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Effects of Acupuncture upon cerebral hemodynamics in cerebral small vessel disease: A pilot study

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ABSTRACT

Background and aims: Recent preclinical studies and meta-analysis of clinical trials suggested that acupuncture may improve cognition in cerebral small vessel disease (CSVD). We investigated the cerebral hemodynamics of acupuncture in subjects with CSVD and compared its impact upon the cerebral hemodynamics in normal elderly subjects

Methods: 10 subjects with CSVD (CSVD group) and 10 aged-matched control subjects who had no or insignificant CSVD (control group) were recruited. A single session of acupuncture was applied for 30 min in both groups. We assessed the effect of our acupuncture intervention on cerebral hemodynamics by transcranial Doppler ultrasound (TCD). Peak systolic velocity (PSV) and pulsatility index (PI) of the middle cerebral artery (MCA) were assessed

Results: We observed that PSV increased by a maximum of 39% at 20 min ($p<0.05$), while there was no significant change in PI in the CSVD group during the acupuncture session. In the control group, although we observed no significant change in PSV during the acupuncture session, there was a significant decrease in PI by a maximum of 22% at 20 min ($p<0.05$). No adverse events were reported during or after the procedure.

Conclusion: This study suggested that our acupuncture prescription was associated with an increase in cerebral blood flow in subjects with established moderate to severe CSVD yet without apparent impact on distal vascular resistance. While, in subjects with no or insignificant CSVD, it may reduce cerebral small vessel distal vascular resistance. A larger study is needed to confirm our findings.

1. Introduction

With aging, changes occur in the structure and function of the cerebral small vessel. These changes may include thickening of the vessel wall and loss of smooth muscle cells in the tunica media, which lead not only to luminal narrowing, but also to impaired endothelial and vasodilatory function, leakage of blood-brain-barrier and weakening or rupture of the vessel wall, which finally resulting in various brain changes or damages [1–3]. Although conventional Magnetic resonance imaging (MRI) is not able to visualize these small vessel pathological changes, MRI can capture these associated brain changes that are commonly manifested as white matter hyperintensity (WMH), lacune or microbleeds on MRI. When these changes become diffuse or affect strategic brain regions, cognitive and/or motor impairment may develop [4]. Cerebral WMH, lacune and cerebral microbleeds are the commonest imaging marker for cerebral small vessel disease (CSVD) and vascular cognitive impairment (VCI) [5]. Apart from aging, hypertension is the most important risk factor for CSVD [6,7]. To date, apart from management of hypertension, there is no established treatment for CSVD [8].

Preclinical studies have shown that acupuncture improves cognitive functions in vascular dementia via improving cerebral blood flow and

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vessel function, as well as via other mechanisms, such as reducing oxidative stress and inflammation, attenuates neurons apoptosis, or improves synaptic plasticity [9]. We recently conducted a systematic review and meta-analysis of clinical trials assessing effects of acupuncture on vascular cognitive impairment associated with CSVD, which suggested that acupuncture could possibly improve cognitive function in VCI associated with CSVD [10]. To date, no clinical study has investigated the cerebral impacts of acupuncture in subjects with CSVD. We hypothesized that acupuncture can improve the cerebral blood flow and small vessel endothelial and/or vasodilatory function in subjects with CSVD. We aimed to investigate the cerebral hemodynamics of acupuncture in subjects with CSVD and compared its impact upon the cerebral hemodynamics in normal elderly subjects in this pilot study.

2. Materials and methods

2.1. Subject recruitment

We recruited CSVD subjects from the CU-RISK (The Chinese University of Hong Kong-Risk Index for Subclinical Brain Lesions in Hong Kong) [11]. Presence of significant CSVD was defined by the presence of multiple (≥2) lacunar infarcts and/or a WMH Fazekas rating of >/=2 on MRI [12]. Those with WMH rating 0–1were classified as having no or insignificant CSVD. Apart from having significant CSVD on MRI, other inclusion criteria were (i) Chinese adult with age ≥65 years; (ii) neurologically stable for the past 7 days prior to recruitment as assessed by a neurologist; (iii) a temporal window could be obtained with transcranial doppler ultrasound (TCD) at least for one side of the brain; and (iv) were able to provide a written informed consent. Subjects were excluded if they: (i) had history of uncontrolled bleeding; (ii) were on anticoagulants; (iii) had changes in neurological condition within 7 days of recruitment; (iv) had history of cerebrovascular disease, intracranial artery stenosis or aneurysm, or significant cardiovascular diseases that may influence cerebral hemodynamic; and (v) were unable to speak or read Chinese. Subjects whose WMH <2 were recruited for comparison. We planned to recruit 40 subjects (20 subjects with CSVD and 20 without significant CSVD) initially but because of social unrest in 2019 and COVID-19 pandemic in 2020 to 2021, we eventually managed to recruit only 20 subjects (10 from each group) into this study.

2.2. Sample size estimation

We adopted a noncentral t-distribution (NCT) approach to estimate the sample size in this pilot study because NCT approach was found to be able to maintain the nominal power requirement and to minimize the overall trial sample size for the pilot and the future main trial as well. As the standardized effect size in the targeted population is not known, a stepped rule of thumbs for setting the pilot study sample size is recommended. A minimum of 10 subjects per group is suggested when using NCT approach to calculate the future main trail sample size in both 80% and 90% powered main trial.

3. Intervention

Traditional Chinese medicine (TCM) theory classified CSVD as "Dai" or "Forgetfulness" syndrome [13–15]. The pathology is believed to be originated from the brain[13,16] and associated with "Kidney" and "Brain Marrow Decline" in view of TCM [13,15,17,18]. TCM believed pathogens called "Wind", "Phlegm" invade, "Brain Orifice" and "Clear Yang" are blocked and "Spirit" is malnourished [13,17].

We chose GV20 (Baihui), Ex-HN1 (Sishencong) and GV24 (Shenting) to open "Brain Orifice" and promote "Brain Marrow"; GB13 (Benshen) and GB20 (Fengchi) to remove "Wind"; BL10 (Tianzhu) and LI4 (Hegu) to promote "Yang" and "Spirit"; PC6 (Neiguan), SP6 (Sanyinjiao) and ST36 (Zusanli) to remove "Phlegm". The technical details of total 20 acupoints used were shown in Table 1. These acupoints were chosen based on the previous clinical trials suggesting their potential effectiveness as well[10,19-25]

Table 1
Location and method of application about the prescribed acupoints in this study.

Acupoint codes (Traditional name)	Number of acupoints	Location of acupoints	Depth and angle of insertion
GV20 (Baihui)	1	On the top of the head, between midline of the body and the line joining the high point of the ears	Along the scalp with 0.5cun*
Ex-HN1 (Sishencong)	4	1 cun anterior, posterior and bilateral to GV 20	
GV24 (Shenting)	1	0.5 cun above the midpoint of the anterior hairline	
GB13 (Benshen)	2	3 cun lateral to GV24	
GB20 (Fengchi)	2	At the depression between the upper part of the sternocleidomastoid muscle and the trapezius muscle	0.8 to 1 cun depth pointing towards to the nose
BL10 (Tianzhu)	2	0.5 cun above the midpoint of posterior hairline and 1.3 cun lateral	0.5 cun depth perpendicular to skin
PC6 (Neiguan)	2	2 cun above the wrist crease	
LI4 (Hegu)	2	between the 1st and 2nd metacarpal bones, in the middle of the radial side of the 2nd metacarpal bone	1 cun depth perpendicular to skin
ST36 (Zusanli)	2	3 cun below the lateral depression around the patella ligament in knee flexed position. And one finger breadth lateral to anterior shaft of tibia	
SP6 (Sanyinjiao)	2	3 cun above the tip of medial malleolus and posterior to the medial border of tibia	

* Cun is a standard unit of measurement for acupuncture; 1 cun = width of thumb, in the middle, at the crease.

Subjects received one session of acupuncture for 30 min, with "De Qi" sensation on each acupoint, and needles were manipulated manually every 10 min. "De Qi" was reported by the participants with dullness or soreness over the acupoints. Subjects were requested to report immediately in case of any pain and discomfort during acupuncture, so that the acupuncturist could adjust the needle accordingly. The study was approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Reference number: NTEC-2018–0131). All subjects gave written informed consent.

3.1. Data collection

Subjects' demographical data including gender, age, history of diabetes, hypertension, hyperlipidemia and WMH rating on MRI brain were collected. We employed transcranial doppler ultrasound(TCD) to evaluate cerebral hemodynamics. We used the change in peak systolic velocity (PSV) of middle cerebral artery (MCA) to reflect change in cerebral blood flow[26] and we used the change in MCA pulsatility index (PI) to reflect change in distal vascular resistance of the cerebral small vessel. PI value was automatically generated in TCD machine according to the following formula: PI=(peak systolic velocity−end diastolic flow velocity)/mean flow velocity. Studies have shown that a PI was associated with severity of CSVD and might reflect endothelial dysfunction and/or pathological structural changes of the small vessel [27].

MCA were recorded through temporal window with 60 mm depth by a 2-MHx pulsed-Doppler probe before acupuncture intervention, every 10 min of needles retention (for three times) and after needles removal. We recorded the PSV and PI values of one side of the MCA which showed the clearest signal as most of the subjects could only present a visible unilateral temporal window only.

3.2. Statistical analysis

We used SPSS software (IBM SPSS version 22) for analysis. Non-parametric tests were used because sample size was small, and the data was not normally distributed. Friedman Test was used to analyze the difference within groups and Pearson's chi-square test were used to analyze the difference between two groups.

4. Results

Thirty subjects were screened but 10 subjects were excluded due to poor temporal window on TCD. Twenty participants were recruited and analyzed, 10 with CSVD (7 male, 3 female; mean age:80±6.35 years old) and 10 healthy controls without or with only insignificant CSVD (3 male, 7 female; mean age:71.5 ± 3.5 years old). The demographic data was shown in table 2. No statistically significant difference in regards of age($p = 0.104$), gender($p = 0.074$) and past medical history including diabetes ($p = 0.639$), hypertension ($p = 0.653$) and hyperlipidemia($p = 0.068$) between CSVD and control group. There was statistically significant difference in regard to WMH rating ($p = 0.00017$) between 2 groups.

We investigated the change of PI and PSV among both CSVD group and control group during 30 min acupuncture intervention.

Fig. 1 and Fig. 2 showed the results of PI changes of CSVD group and control group, respectively.

At baseline, CSVD group had a higher PI than control group (1.75 ±0.88 vs 1.64±0.46). A steady trend of PI change was noted in CSVD group while a decreasing trend of PI change was found in control group. There was no statistically significant change of PI in the CSVD group (1.75±0.88 to 1.84±0.94, $p = 0.651$) during needle retention up to removal. In contrast, there was a significant decreasing in PI in the control group (1.64±0.46 to 1.36±0.33, $p = 0.03$) during needle retention up to removal, and reached a maximum decrease of 22% at 20 min of needle retention. In order to highlight exactly where the significant change occur in PI in the control group, a post-hoc test was adopted. As multiple comparison was taken in the post hoc test, p value will be adjusted to the smallest familywise significance level at which a particular comparison will be declared. And a post-hoc test showed statistically significant decrease in PI in the control group was at 20 min of needles retention. ($p = 0.002$, <0.024(Adjusted significance)).

Fig. 3 and Fig. 4 showed the results of PSV change of MCA among CSVD and control groups, respectively.

At baseline, control group had a higher PSV than CSVD group (82.76 ±25.85 cm/s vs 63.55±23.57 cm/s,). An increasing trend of PSV change was noted in CSVD group while a steady trend of PSV change was found in control group. There was a statistically significant increase of PSV in CSVD group (63.55±23.57 cm/s to 81.14±29.40 cm/s, $p = 0.000439$) during needle retention up to removal and reached a maximal increase of 39% at 20 min. There was no significant change of PSV in the control group (82.76±25.85 cm/s to 75.88±25.11 cm/s, $p = 0.379$) during needle retention up to removal.

There was a statistically significant change in PSV in CSVD group ($p = 0.000439$, <0.05; 95% CI); post-hoc test showed statistically significant increase in PSV at 20 min ($p = 0.0004$, <0.0005 (Adjusted significance)), 30 min ($p = 0.001$, <0.015(Adjusted significance)) and needle removal ($p = 0.001$, <0.009(Adjusted significance))

Table 2
Demographic data of the participants.

		CSVD group	HC group	P value
Gender	Male (%)	7 (70%)	3 (30%)	$P = 0.074$
	Female (%)	3 (30%)	7 (70%)	
Age (Mean±*S*.D)		80±6.25	71.5 ± 3.5	$P = 0.104$
Diabetes (%)		4 (40%)	3 (30%)	$P = 0.639$
Hypertension (%)		4 (40%)	5 (50%)	$P = 0.653$
Hyperlipidemia (%)		8 (80%)	4 (40%)	$P = 0.068$
WMH rating	0 (%)	0	4 (40%)	$P = 0.00017$
	1 (%)	0	6 (60%)	
	2 (%)	4 (40%)	0	
	3 (%)	6 (60%)	0	

*CSVD, cerebral small vessel disease; †HC, healthy control; ‡CI, confidence intervals; S.D, standard deviation; WMH, white matter hyperintensity.

5. Adverse event

Minor bleeding at the needle sites was found in 5 cases (20%). Bleeding was stopped immediately on their own and no discomfort was reported. No other adverse events were reported during or after the procedure.

6. Discussion

This was the first study investigating the effect of acupuncture on cerebral hemodynamics in CSVD. During our acupuncture intervention among subjects with CSVD, we observed an increase in PSV suggesting an increase in cerebral blood flow. However, this was not associated with any significant change in PI, suggesting the effect upon distal vascular resistance was neutral. Therefore, it is likely that our acupuncture intervention may improve cerebral perfusion without affecting distal vascular resistance in CSVD subjects. In subjects without significant CSVD, we observed a decrease in PI, suggesting an improvement in vascular resistance, yet without apparent change in PSV.

Our pilot study showed an interesting finding about our acupuncture prescription in CSVD and normal elderly subjects. An increase in PSV was found only in CSVD subjects but not in normal elderly subjects. We postulated that the increase in PSV associated with acupuncture observed in CSVD subjects could reflect that the cerebral autoregulation was impaired in those with CSVD, whereas in relatively healthy subjects with intact cerebral autoregulation, any rise in cerebral blood flow would be counteracted by the intact cerebral autoregulation [28].

Note that previous study showed that acupuncture could induce an increase in cerebral blood flow when applied in normal subjects[29], which was different to that observed in our present study. This difference might be related to the difference in acupoints selected between the studies. It has been established that the cerebral effects of acupuncture vary with the specific acupoints selected[30–33]In the present study, we selected our acupoints based on previous clinical studies that showed a potential benefit in subjects with CSVD [10,19-25]. To our knowledge, the present study was the first to investigate the cerebral hemodynamics of these specific acupoints in subjects with CSVD and in normal elderly subjects.

On the other hand, a drop in PI without apparent change in PSV during our acupuncture intervention was observed in healthy subjects, suggesting a reduction in distal vascular resistance, which might be related to vasodilation and/or an improvement in arteriole elasticity, resulting in a rise in end diastolic velocity. Note that our control group subjects were also at risk of further developing of CSVD, as these subjects carried risk factors such as aging, diabetes, hypertension and/or hyperlipidemia. Our findings suggested that our acupuncture prescription may improve distal vascular resistance in subjects with no or with insignificant CSVD. A larger study should be conducted in the future. Whether our acupuncture prescription could help to prevent development of severe CSVD among at risk subjects is worth exploring.

Noteworthy is that the maximal benefit of our acupuncture intervention in improving PSV among CSVD subjects or improving PI among control subjects was seen at around 20 min. This suggests that the time from start of acupuncture to maximal effects upon the cerebral blood flow may take around 20 min. This provides a reference for determining

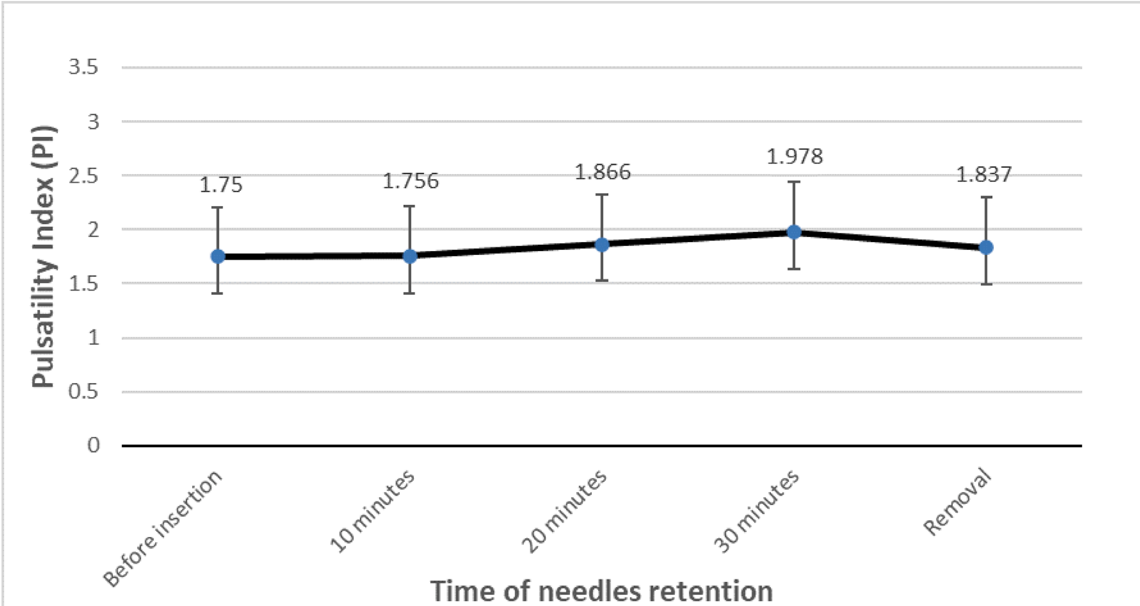

Fig. 1. PI values (means±*S*.D) among CSVD group during 30 min acupuncture intervention.

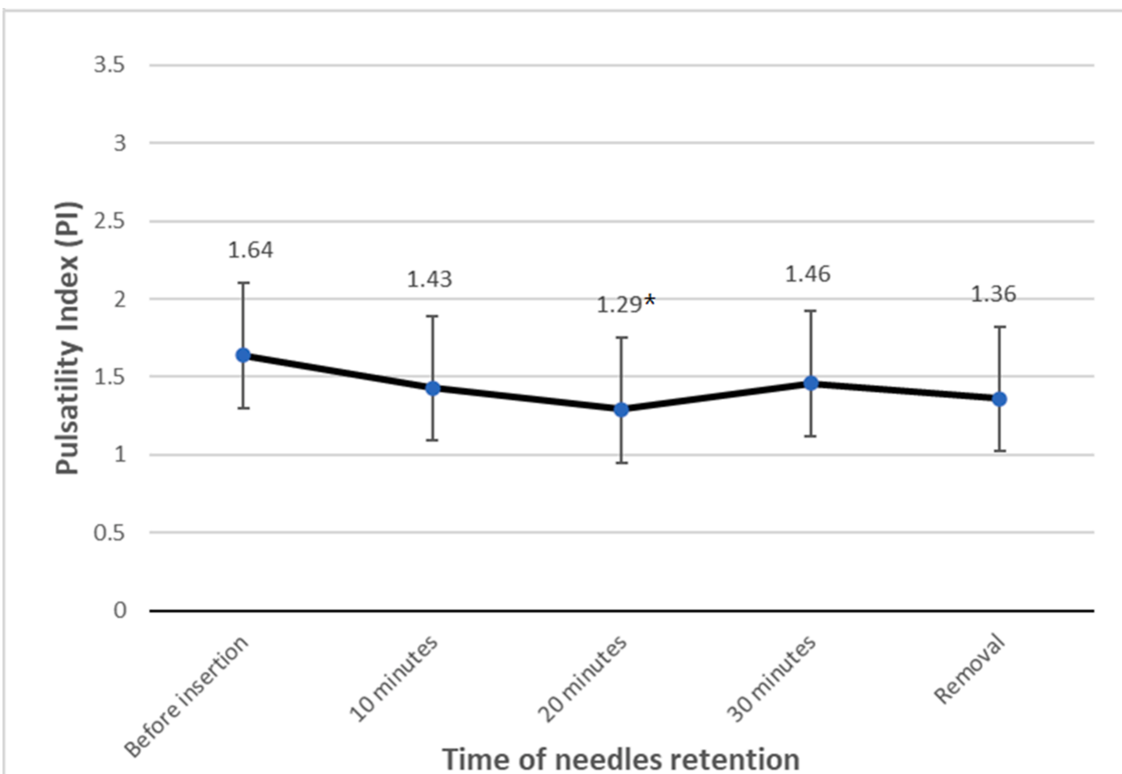

Fig. 2. PI values (means±*S*.D) among control group during 30 min acupuncture intervention. *implies $p<0.05$.

the minimal duration of each acupuncture session in CSVD subjects.

We acknowledged several limitations of this study. First, our sample size was small, outcomes could be strongly influenced by individual subject-related factors. Second, our study was an open-label design and we could not rule out placebo effects. Third, we did not have a true control group. The effect of our acupuncture intervention cannot be compared to those receiving sham acupuncture. Fourth, our study only underwent a single session of acupuncture, while in TCM, several sessions of acupuncture are usually needed to achieve a full clinical effect. Fifth, some confounding factors that may influence the result could not be ruled out, such as subjects' smoking status, pain status, and their use of statins and antihypertensive drugs, which were not captured in our study. Sixth, TCD-derived PI and PSV are only fair surrogates for intracranial pulsatility and CBF, respectively. Ideally, other more accurate imaging methods, such as MRI based technologies should be used for evaluating intracranial pulsatility and cerebral blood flow [34,35].

Last, we did not measure the clinical effects (e.g., cognitive performance) of the subjects. Hence, we were not able to determine whether

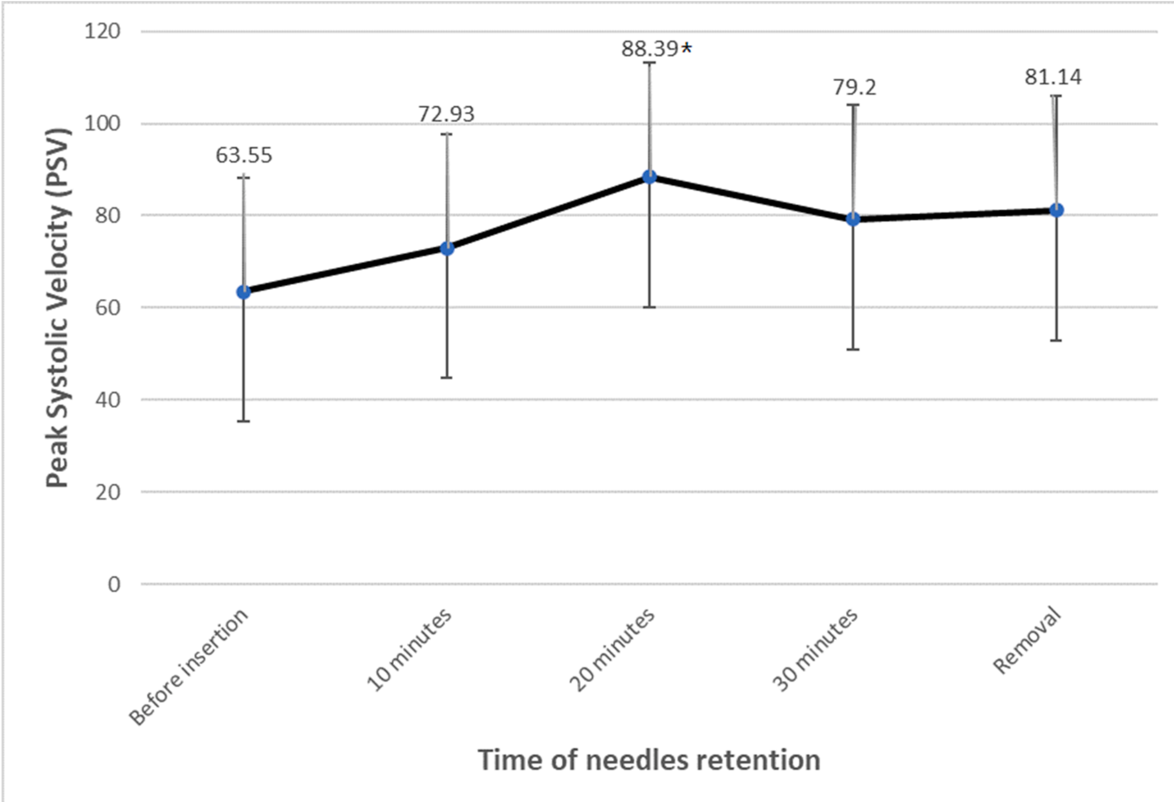

Fig. 3. PSV values (means±*S*.D) among CSVD group during 30 min acupuncture intervention. *implies $p<0.05$.

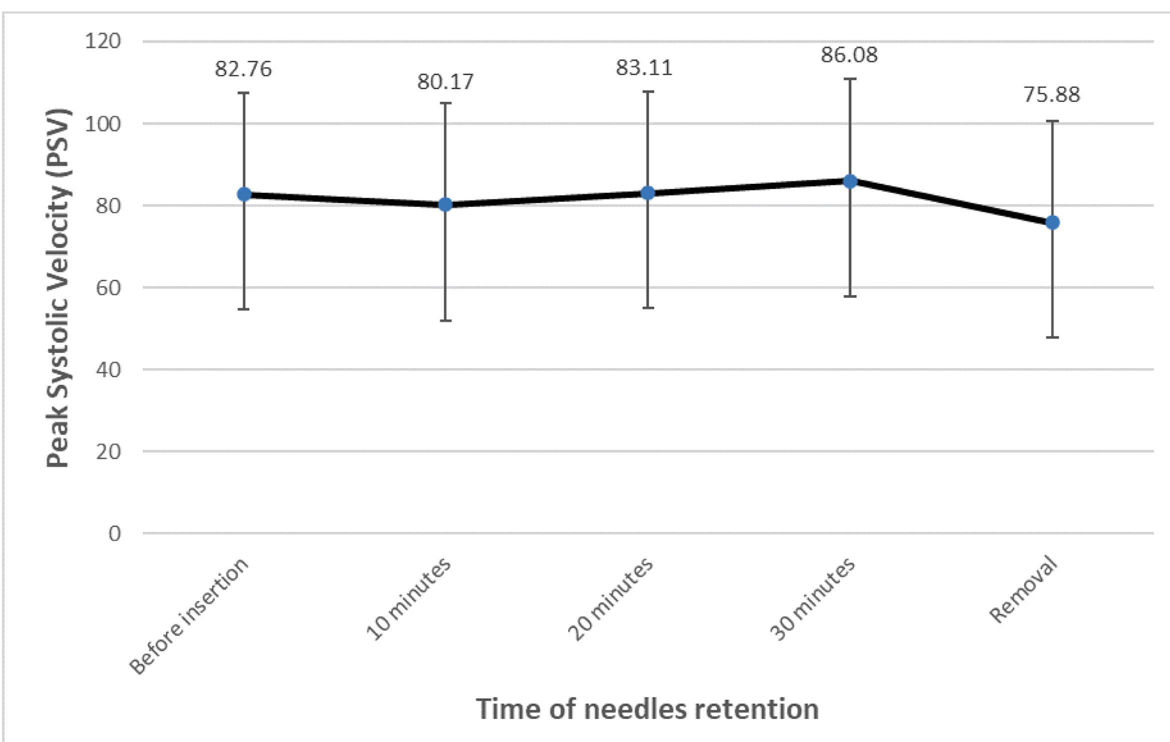

Fig. 4. PSV values (means±*S*.D) among control group during 30 min acupuncture intervention.

the change in cerebral hemodynamics was associated with improvement or worsening of clinical outcomes.

7. Conclusion

From this pilot study, our acupuncture prescription may be able to improve cerebral blood flow without affecting distal vascular resistance in subjects with established moderate to severe CSVD. In subjects with no or insignificant CSVD, our acupuncture intervention may help mainly in reducing distal vascular resistance. As such, our acupuncture prescription may have the potentials of preventing development of CSVD. A larger clinical trial including multiple sessions of acupuncture, cognitive outcomes and sham acupuncture group over a longer period of time upon CSVD and those without CSVD, respectively is needed to confirm our findings.

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Declaration of Competing Interest

None

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Nil

Reference

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