

# Acupuncture attenuates postoperative inflammation in patients after craniotomy

## A prospective, open-label, controlled trial

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### Abstract

**Background:** It is important to manage inflammation after craniotomy. It may be prudent to reduce the excessive usage of antibiotics and to add supplementary treatments like acupuncture, which would be effective and safe. However, there are only a few studies available to date on the effects of acupuncture on anti-inflammatory response after craniotomy. The aim of this study was to explore the anti-inflammatory effects of acupuncture in patients after a craniotomy.

**Methods:** This study was a single-center, prospective, open-label, controlled trial. Forty-four subjects who underwent craniotomy for an unruptured aneurysm, facial spasm, or brain tumor were allocated to either an acupuncture group or a control group. Both groups received postoperative routine care in the Department of Neurosurgery. The subjects in the acupuncture group also received a total of 6 acupuncture treatments sessions within 8 days after craniotomy. Acupuncture treatments included acupuncture, electroacupuncture, and intradermal acupuncture. The serum interleukin (IL)-1 $\beta$  and IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), C-reactive protein (CRP), and erythrocyte sedimentation rate levels were assessed four times within 7 days after surgery. The presence of fever, use of additional antibiotics, presence of infection including pneumonia or urinary tract infection, and safety were also reviewed.

**Results:** The IL-1 $\beta$  levels of subjects who underwent aneurysmal clipping were significantly lower in the acupuncture group ( $P = .02$ ). TNF- $\alpha$  levels of subjects who underwent aneurysmal clipping at the seventh postoperative day were also significantly lower in the acupuncture group ( $P = .03$ ). Six cases of fever of unknown origin were observed in the control group, while none were seen in the acupuncture group, revealing that the incidence of fever was significantly lower in the acupuncture group ( $P = .02$ ). No adverse events occurred during the trial.

**Conclusion:** Acupuncture showed a possibility of alleviating inflammation by attenuating the levels of proinflammatory cytokines and significantly reduced the incidence of fever of unknown origin in patients after craniotomy. Acupuncture would be suitable as an adjunctive therapy to alleviate inflammation after craniotomy.

**Abbreviations:** ANCOVA = analysis of covariance, CRP = C-reactive protein, ELISA = Enzyme-linked immunosorbent assay, ESR = erythrocyte sedimentation rate, IL = interleukin, MVD = microvascular decompression, POD = postoperative day, TNF- $\alpha$  = tumor necrosis factor alpha.

**Keywords:** acupuncture, craniotomy, cytokine, electroacupuncture, inflammation, neurosurgery

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## 1. Introduction

A craniotomy is a surgical operation of opening skull which is performed on patients suffering from brain lesions such as brain tumor, facial spasm, and cerebral aneurysm. Complications such as infection, pneumonia, or brain swelling can occur following craniotomy.<sup>[1]</sup>

Antibiotic therapy has significantly reduced the incidence of surgical-site infections, but antibiotic resistance and antibiotic-induced complications such as kidney injury still occur.<sup>[2,3]</sup> Therefore, it is highly recommended to reduce the excessive usage of antibiotics and to add supplementary treatments like acupuncture that are effective and safe. A decrease in the inflammatory response is key for rapid recovery and prevention of complications after surgery.

To date, there have been some acupuncture studies conducted involving patients after craniotomy, but most of them have focused on controlling pain,<sup>[4]</sup> postoperative nausea and vomiting,<sup>[5]</sup> and alleviating intraoperative immunosuppression.<sup>[6]</sup> There are only a few studies available on the effects of acupuncture on the anti-inflammatory response after a craniotomy. Therefore, in the present study, we sought to explore the anti-inflammatory effects of acupuncture by measuring the levels of inflammatory cytokines interleukin (IL)-1 $\beta$ , IL-6, tumor necrosis factor alpha (TNF- $\alpha$ ), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) in patients after craniotomy.

## 2. Methods

### 2.1. Ethics

This study was carried out in accordance with the Declaration of Helsinki and the Korean Good Clinical Practice Guidelines. It was approved by the ethical committee of Kyung Hee University Hospital at Gangdong (KHNMC-OH-IRB 2016-01-005) and has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT02761096). Study protocol of this study was published online.<sup>[7]</sup>

### 2.2. Participants

**2.2.1. Inclusion criteria.** Subjects were required to meet all of the following criteria to be included:

- (1) scheduled to undergo a regular craniotomy operation performed for aneurysmal clipping of unruptured aneurysm, microvascular decompression (MVD) for hemifacial spasm, or removal of brain tumor;
- (2) a maximal diameter of craniotomy larger than 3 cm for a supratentorial or infratentorial lesion;
- (3) age > 18 years;
- (4) agreement that acupuncture treatment can start within 48 hours after craniotomy; and
- (5) voluntary participation and provision of a signed informed consent form.

**2.2.2. Exclusion criteria.** Conversely, subjects who met any of the following conditions were excluded:

- (1) serum CRP level  $\geq$  1.0 mg/dL within two days before the craniotomy;
- (2) those with a condition other than unruptured aneurysm, facial spasm, or brain tumor as an indication for craniotomy;
- (3) those who underwent craniotomy for an infectious brain disease such as brain abscess or subdural empyema;

- (4) those currently using medication that can affect the immune system or white blood cell count, such as antibiotics, immunosuppressive drugs, steroids, or anticancer drugs, or having used these medications within one month prior to the craniotomy;
- (5) those with a history of surgery at the same site;
- (6) those undergoing emergency surgery;
- (7) those with a severe concurrent medical disease, such as congestive heart failure, chronic renal failure, or autoimmune disorder;
- (8) those with a pacemaker or implantable cardioverter-defibrillator; or
- (9) anyone who was pregnant.

### 2.3. Trial design

This study was a single-center, prospective, open-label, non-randomized controlled trial. The clinical trial was conducted at Kyung Hee University Hospital in Gangdong, Seoul, Korea. Patients who were scheduled to undergo craniotomy for an unruptured aneurysm, facial spasm, or brain tumor were considered for this study. In this study, inflammation after surgery to open the skull was focused, so three different kinds of operation were included. After written informed consent was obtained, eligible patients were allocated to an acupuncture group or a control group according to intention. Patients who agreed to receive additional acupuncture treatment were allocated to the acupuncture group. Regardless of the type of operation, subjects were recruited until 22 patients were recruited in one group, and then another group was recruited according to the operation type of that group.

### 2.4. Intervention

Both groups received postoperative routine care in the Department of Neurosurgery. The conventional treatment protocol included general management methods in the Department of Neurosurgery such as pain control, perioperative antibiotic prophylaxis, and other intravenous fluid or oral drug therapy required based on the condition of the subject.

In addition, the subjects in the acupuncture group also received acupuncture treatments, beginning after the craniotomy. The acupuncture treatment started within 48 hours after the craniotomy and was administered once a day for 6 days (for a total of 6 sessions within 8 days). All interventions were performed by one Korean Medicine doctor with more than 5 years of working experience and with a college education of 6 years. The doctor was trained in the study protocol prior to the start of the trial. Since there was no previous study investigating the effect of acupuncture on postoperative inflammation after craniotomy, the acupuncture points were selected with reference to studies reporting anti-inflammatory effect of acupuncture.<sup>[8–10]</sup>

Acupuncture, electroacupuncture, and intradermal acupuncture were performed during each session. Sterile disposable stainless steel acupuncture needles (0.25 mm  $\times$  30 mm; Dong Bang Acupuncture Inc., Chungnam, Korea) were used. Acupuncture needles were inserted at the following acupuncture points: LI4, LI11, and PC6 on both sides, which are located in the upper extremity; ST36, GB39, and LR3 on both sides, which are located in the lower extremity; and GV20, which is located at the top of the middle part of the head. If GV20 was too close to

the surgical site, needle insertion there was skipped. After insertion to a depth of approximately 0.5 cm to 1.5 cm, the needles were manually stimulated until attainment of *deqi*, which is a subjective experience in which subjects feel multidimensional and intense needling sensations such as numbness, soreness, distention, heaviness, dull pain, and sharp pain during acupuncture stimulation that indicates effective needling. At the same time, an electric stimulator (ES-160; ITO Co., Tokyo, Japan) was connected to the handle of each needle at LI4 to LI11 and ST36 to LR3. A current of 5 Hz was applied. The current intensity was increased until light muscle contraction was evident and reached approximately 70% of the bearable intensity. The needles were left in place for 15 minutes and then removed. The practitioner regulated the intensity if there was a request from the subjects.

After the needles were removed, intradermal acupuncture needles with tape (DB130A, 0.25 mm × 1.5 mm; Dong Bang Acupuncture Inc., Chungnam, Korea) were inserted at the same acupoints (i.e., LI4, LI11, PC6, ST36, GB39, and LR3 bilaterally and GV20) and left in place until the next session.

### 2.5. Dropout criteria

Subjects who met any of the following criteria were excluded from the final study analysis:

- (1) missed more than one session (out of a total of 6);
- (2) need for a repeat operation or other type of surgery;
- (3) development of serious neurological deficits after the surgery and/or a significantly worse level of consciousness and motor skills compared with in the preoperative condition;
- (4) nonconventional antibiotics received immediately after surgery;
- (5) withdrawal of consent;
- (6) development of serious adverse reactions and inability to continue the trial;
- (7) worsening condition in which it is no longer appropriate for the subject to continue to participate in the study (as decided by the investigator); or
- (8) a decision by the principal investigator that it is not possible for the subject to participate in the study as planned.

### 2.6. Measurement

The serum IL-1 $\beta$ , IL-6, TNF- $\alpha$ , CRP, and ESR levels were assessed 4 times within 48 hours before the surgery and at 2, 4, and 7 days after surgery. A blood sample was drawn from the brachial vein at a fixed time in the morning before breakfast. An enzyme-linked immunosorbent assay (ELISA) kit (eBioscience, San Diego, CA) was used to determine the concentrations of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in the samples as recommended by the manufacturer. Turbidimetric immunoassay was performed for measurement of CRP, and the photometrical capillary method was performed for measurement of ESR. Body temperature was measured in the armpits at 6:00, 10:00, 18:00, and 22:00 every day by digital thermometers which use electronic heat sensors to record body temperature.

#### 2.6.1. Outcome measures. Primary outcome measurements:

Changes in serum CRP level from baseline to the 2 days after surgery were compared between the two groups.

Secondary outcome measurements:

1. Changes in serum IL-1 $\beta$ , IL-6, TNF- $\alpha$ , CRP, and ESR levels from baseline to 2, 4, and 7 days after surgery were compared

between the 2 groups, except the serum CRP level from baseline to 2 days after surgery.

2. Fever, defined as a body temperature greater than 38.0°C, was evaluated.
3. Antibiotic use in addition to the conventional antibiotics prescribed after the surgery was considered.
4. Pneumonia was diagnosed by at least 2 symptoms of the 4 needed to be present; fever, cough, dyspnea, and chest pain. An internal medicine doctor diagnosed pneumonia based on these symptoms and the following findings: abnormal bubbling or crackling sounds heard with a stethoscope; findings of a new infiltrate on chest radiograph; or bacteria or fungi in sputum culture.
5. Urinary tract infection was diagnosed if the subject had three or more of the following signs and symptoms: fever ( $\geq 38^\circ\text{C}$ ) or chills; new or increased burning pain on urination, frequency, or urgency; new flank pain or suprapubic pain or tenderness; change in character of urine; or worsening mental or functional status.
6. Other symptoms and findings consistent with an infection were noted.

### 2.7. Safety evaluation

Any adverse events or abnormalities were recorded on the case report forms. Severity was quantified as either mild, moderate, or severe. Events that occurred during or after the intervention were categorized as unrelated, possibly related, or related.

If any serious adverse events did occur, the study was stopped immediately, and appropriate action was taken in the affected patient. This was reported promptly to the institutional review board in accordance with the protocol.

### 2.8. Sample size estimation

The primary outcome of change in serum CRP level from baseline to the second day after surgery was used to calculate the sample size. Power analysis indicated that a sample size of 20 subjects per group was required to detect a serum CRP difference of 3.2 mg/dL with a standard deviation of 3.537 with 80% power and a significance level of 5% in analysis of covariance (ANCOVA). Thus, we enrolled a total of 44 subjects, with 22 in the acupuncture group and 22 in the control group, allowing for a 20% withdrawal rate.<sup>[11]</sup>

### 2.9. Statistical analyses

The statistical analyses were performed by a researcher who was blinded to the allocation. All data were analyzed using the Statistical Package for the Social Sciences software (version 18.0; IBM Corp., Armonk, NY), and the results were presented as mean  $\pm$  standard deviation (SD) or number (%).

The differences in pre- and postsurgery blood test results between the 2 groups were compared using a linear mixed model. The fixed effects were group, time, and group-by-time. Individual was included as a random effect, while baseline result, age, sex, duration of surgery, and type of surgery were included as a covariance structure.

The differences from baseline to 2, 4, and 7 days after surgery between the two groups were compared using ANCOVA. Baseline result, age, sex, duration of surgery, and type of surgery were included as a covariance structure. Exceptionally, when

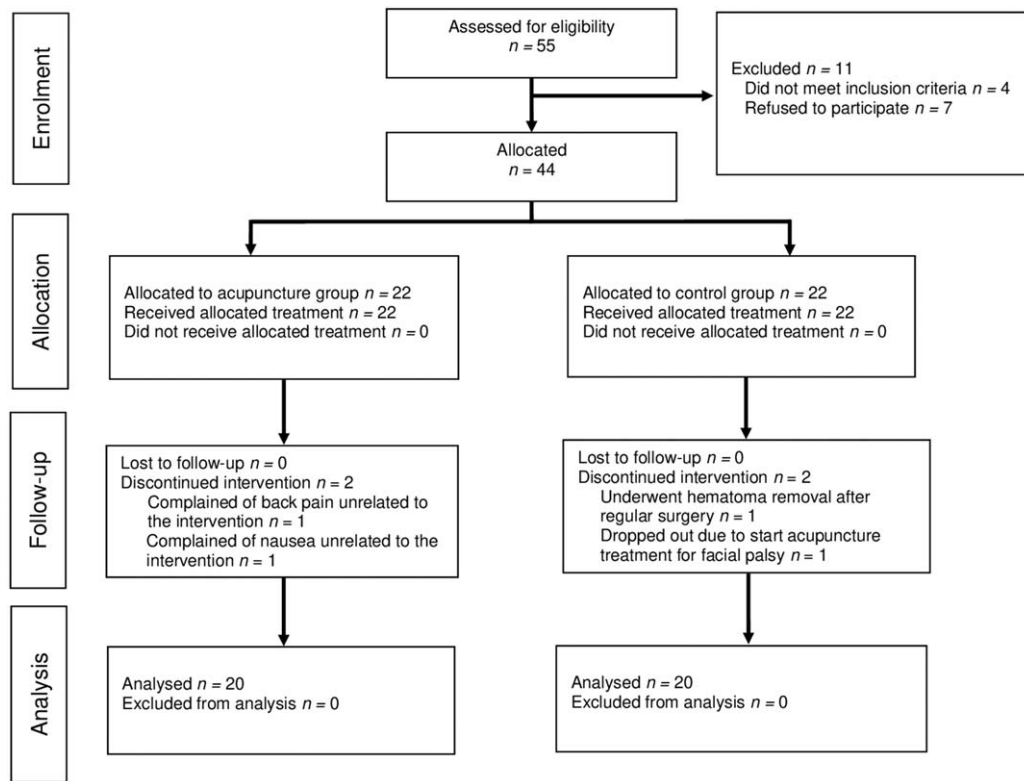


Figure 1. CONSORT diagram for the study.

analyzing a subject who underwent tumor removal, sex was excluded from covariance because the number of subjects who underwent tumor removal was too small.

Following the per-protocol principle, to compare the events of fever; infections such as pneumonia, urinary tract infection, or other diseases; and addition of antibiotics, either the Chi-squared test or Fisher exact test was used.

To compare the duration of surgery; average number of days of altered consciousness; maintenance of Foley catheter, central-line, or tracheal cannula; and sore existence between the two groups, either a *t* test or a Mann-Whitney *U* test was used.

If the data were normally distributed, parametric methods such as Chi-squared test or *t*-test were used; if the data were not normally distributed, nonparametric methods such as Fisher exact test or the Mann-Whitney *U* test were used.

Confidence limits of 95% were calculated, and results with *P* value less than .05 were considered statistically significant.

### 3. Results

A total of 44 subjects (23 subjects of MVD, 14 subjects of aneurysmal clipping, and seven subjects of tumor removal) participated in this trial between March 2016 and September 2017. Twenty-two subjects were assigned to each the acupuncture treatment group and the control group. Four subjects ultimately dropped out (Fig. 1). Two MVD subjects in the acupuncture group were dropped out because it was difficult to continue acupuncture due to postoperative nausea or backpain that had existed before the operation.

There were no significant differences between the groups in terms of baseline characteristics such as age, sex, and duration of

Table 1

#### Baseline characteristics.

	Acupuncture group (n = 22)	Control group (n = 22)	<i>P</i> value
Type of surgery			.911*
MVD	12	11	
Aneurysmal clipping	7	7	
Tumor removal	3	4	
Total surgery			
Age (years)	57.8 ± 11.5	57.3 ± 11.5	.876 <sup>†</sup>
Sex			.517*
Male	8	6	
Female	14	16	
Duration of Surgery (hours)	4.9 ± 2.7	5.1 ± 2.1	.571 <sup>‡</sup>
Microvascular decompression			
Age (years)	52.7 ± 10.9	53.6 ± 11.6	.853 <sup>†</sup>
Sex			.069 <sup>§</sup>
Male	6	1	
Female	6	10	
Duration of Surgery (hours)	3.5 ± 0.5	3.6 ± 0.7	.740 <sup>‡</sup>
Aneurysmal clipping			
Age (years)	65.1 ± 9.9	58.9 ± 11.2	.286 <sup>†</sup>
Sex			1.000 <sup>§</sup>
Male	2	2	
Female	5	5	
Duration of Surgery (hours)	5.4 ± 1.4	5.3 ± 1.5	.857 <sup>†</sup>
Tumor removal			
Age (years)	61.3 ± 9.1	64.8 ± 9.6	.655 <sup>†</sup>
Sex			.143 <sup>§</sup>
Male	0	3	
Female	3	1	
Duration of Surgery (hours)	9.3 ± 5.1	8.5 ± 1.3	.761 <sup>†</sup>

Values are mean ± SD. MVD = microvascular decompression, SD = standard deviation.

\* Statistical comparisons between groups were performed using the Chi-squared test.

<sup>†</sup> Statistical comparisons between groups were performed using *t* test.

<sup>‡</sup> Statistical comparisons between groups were performed using Mann-Whitney *U* test.

<sup>§</sup> Statistical comparisons between groups were performed using Fisher exact test.

**Table 2**  
Existence of fever of unknown origin, pneumonia and urinary tract infection in both groups.

	Acupuncture group (n=20)	Control group (n=20)	P value*
Fever of unknown origin			
Total surgery	0	6	.02†
MVD	0	2	.47
Aneurysmal clipping	0	2	.46
Tumor removal	0	2	.40
Pneumonia	1	0	1.00
UTI	0	0	–

MVD = microvascular decompression, UTI = urinary tract infection.

\* Statistical comparisons between groups were performed using Fisher's exact test.

† P value < .05 vs the control group.

surgery (Table 1). As four subjects dropped out, data for 20 subjects were analyzed in both groups, and there were no significant differences between the groups in baseline characteristics.

Six cases of fever of unknown origin were observed in the control group, while none were seen in the acupuncture group, showing that the incidence of fever was significantly lower in the acupuncture group (P = .02; Table 2). Fever of unknown origin refers to fever (≥38°C) that could not be identified by the following signs and symptoms: surgical site infection findings; common postoperative complications such as pneumonia and UTI; other diseases that can be diagnosed based on general blood tests, radiographs, or symptoms. All fever cases measured between 38 and 39 degrees, and the duration of fever appeared for several hours, while only one case lasted more than 24 hours.

There were no significant differences in the levels of IL-1β, IL-6, TNF-α, CRP, and ESR between the 2 groups, as determined by analyzing the data for all types of surgery (Table 3).

By analyzing the data for subjects who underwent aneurysmal clipping, IL-1β level was found to be significantly lower in the

acupuncture group (P = .02). IL-1β level at postoperative day (POD) 2 were significantly lower in the acupuncture group (P = .03) and showed a tendency to be lower in the acupuncture group at POD 4 and POD 7 (P = .07 at POD 4 and P = .09 at POD 7). In addition, TNF-α level at POD 7 was significantly lower in the acupuncture group (P = .03) and showed a tendency to be lower in the acupuncture group at POD 4 (P = .07; Table 4).

By analyzing IL-1β additionally, it was found that subjects who underwent tumor removal showed a tendency of a difference between the two groups (P = .05), with the subjects of all surgery types at POD 2 showing a tendency of lower IL-1β level in the acupuncture group (P = .07; Table 5).

There were no significant differences between the two groups in terms of clinical characteristics such as use of antibiotics, condition of consciousness, Foley catheter maintenance, central-line maintenance, tracheal cannula maintenance, and sore existence (Table 6).

There were no adverse events that occurred during the trial.

#### 4. Discussion

The key findings of the present study include the potential roles of acupuncture in attenuation of the levels of inflammatory cytokines such as IL-1β after craniotomy and in reducing the incidence of fever of unknown origin. Fever of unknown origin was observed in six cases in the control group, while no instance was observed in the acupuncture group. In addition, acupuncture was found to attenuate the levels of IL-1β, which were elevated after craniotomy. The proinflammatory cytokines IL-1β, TNF-α, and IL-6 have been identified as endogenous pyrogens.<sup>[12]</sup> The experimental evidence indicated that the cytokine levels in the plasma were correlated with fever, demonstrating the role of cytokines in modulating body temperature.<sup>[13]</sup> Therefore, it can be speculated that acupuncture attenuates the levels of IL-1β to reduce the rate of fever occurrence.

IL-1β plays important roles in innate and adaptive immune responses and in the centrally-mediated sickness response.

**Table 3**  
The levels of IL-1β, IL-6, TNF-α, CRP, and ESR in study subjects after craniotomy.

LAB	Time	Acupuncture group (n=20) LS Mean (SE)	Control group (n=20) LS Mean (SE)	group-by-visit interaction P value*	Acupuncture group (n=20) LS Mean (SE)	Control group (n=20) LS Mean (SE)	P value†
IL-1β (pg/ml)	POD2	7.72 (0.69)	9.57 (0.69)	.10	7.69 (0.70)	9.18 (0.70)	0.07
	POD4	7.37 (0.50)	7.84 (0.50)		7.29 (0.51)	7.67 (0.51)	0.50
	POD7	6.75 (0.52)	7.30 (0.51)		6.86 (0.57)	7.48 (0.540)	0.33
IL-6 (pg/ml)	POD2	27.91 (3.53)	28.74 (3.52)	.81	27.07 (3.59)	27.25 (3.57)	0.97
	POD4	17.86 (2.90)	19.46 (2.87)		18.26 (2.91)	20.01 (2.89)	0.60
	POD7	16.20 (3.92)	20.27 (3.86)		14.56 (4.63)	18.87 (4.37)	0.42
TNF-α (pg/ml)	POD2	17.22 (1.32)	16.73 (1.33)	.39	17.69 (1.43)	17.19 (1.45)	0.76
	POD4	15.68 (1.20)	16.22 (1.22)		15.80 (1.25)	16.43 (1.27)	0.66
	POD7	15.43 (1.14)	16.23 (1.15)		15.35 (1.21)	16.13 (1.17)	0.58
CRP (mg/l)	POD2	7.240 (1.32)	7.70 (1.32)	.94	7.96 (0.91)	8.15 (0.92)	0.86
	POD4	2.22 (0.44)	2.18 (0.44)		2.41 (0.46)	2.31 (0.46)	0.85
	POD7	0.70 (0.23)	0.56 (0.22)		0.75 (0.23)	0.59 (0.22)	0.57
ESR (mm/h)	POD2	26.20 (3.09)	26.93 (3.12)	.23	26.33 (3.21)	27.11 (3.26)	0.83
	POD4	33.44 (3.23)	27.12 (3.22)		33.04 (3.53)	26.55 (3.53)	0.11
	POD7	20.76 (3.37)	18.77 (3.35)		21.08 (3.75)	19.35 (3.61)	0.68

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IL-1β = Interleukin-1β, IL-6 = Interleukin-6, LS = least squares, POD = postoperative day, SE = standard error, TNF-α = tumor necrosis factor-α.

\* Statistical comparisons between groups were performed using linear mixed model.

† Statistical comparisons between groups were performed using ANCOVA.

Baseline result, age, sex, duration of surgery, and type of surgery were added as covariates.

**Table 4**  
The levels of IL-1β, IL-6, TNF-α, CRP, and ESR in study subjects who underwent aneurysmal clipping.

LAB	Time	Acupuncture group (n=20)	Control group (n=20)	group-by-visit interaction	Acupuncture group (n=20)	Control group (n=20)	P value <sup>†</sup>
		LS Mean (SE)	LS Mean (SE)	P value <sup>*</sup>	LS Mean (SE)	LS Mean (SE)	
IL-1β (pg/ml)	POD2	6.19 (0.65)	9.53 (0.66)	.02 <sup>‡</sup>	6.65 (0.67)	9.31 (0.68)	.03 <sup>‡</sup>
	POD4	5.98 (0.76)	7.28 (0.77)		5.63 (0.78)	8.12 (0.78)	.07
	POD7	5.56 (0.70)	5.76 (0.70)		4.88 (0.60)	6.64 (0.60)	.09
IL-6 (pg/ml)	POD2	29.18 (6.02)	38.28 (6.01)	.45	28.29 (6.88)	39.74 (6.86)	.29
	POD4	12.43 (4.81)	24.19 (4.80)		12.88 (5.09)	25.07 (5.07)	.14
	POD7	13.14 (4.25)	19.59 (4.23)		13.12 (4.29)	19.21 (4.28)	.37
TNF-α (pg/ml)	POD2	16.02 (1.57)	19.41 (1.57)	.89	16.19 (1.65)	19.99 (1.66)	.14
	POD4	14.35 (1.28)	18.11 (1.29)		14.48 (1.37)	18.58 (1.38)	.07
	POD7	13.57 (1.09)	17.79 (1.10)		13.56 (1.09)	17.70 (1.10)	.03 <sup>‡</sup>
CRP (mg/l)	POD2	15.58 (1.65)	13.25 (1.65)	.60	15.97 (1.97)	13.13 (1.96)	.32
	POD4	4.15 (0.67)	3.74 (0.67)		3.96 (0.76)	3.53 (0.75)	.69
	POD7	1.34 (0.53)	0.94 (0.52)		1.49 (0.54)	1.04 (0.53)	.56
ESR (mm/h)	POD2	34.11 (5.35)	36.25 (5.23)	.28	35.21 (5.40)	35.69 (5.24)	.95
	POD4	48.82 (5.94)	35.97 (5.83)		47.60 (6.47)	35.80 (6.28)	.22
	POD7	31.96 (5.77)	26.82 (5.66)		31.23 (5.99)	28.823 (5.81)	.78

CRP = C-reactive protein, ESR = Erythrocyte sedimentation rate, IL-1β = Interleukin-1β, IL-6 = Interleukin-6, LS = Least squares, POD = Postoperative day, SE = Standard error, TNF-α = Tumor necrosis factor-α.

\* Statistical comparisons between groups were performed using linear mixed model.

† Statistical comparisons between groups were performed using ANCOVA.

‡ P value < .05 vs the control group.

Baseline result, age, sex, and duration of surgery measures were added as covariates.

Additionally, IL-1β promotes the expression of inflammatory molecules such as cyclooxygenase type 2 and nitric oxide, among others.<sup>[14]</sup> Intracerebroventricular injection of IL-1β induces rapid sickness behaviors in rodents,<sup>[15,16]</sup> while blocking IL-1β signaling attenuates sickness behaviors in response to the bacterial endotoxin.<sup>[17]</sup>

In the present study, the mechanisms of acupuncture attenuating proinflammatory cytokines, especially IL-1β, remain to be elucidated. Possible mechanisms of acupuncture attenuating inflammation have been evaluated to date by a number of investigators. For example, it was suggested that acupuncture stimulation may activate the splenic nerve via vagus nerve

activity,<sup>[18]</sup> and that electroacupuncture may reduce the release of proinflammatory cytokines by activating the cholinergic anti-inflammatory pathway.<sup>[19]</sup> In addition, electroacupuncture may control systemic inflammation by inducing vagal activation of aromatic L-amino acid decarboxylase, leading to production of dopamine in the adrenal medulla.<sup>[20]</sup> Furthermore, acupuncture might improve wound healing by decreasing the proinflammatory response.<sup>[21]</sup>

The effects of attenuating postoperative inflammation were more evident in subjects who underwent aneurysmal clipping. Postoperative inflammation was lower in cases of MVD, probably because MVD is a less invasive procedure than the

**Table 5**  
The levels of IL-1β of subjects after craniotomy, analyzed by type of surgery.

Type of surgery	Time	Acupuncture group (n=20)	Control group (n=20)	group-by-visit interaction	Acupuncture group (n=20)	Control group (n=20)	p value <sup>†</sup>
		LS Mean (SE)	LS Mean (SE)	P value <sup>*</sup>	LS Mean (SE)	LS Mean (SE)	
Total surgery	POD2	7.72 (0.69)	9.57 (0.69)	.10	7.69 (0.70)	9.18 (0.70)	0.07
	POD4	7.37 (0.450)	7.84 (0.50)		7.29 (0.51)	7.67 (0.51)	0.50
	POD7	6.75 (0.52)	7.30 (0.51)		6.86 (0.57)	7.48 (0.54)	0.33
Microvascular decompression	POD2	8.70 (1.11)	8.69 (1.21)	.74	8.30 (0.97)	8.08 (1.22)	0.89
	POD4	7.80 (0.68)	6.98 (0.83)		7.61 (0.66)	6.77 (0.83)	0.43
	POD7	7.21 (0.68)	6.48 (0.81)		7.36 (0.79)	6.58 (0.93)	0.50
Aneurysmal clipping	POD2	6.19 (0.65)	9.53 (0.66)	.02 <sup>‡</sup>	6.65 (0.67)	9.31 (0.68)	0.03 <sup>‡</sup>
	POD4	5.98 (0.76)	7.28 (0.77)		5.63 (0.78)	8.12 (0.78)	0.07
	POD7	5.56 (0.70)	5.76 (0.70)		4.88 (0.60)	6.64 (0.60)	0.09
Tumor removal	POD2	6.88 (3.78)	5.894 (2.89)	.05	5.35 (1.44)	6.81 (1.44)	0.68
	POD4	8.22 (3.77)	5.369 (2.87)		5.58 (0.38)	7.39 (0.38)	0.24
	POD7	7.01 (3.83)	6.939 (2.95)		4.47 (2.31)	8.86 (2.31)	0.50

LS = least squares, POD = postoperative day, SE = standard error.

\* Statistical comparisons between groups were performed using linear mixed model.

† Statistical comparisons between groups were performed using analysis of covariance.

‡ P value < .05 vs the control group.

Baseline result, age, sex, duration of surgery, and type of surgery measures were added as covariates.

**Table 6**  
**Clinical characteristics.**

	Acupuncture group (n=20)	Control group (n=20)	P value
Add antibiotics	1	2	1.000 <sup>*</sup>
Altered consciousness (n)	2	4	.661 <sup>†</sup>
F/C kept (n)	20	20	–
C-line kept (n)	9	4	.091 <sup>†</sup>
T/C kept (n)	0	0	–
Sore existence (n)	0	0	–
Altered Consciousness (days)	0.40 ± 1.57	0.80 ± 1.94	.602 <sup>‡</sup>
F/C kept (days)	2.60 ± 1.67	2.25 ± 1.52	.495 <sup>‡</sup>
C-line kept (days)	1.55 ± 2.31	1.05 ± 2.44	.231 <sup>‡</sup>

C-line = central line, F/C = foley catheter, T/C = tracheal cannula.

<sup>\*</sup>Statistical comparisons between groups were performed using Fisher exact test.

<sup>†</sup>Statistical comparisons between groups were performed using Chi-squared test.

<sup>‡</sup>Statistical comparisons between groups were performed using Mann–Whitney test.

other types of surgery considered. The average duration of operation for MVD was  $3.6 \pm 0.6$  hours, that for aneurysmal clipping was  $5.4 \pm 1.4$  hours, and that for tumor removal was  $8.9 \pm 3.1$  hours. On the other hand, the total number of subjects who underwent tumor removal was seven; thus, it may be difficult to obtain statistically reliable results in this study.

Noxious stimulus during neurosurgical procedures such as insertion of cranial pins and scalp incision can induce neurohormonal responses, which may lead to the release of proinflammatory cytokines and subsequent production of acute phase proteins.<sup>[22]</sup> However, in this study, TNF- $\alpha$  level was not increased after craniotomy. A previous study reported that TNF- $\alpha$  level was increased on the day of operation in patients compared with a healthy control group, but decreased quickly.<sup>[22]</sup> Thus, the effects of acupuncture could not be observed in this study, probably because the levels of TNF- $\alpha$  remained almost the same in the subjects two days after craniotomy.

There were no significant differences in the levels of IL-6, CRP, and ESR between the two groups. In this study, complications rarely occurred, so it was difficult to compare the effect of acupuncture between the 2 groups. This is presumably because broad spectrum antibiotics were started after surgery for prophylactic purposes.

Three different methods of acupuncture in which acupuncture, electroacupuncture, and intradermal acupuncture were performed during every session. The purpose of using three acupuncture modalities was to enhance effectiveness. Electroacupuncture which is providing electric stimulation at acupoints was used to give constant standardized additional stimulation. Intradermal acupuncture was used to give continuous stimulation at acupoints to consolidate the curative effect.

There were no adverse events that occurred during the present trial. Acupuncture, electroacupuncture, and intradermal acupuncture turned out to be safe, even if they were conducted within one day after craniotomy.

The primary limitation of this study was its small sample size, as only 44 subjects were initially enrolled. A larger number of subjects would be required for statistically reliable measurement of cytokines.

This was an open label, non-randomized study. It was difficult to blind subjects or enroll subjects randomly into the acupuncture group or the control group because they were

nervous and reluctant before the craniotomy, so the subjects were allocated by intention. Potential selection bias was possible, but there were no significant differences between the groups in baseline characteristics and clinical characteristics such as duration of surgery and duration of altered consciousness. Therefore, it might be speculated that the severity of condition after craniotomy was similar among the patients in the two groups.

Further studies are needed to investigate the additional effects of acupuncture on preoperative or interoperative inflammatory response and with respect to different methods of acupuncture. Needling near the wound is known to be a method for promoting blood circulation, which may be recommended for use in further studies. To identify the mechanism of the anti-inflammatory effect of acupuncture, signaling pathways involved in acupuncture effects may be elucidated using animal models. In addition, it would be useful to analyze the effects of acupuncture on blood flow and the correlation between blood flow and the anti-inflammatory effect. Furthermore, the results of this study showed different results according to the three surgical groups, so it might be necessary to divide the surgical groups in future studies.

Acupuncture showed a possibility of attenuating the levels of proinflammatory cytokines, especially IL-1 $\beta$ , and significantly reduced the incidence of fever of unknown origin in patients after craniotomy. Therefore, acupuncture perhaps could be recommended as an adjunctive therapy to alleviate inflammation after craniotomy.

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## References

- van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med* 2010;362:146–54.
- Liu W, Ni M, Zhang Y, et al. Antibiotic prophylaxis in craniotomy: a review. *Neurosurg Rev* 2014;37:407–14.
- Alotaibi AF, Mekary RA, Zaidi HA, et al. Safety and efficacy of antibacterial prophylaxis after craniotomy: a decision model analysis. *World Neurosurg* 2017;105:906–12.
- Asmussen S, Maybauer DM, Chen JD, et al. Effects of acupuncture in anesthesia for craniotomy: a meta-analysis. *J Neurosurg Anesthesiol* 2017;29:219–27.
- Xu M, Zhou SJ, Jiang CC, et al. The effects of P6 electrical acustimulation on postoperative nausea and vomiting in patients after infratentorial craniotomy. *J Neurosurg Anesthesiol* 2012;24:312–6.
- Li G, Li S, An L, et al. Electroacupuncture alleviates intraoperative immunosuppression in patients undergoing supratentorial craniotomy. *Acupunct Med* 2013;31:51–6.
- Cho SY, Yang SB, Shin HS, et al. Anti-inflammatory and immune regulatory effects of acupuncture after craniotomy: study protocol for a parallel-group randomized controlled trial. *Trials* 2017;18:10.

- [8] Zhu SF, Guo H, Zhang RR, et al. Effect of electroacupuncture on the inflammatory response in patients with acute pancreatitis: an exploratory study. *Acupunct Med* 2015;33:115–20.
- [9] Song Q, Hu S, Wang H, et al. Electroacupuncture at Zusanli point (ST36) attenuates pro-inflammatory cytokine release and organ dysfunction by activating cholinergic anti-inflammatory pathway in rat with endotoxin challenge. *Afr J Tradit Complement Altern Med* 2014;11:469–74.
- [10] Zhang CJ, Yang F, Li M. Effect of electroacupuncture combined with cervical plexus block on stress responses in patients undergoing thyroid surgery. *Zhen Ci Yan Jiu* 2013;38:1–6.
- [11] Shuster JJ. *Practical Handbook of Sample Size Guidelines Clinical Trials* MAC. 1992;CRC Press,
- [12] Rothwell NJ, Busbridge NJ, Lefevre RA, et al. Interleukin-6 is a centrally acting endogenous pyrogen in the rat. *Can J Physiol Pharmacol* 1991;69:1465–9.
- [13] Conti B, Tabarean I, Andrei C, et al. Cytokines and fever. *Front Biosci* 2004;1:1433–49.
- [14] Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009;27:519–50.
- [15] Braun TP, Grossberg AJ, Veleva-Rotse BO, et al. Expression of myeloid differentiation factor 88 in neurons is not requisite for the induction of sickness behavior by interleukin-1beta. *J Neuroinflammation* 2012;9:229.
- [16] Grossberg AJ, Zhu X, Leininger GM, et al. Inflammation-induced lethargy is mediated by suppression of orexin neuron activity. *J Neurosci* 2011;31:11376–86.
- [17] Laye S, Gheusi G, Cremona S, et al. Endogenous brain IL-1 mediates LPS-induced anorexia and hypothalamic cytokine expression. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R93–8.
- [18] Lim HD, Kim MH, Lee CY, et al. Anti-inflammatory effects of acupuncture stimulation via the vagus nerve. *PLoS One* 2016;11: e0151882.
- [19] Torres-Rosas R, Yehia G, Peña G, et al. Dopamine mediates vagal modulation of the immune system by electroacupuncture. *Nat Med* 2014;20:291–5.
- [20] Park SI, Sunwoo YY, Jung YJ, et al. Therapeutic effects of acupuncture through enhancement of functional angiogenesis and granulogenesis in rat wound healing. *Evid Based Complement Alternat Med* 2012;2012:464586.
- [21] Slaats J, Ten Oever J, van de Veerdonk FL, et al. IL-1 $\beta$ /IL-6/CRP and IL-18/ferritin: distinct inflammatory programs in infections. *PLoS Pathog* 2016;12:e1005973.
- [22] Mokart D, Capo C, Blache JL, et al. Early postoperative compensatory anti-inflammatory response syndrome is associated with septic complications after major surgical trauma in patients with cancer. *Br J Surg* 2002;89:1450–6.