Acupuncture and Acupressure Applied on the Extra-1 (*Yintang*) Acupoint in Healthy Volunteers Do Not Affect Regional Cerebral Blood Flow as Assessed by the Pulsatility Index: A Cohort Observational Study

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ABSTRACT

Objective: Acupressure applied on the Extra-1 (*Yintang*) point decreases bispectral index (BIS) values and stress in healthy volunteers. The current authors hypothesized that acupressure and/or acupuncture could alter regional cerebral oxygenation as expressed by middle cerebral-artery velocity. This study was conducted to test that hypothesis.

Materials and Methods: After giving written informed consent, healthy volunteers received, randomly, (1) acupressure on the Extra-1 (*Yintang*) point, (2) acupressure on a sham point lying 2 cm over the lateral end of the right eyebrow, (3) no acupressure, or (4) modified manual acupuncture on the Extra-1 (*Yintang*) point. Each intervention lasted 10 minutes, except for acupuncture, which lasted for 20 minutes. The flow velocity of the left middle cerebral artery—as expressed by the Pulsatility Index (PI), heart rate (HR), and hemoglobin oxygen saturation (SpO₂)—was recorded before each intervention, every 2 minutes during the intervention, and 10 and 70 minutes after the end of the intervention. A 2-MHz hand-held probe of a transcranial Doppler system (Companion II Micro TCD Nikolet Biomedical Inc., Madison, WI) was used to isolate the left middle cerebral artery via a transtemporal approach.

Results: There was no difference among the four interventions at any timepoint in PI ($P=0.431$; $F=0.929$), HR ($P=0.948$; $F=0.121$), and SpO₂ ($P=0.708$; $F=0.465$), as well as in systolic arterial pressure ($P=0.857$; $F=0.255$) or diastolic arterial pressure ($P=0.991$; $F=0.036$).

Conclusions: There were no changes in PI measurements when acupuncture or acupressure was applied on the Extra-1 (*Yintang*) point once and for a limited time duration.

Keywords: acupuncture, acupressure, transcranial Doppler, cerebral oximetry

INTRODUCTION

ACUPUNCTURE AND RELATED INTERVENTIONS interfere with processes governed by the nervous system, such as pain, anxiety, and cognitive function. In rats anesthetized with propofol, electroacupuncture (EA) ameliorated post-

anesthesia cognitive dysfunction. This neuroprotective effect of EA was attributed to reversal of the decrease of 3 β [pGSK-3 β] in the hippocampus.¹

Acupressure and acupuncture application on the Extra-1 (*Yintang*) acupoint ameliorated anxiety and decreased bispectral index (BIS) values in both volunteers and patients

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scheduled for surgery.²⁻⁶ The method is simple and is acceptable to patients. However, a healthcare provider with experience in acupuncture is required.

These results were reproduced in healthy volunteers and extended by further applications of manual acupressure, acupuncture, and laser-needle acupuncture on the same acupuncture and sham points. Recordings were obtained for changes in the BIS as well as in the left and right spectral-edge frequency values.³ The decreases in BIS and spectral-edge frequency values due to these interventions on the Extra-1 (*Yintang*) point were significant and clinically relevant. The changes observed after the same interventions at the control point were statistically significant but not clinically important. In a randomized controlled trial, acupuncture application for 15 minutes on the Extra-1 (*Yintang*) point was associated with a within-group decrease in BIS values.⁴

Agarwal et al.⁷ applied acupressure similarly as in the previous studies^{2,3} in patients scheduled for elective surgery for 10 minutes after arrival in the preoperative holding area.⁷ These researchers observed significantly lower anxiety and BIS values in patients who were exposed to Extra-1 (*Yintang*) acupressure, compared with patients receiving acupressure on the control point. However, these effects were not detectable 30 minutes after termination of the acupressure. In another study—with parents—pressure on the Extra-1 (*Yintang*) point applied by an acupressure bead decreased preoperative parental anxiety significantly, compared to anxiety reported by parents in a control group, who received similar pressure to a sham point.⁸

The mechanism(s) of how acupressure or acupuncture works has not been elucidated. Release of endogenous peptides and changes of autonomous system activity have been proposed to interpret acupressure/acupuncture effects. Nevertheless, responses of individuals to acupuncture-point stimulation are not uniform and the mode of acupuncture action could be more complex.

In a previous study, researchers could not demonstrate changes in melatonin and β -endorphin levels after acupressure application to the Extra-1 (*Yintang*) point, despite the decreases observed in BIS values.⁵ To the authors' knowledge, none of the previous studies related to Extra-1 (*Yintang*) point stimulation investigated the mechanism of BIS and/or stress decreases. Acupressure and acupuncture on the Extra-1 (*Yintang*) point might cause changes in brain activity expressed by changes in regional cerebral blood flow as assessed by the Pulsatility Index (PI) during, or shortly after, the intervention.

The current authors hypothesized that stimulation of the Extra-1 (*Yintang*) point provokes changes in regional cerebral blood flow. The aim of the current study was to investigate the flow velocity of the left middle cerebral artery as assessed by the PI during acupressure and acupuncture application on the Extra-1 (*Yintang*) point.

MATERIALS AND METHODS

Subjects

After obtaining approval from the institutional review board of the Aretaieio University Hospital, Athens, Greece, 25 healthy right-handed volunteers were enrolled in the study. All volunteers gave written informed consent to participate in the study and were tested the day before to establish an acoustic window using a transcranial Doppler (TCD) system (Companion II Micro TCD Nikolett Biomedical Inc., Madison, WI). Exclusion criteria were body mass index >35, use of anticoagulants, and inability to obtain an acoustic window for the TCD measurements.

Study Design

The study was performed according to the *Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)*.⁹

The procedure and the interventions implemented were explained, during a preliminary visit, to all volunteers who were naïve regarding acupuncture and acupressure effects. Each volunteer was scheduled to receive four interventions, each on a different day as follows: (1) acupressure on the Extra-1 (*Yintang*) point; (2) acupressure on a sham point, 2 cm over the lateral end of the right eyebrow; (3) no acupressure or acupuncture; and (4) modified manual acupuncture on the Extra-1 point (*Yintang*).

During each procedure, the volunteer sat in an armchair and relaxed with eyes closed. Each intervention of the study protocol was applied once, with no other components of treatment, such as EA, moxibustion, or distal acupuncture points. The interventions were 1–2 days apart. Point selection was based on previous studies demonstrating that application of acupressure on the Extra-1 (*Yintang*) point decreased BIS values.^{2,4,5}

The sequence of interventions was randomized, using four different sealed envelopes, with each containing one of the four interventions to be performed.

Acupressure and Placebo Intervention Details

The current authors applied acupressure and acupuncture on the Extra-1 (*Yintang*) point according to Traditional Chinese Medicine to test if these interventions influenced the flow velocity of the left middle cerebral artery. Acupressure was applied similarly as in previous studies, thus, with the thumb of the therapist performing circular movements with a frequency of 20–25 movements per minute.^{2,5}

The reason for these maneuvers was not intended to provide treatment but rather to explore possible mechanisms for reducing BIS values and stress in volunteers after acupressure and acupuncture were applied to the Extra-1 (*Yintang*) point. The current authors hypothesized that these maneuvers might be associated with increases in cerebral

blood flow.^{2,4} All volunteers received the same standardized treatments in a randomized order that was focused on the objective of the study—a possible effect on the cerebral flow. The study design did not require specific responses to acupressure or acupuncture treatment. No other interventions were applied.

The sham acupressure point was located 2 cm from the lateral end of the left eyebrow and has been used in previous studies^{2,5} as a sham point not corresponding to an acupuncture point. This sham point was treated the same way as the Extra-1 (*Yintang*) point was with respect to acupressure application. Acupressure on the Extra-1 (*Yintang*) point and on the sham point lasted for 10 minutes. During the no-acupressure intervention, the volunteer was resting for the same time period without receiving acupressure or acupuncture.

Needling Details

One of the four interventions was acupuncture with 0.25×24-mm, stainless-steel sterile needles (Maja International, Sette, France) at the Extra-1 (*Yintang*) point, which is located at the root of the nose between the medial ends of the two eyebrows. Point selection was based on previous studies demonstrating that Extra-1 (*Yintang*) point acupressure decreased BIS values.^{2,4} Three needles were used instead of 1, with 1 needle on the acupuncture point and 1 needle on each side, needling the same area that was subjected to acupressure. The depth of insertion was ~0.8–1 cm. No manual or electrical needle stimulation or needle manipulations aiming to provoke a feeling of heaviness close to the needle area were performed. Needle-retention time lasted 20 minutes.

The physician who performed acupuncture and acupressure (A.F.) had attended a 2-year accredited course and received a diploma after taking examinations in Athens. She also attended courses in China and has performed and published relevant studies.

Measurements

To measure the flow velocity of the left middle cerebral artery as expressed by the PI, a 2-MHz hand held probe of the TCD system was used to isolate left middle cerebral artery via a transtemporal approach. The PI is calculated by peak systolic velocity minus end diastolic velocity, divided by the mean velocity of the left middle cerebral artery.¹⁰

PI, heart rate (HR), and hemoglobin oxygen saturation (SpO₂) were recorded before each intervention, every 2 minutes during the intervention, and 10 and 70 minutes after the end of the intervention. Noninvasive systolic arterial blood pressure (SAP) and diastolic arterial blood pressure (DAP) were measured before the intervention, and 10 and 70 minutes after the intervention. The current authors did not measure blood pressure (BP) during the measurements period, as inflation of the pressure cuff elicits pain and might have interfered with the measurements.

The primary outcome of the study was the PI measurements 70 minutes after the end of the intervention. Secondary outcomes were the PI measurements before, during, and 10 minutes after the end of each intervention. HR and SpO₂ were recorded at the same timepoints +70 minutes after the end of the intervention, and arterial BP was measured before, and 10 and 70 minutes after each intervention.

Statistics

Data were analyzed per an intention-to-treat analysis.

Patient characteristics, including age, body weight, and height, were analyzed with frequencies. PI, HR, and SpO₂ among the four interventions for all the timepoints measured (before, 2, 4, 6, 8, 10, during, and 10 and 70 minutes after the end of the intervention) were analyzed with analysis of variance (ANOVA) repeated measures. Similarly, SAP and DAP among the four interventions—measured before, and 20 and 70 minutes after the beginning of the intervention—were analyzed with ANOVA repeated measures. An α -level

FIG. 1. Flow diagram of the study.

TABLE 1. PI AT DIFFERENT TIMEPOINTS^a

Intervention	Before	2 min	4 min	6 min	8 min	10 min	+10 min	70 min
AcuPR ^b to Extra-1 (N=21)	0.87±0.21	0.91±0.16	0.91±0.16	0.90±0.12	0.96±0.32	0.95±0.37	0.85±1.34	0.98±0.24
AcuPUN ^b to Extra-1 (N=21)	0.94±0.15	1.18±0.63	1.02±0.35	0.97±0.29	0.89±0.2	0.94±0.27	1.03±0.33	0.99±0.19
Sham (N=21)	0.99±0.27	1.06±0.41	0.96±0.20	1.04±0.47	0.95±0.17	0.94±0.18	0.89±0.17	0.90±0.17
Control ^b (N=21)	0.90±0.16	0.93±0.18	0.92±0.16	0.90±0.19	0.91±0.19	0.91±0.25	0.89±0.18	0.96±0.25

$F=0.929$; $df=3$; $P=0.431$

^aBefore, and 2, 4, 6, 8, and 10 minutes during as well as +10 and 70 minutes after each intervention.

^bAcuPR and AcuPUN were applied to the Extra-1 (*Yintang*) point; control was no acupressure. Values are mean±standard deviation.

PI, Pulsatility Index; min, minutes; AcuPR, acupressure; AcuPUN, acupuncture.

of <0.05 was considered to be statistically significant. Data were analyzed with SPSS (version 22.0, Chicago IL).

RESULTS

Twenty-one patients (8 men and 13 women) completed the study. Their mean age was 37 ± 9.9 years, mean body weight was 49 ± 15 kg, and mean height was 156 ± 8.4 cm. In 1 patient, arterial BP and SpO₂ measurements were not accomplished due to technical reasons. Patient dropouts are shown in the flow diagram of the study (Fig. 1).

The PI did not differ among the four interventions ($F=0.929$; $df=3$; $P=0.431$). See Table 1. Similarly, no significant changes were observed among the four interventions regarding HR ($F=0.121$; $df=3$; $P=0.948$)—see Table 2—or SpO₂ ($F=0.465$; $df=3$; $P=0.708$)—see Table 3—measured and recorded at the predetermined timepoints. In addition, the four interventions had no effect on SAP ($F=0.255$; $df=3$; $P=0.857$) or DAP ($F=0.036$; $df=3$; $P=0.991$). See Table 4.

DISCUSSION

The results of the present study did not demonstrate changes in the PI and, therefore, in the flow in the middle cerebral artery during acupuncture or acupressure of the Extra-1 (*Yintang*) point as assessed by TCD. Patients' he-

modynamics did not change significantly during the same timepoints that the PI was recorded.

The effect of acupressure and acupuncture applied on the Extra-1 (*Yintang*) acupuncture point on BIS values and anxiety has been evaluated in both healthy volunteers and surgical patients.⁵ In healthy volunteers, acupressure applied on the Extra-1 (*Yintang*) acupuncture point for 10 minutes decreased BIS values and enhanced sedation scores, compared to the values obtained after pressure application on a sham point.² However, application of acupressure on the Extra-1 (*Yintang*) point for 10 minutes had no effect on the volunteers' melatonin or β -endorphin levels at the end of the intervention as well as 1 hour later.⁵

In a preliminary study of 18 subjects with symptoms of insomnia, 10 sessions of acupuncture, each of 1-hour duration, implemented for 5 weeks reduced volunteers' sleep disturbances. State- and trait-anxiety scores were decreased. Increases in nocturnal endogenous melatonin secretion, as measured by concentrations of aMT6s [6-sulfur toxy-melatonin], a major melatonin metabolite, in urine were noted.¹¹ However, the investigators did not name the stimulated acupuncture points used.

In 1 study, healthy patients scheduled for minor or moderate surgery who received acupuncture, the evening before the procedure, on the Extra-1 (*Yintang*) point or on a sham point showed decreased BIS values in the group receiving acupuncture on the Extra-1 (*Yintang*) point, but a decrease in anxiety was observed in both groups.⁴

The mechanism of sedation produced by stimulation of the Extra-1 (*Yintang*) point with acupressure or acupuncture

TABLE 2. HR AT DIFFERENT TIMEPOINTS^a

Intervention	Before	2 min	4 min	6 min	8 min	10 min	+10 min	70 min
AcuPR ^b to Extra-1 (N=20)	80±12.4	75±11	75±11.8	74±12	76±12.8	74±11.5	77±11	77±10.2
AcuPUN ^b to Extra-1 (N=20)	84±11	75±12	74±12	75±11	74±11.7	75±12	75±10.5	77±11.9
Sham (N=20)	79±11.4	75±9	76±10	76±10.3	76±10.2	76±10.6	78±9.3	79±11.4
Control ^b (N=20)	75±11.8	73±11	74±10.3	74±11	75±11.5	74±10.6	77±11.7	77±11.5

$F=0.121$; $df=3$; $P=0.948$.

^aBefore, and 2, 4, 6, 8, and 10 minutes during as well as +10 and 70 minutes after each intervention.

^bAcuPR and AcuPUN were applied to the Extra-1 (*Yintang*) point; control was no acupressure. Values are mean±standard deviation.

HR, heart rate; min, minutes; AcuPR, acupressure; AcuPUN, acupuncture.

TABLE 3. SpO₂ AT DIFFERENT TIMEPOINTS^a

Intervention	Before	2 min	4 min	6 min	8 min	10 min	+10 min	70 min
AcuPR ^b to Extra-1 (N=20)	99±1.1	98±0.9	98±1	97±1	97±0.8	98±0.8	98±1.2	98±0.8
AcuPUN ^b to Extra-1 (N=20)	98±0.6	98±1	98±0.8	98±1	98±0.9	98±0.9	98±1.1	98±0.9
Sham (N=20)	98±1.1	97±0.9	97±0.8	97±0.8	97±0.9	97±0.8	98±0.9	98±0.7
Control ^b (N=20)	98±1	97±0.9	97±1	97±0.9	98±0.9	97±1.3	98±0.9	98±0.7

$F=0.465$; $df=3$; $P=0.708$.

^aBefore, and 2, 4, 6, 8, and 10 minutes during as well as +10 and 70 minutes after each intervention.

^bAcuPR and AcuPUN were applied to the Extra-1 (Yintang) point; control was no acupressure. Values are mean±standard deviation.

SpO₂, hemoglobin oxygen saturation; min, minutes; AcuPR, acupressure; AcuPUN, acupuncture.

stimulation remains unknown. HR variability (HRV) is considered to provide information about the autonomic system's impact on the HR. In female volunteers acupressure on the Extra-1 (Yintang) point decreased needle insertion pain and the low-frequency/high-frequency (LF/HF) ratio related to needle insertion, which indicated decreased sympathetic nerve activity.¹² In volunteers of both genders, electroencephalogram spectral entropy was reduced after application of 5 minutes of acupressure on the Extra-1 (Yintang) point, with values significantly lower than those noted in a control group. The overall values for the LF/HF ratio of the HRV were decreased, but analysis for each gender showed significant decreases only for the female volunteers.⁶

A meta-analysis including 51 experiments of acupoint stimulations and 10 placebo experiments of nonpenetrating needles or superficial pricking with von Frey filaments, using functional magnetic resonance imaging (fMRI), showed that acupoint stimulation activated brain areas involved in various types of pain sensations and deactivated the limbic–

paralimbic–neocortical areas. Thus, puncturing acupoints could be associated with hemodynamic changes in the brain reflecting various aspects of pain.¹³

Electrical stimulation applied on the LI 4 (Hegu) acupuncture point with maximal but pain-free intensity caused changes in the limbic system and subcortex, which, however, deviated from changes observed with LF electrical stimulation for some brain areas. A number of studies have explored the effects of HF/LF of cerebral blood flow and bold signals using fMRI.¹⁴

Limitations of the present study was the short time course for each intervention and that the intervention was applied only once. Another limitation was the limited duration of monitoring of the mean velocity flow of the left middle cerebral artery. In addition, the effect of a single acupuncture point on a limited brain area was investigated, as this method allowed measuring only the mean velocity of the left middle cerebral artery. Another limitation that can be considered is the lack of concurrent BIS monitoring and recording due to technical reasons. However, the effect of acupressure and acupuncture on the BIS has been previously demonstrated and reproduced in several studies.^{2–6} In a previous study,⁶ the current authors could not demonstrate changes in melatonin or β -endorphin blood levels after applying acupressure on the Extra-1 (Yintang) point, but this result could have been due to the great variability of melatonin values or the lack of adequate power. Further studies on the mechanism of acupressure on the Extra-1 (Yintang) point may be performed, using fMRI to map different brain areas.

Strengths of the study are that each volunteer received, in a random order, all four interventions, thus, minimizing interindividual variability. In addition, both acupressure and acupuncture interventions were used. The acupuncture and sham points that were used have been studied extensively in previous studies involving the current investigators and other investigators.

CONCLUSIONS

In the present study, the results showed that stimulation of the Extra-1 (Yintang) point by acupuncture or acupressure,

TABLE 4. SAP AND DAP (IN MM HG) AT DIFFERENT TIMEPOINTS^a

Intervention	Before	+ 10 min	70 min
SAP			
AcuPR ^b to Extra-1 (N=20)	119±10	118±10.3	121±10.9
AcuPUN ^b to Extra-1 (N=20)	118±16.86	116±10.4	117±11.09
Sham (N=20)	121±11.7	115±11.4	120±15.9
Control ^b (N=20)	113±27.1	117±12	118±15.2
$F=0.255$; $df=3$; $P=0.857$.			
DAP			
AcuPR ^b to Extra-1 (N=20)	78±8.2	79±8.7	75±10.8
AcuPUN ^b to Extra-1 (N=20)	79±11.8	79±8	79±10.8
Sham (N=20)	79±10.2	79±12	76±10.9
Control ^b (N=20)	79±11.1	80±11	75±10.8
$F=0.036$; $df=3$; $P=0.991$.			

^aBefore, +10, and 70 minutes after each intervention.

^bAcuPR and AcuPUN were applied to the Extra-1 (Yintang) point; control was no acupressure. Values are mean±standard deviation.

SAP, systolic arterial pressure; DAP, diastolic arterial pressure; min, minutes; AcuPR, acupressure; AcuPUN, acupuncture.

both once and for a short period of time, had no effect on regional blood flow, as assessed by the PI measured by means of TCD.

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AUTHOR DISCLOSURE STATEMENT

No financial conflicts of interest exist.

REFERENCES

1. Liu Y, Wang XJ, Wang N, Cui CL, Wu LZ. Electroacupuncture ameliorates propofol-induced cognitive impairment via an opioid receptor-independent mechanism. *Am J Chin Med*. 2016;44(4):705–719.
2. Fassoulaki A, Paraskeva A, Patris A, Pourgiezi T, Kostopanagiotou G. Pressure applied on the Extra 1 acupuncture point reduces bispectral index values and stress in volunteers. *Anesth Analg*. 2003;96(3):885–890.
3. Litscher G. Effects of acupressure, manual acupuncture and laser needle acupuncture on EEG bispectral index and spectral edge frequency in healthy volunteers. *Eur J Anaesthesiol*. 2004;21(1):13–19.
4. Paraskeva A, Melemenis A, Petropoulos G, Siafaka I, Fassoulaki A. Needling of the Extra 1 point decreases BIS values and preoperative anxiety. *Am J Chin Med*. 2004;32(5):789–794.
5. Fassoulaki A, Paraskeva A, Patris A, Kostopanagiotou G, Tsakalozou E, Markantonis S. Acupressure on the Extra 1 acupoint: The effect on bispectral index, serum melatonin, plasma β -endorphin, and stress. *Anesth Analg*. 2007;104(2):312–317.
6. Arai Y-CP, Ushida T, Matsubara T, et al. The influence of acupressure at Extra 1 acupuncture point on the spectral entropy of the EEG and the LF/HF ratio of heart rate variability. *Evid Based Complement Alternat Med*. 2011;2011:503698.
7. Agarwal A, Ranjan R, Dhiraaj S, Lakra A, Kumar M, Singh U. Acupressure for prevention of pre-operative anxiety: A prospective, randomised, placebo controlled study. *Anaesthesia*. 2005;60(10):978–981.
8. Wang S-M, Gaal D, Maranets I, Caldwell-Andrews A, Kain ZN. Acupressure and preoperative parental anxiety: A pilot study. *Anesth Analg*. 2005;101(3):666–669.
9. MacPherson H, Altman DG, Hammerschlag R, et al., on behalf of the STRICTA Revision Group. Revised *ST*andards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement. *PLoS Med*. 2010;7(6):e1000261.
10. Naqvi J, Yap KH, Ahmad G, Ghosh J. Transcranial Doppler ultrasound: A review of the physical principles and major applications in critical care. *Int J Vasc Med*. 2013;2013:629378.
11. Spence WD, Kayumov L, Chen A, et al. Acupuncture increases nocturnal melatonin secretion and reduces insomnia and anxiety: A preliminary report. *J Neuropsychiatry Clin Neurosci*. 2004;16(1):19–28.
12. Arai Y-CP, Ushida T, Osuga T, et al. The effect of acupressure at the Extra 1 Point on subjective and autonomic responses to needle insertion. *Anesth Analg*. 2008;107(2):661–664.
13. Chae Y, Chang D-S, Lee S-H, et al. Inserting needles into the body: A meta-analysis of brain activity associated with acupuncture needle stimulation. *J Pain*. 2013;14(3):215–222.
14. Zhang Y, Glielmi CB, Jiang Y, et al. Simultaneous CBF and BOLD mapping of high frequency acupuncture induced brain activity. *Neurosci Lett*. 2012;530(1):12–17.

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