) and at different twisting frequencies (60 or 120 twists per minute) when conducted by a qualified acupuncturist, is relatively safe. Further research is needed to explore acupuncture safety under different conditions and for longer treatment periods.

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Author contributions: *ZHM and XFZ conceived the study and prepared the initial protocol. YW and CZ drafted the paper and participated in the study design. SZD, SH and LHH completed the study. GT analyzed the data. All authors*

approved the final version of the paper.

Conflicts of interest: *None declared.*

Plagiarism check: *This paper was screened twice using Cross-Check to verify originality before publication.*

Peer review: *This paper was double-blinded and stringently reviewed by international expert reviewers.*

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