A pilot study in acute subarachnoid hemorrhagic patients after aneurysm clipping with complementary therapies of Chinese Medicine

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Running title: Complementary therapies in acute subarachnoid hemorrhage patients

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Summary

Objectives: Acute subarachnoid haemorrhage still has high mortality and morbidity despite the use of modern standard treatment. In Taiwan, complementary therapies of Chinese medicine are usually used to treat stroke patients. The aim of this study was to investigate the effect of complementary therapies of Chinese medicine on patients with acute subarachnoid haemorrhage after aneurysm clipping.

Design: This study was designed as a pilot study. A total of 32 patients with acute subarachnoid haemorrhage were randomly assigned to either an experimental group (EG) in which the patients were given complementary therapies of Chinese medicine and modern standard treatment or a control group (CG) in which patients were given modern standard treatment only.

Main outcome measures: Glasgow Outcome Scale scores, which were assessed by an evaluator who was blinded to the groups, 3 months after admission, and total admission days including intensive care unit stay days.

Results: The average Glasgow Outcome Scale score 3 months after admission was 3.7±1.4 in the EG which was higher than the score of 3.0±1.7 in the control group ($p < 0.05$). Average total admission days were 34.0±24.3 for the CG which a longer stay than the 25.2±24.5 days for the EG ($p < 0.05$).

Conclusion: Traditional Chinese medicine for the treatment of patients with acute subarachnoid haemorrhage are of value because they can increase Glasgow Outcome Scale scores 3 months after admission and also because they can reduce total admission days.

Keywords: Complementary therapies; Chinese Medicine; Acute subarachnoid haemorrhage; Glasgow outcome scale.

Introduction

The use of complementary therapies of Chinese medicine (CM) including Chinese herbs and acupuncture to treat patients with chronic or subacute stage of stroke is popular in Taiwan. *Salviae miltiorrhizae* may increase recovery rate of patients with acute subarachnoid haemorrhage (SAH) had been reported.[1] SAH is an acute emergency. About 85% of cases result from the rupture of an aneurysm.[2] The incidence of SAH is about 6 cases per 100,000 patient years.[2] The overall case mortality rate of SAH is 42% during the first 28 days.[3] Although ultra-early aneurysm clipping (within 3 days after onset) is used for the treatment of SAH, higher mortality and morbidity rates are still noted compared with the other cerebral diseases due to occurrence of vasospasm following SAH, which may cause cerebral ischaemia.[4]

Aneurysm rupture with SAH may cause inflammation resulting in fatal vasospasm and central pyrexia.[5] Patients with SAH who have complicated fever may have a prolonged stay in the ICU and a poorer outcome.[6,7] Mechanical compression of the brainstem and hypothalamus may induce the production and release of pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and S100B as a calcium-binding protein of astrocytes, causing central pyrexia.[8-10] The pro-inflammatory cytokine levels increase in brain tissues, cerebrospinal fluid (CSF), and blood in patients with traumatic brain injury or stroke.[11-25]

Traditional Chinese medicine (TCM) such as acupuncture, Chinese herbs, and CM formula has been used to treat stroke for centuries in China. Our previous studies have shown that *Gastrodia elata* plays a neuroprotective role in kainic acid-treated rats[26] and may reduce IL-1β and TNF-α levels in brain tissue of kainic acid-treated rats.[27] *Paeonol,* a major component of Moutan Cortex of *Paeonia suffruticosa* Andrews and the root of *Paeonia lactiflora* Pall, has anti-inflammation and anti-oxidant effects in transient ischaemia-reperfusion injury rats.[28] Therefore, we designed a pilot study to investigate the effect of complementary therapies of CM on patients with acute SAH. The therapeutic effect was evaluated by Glascow Outcome Scale (GOS) score and total admission days including ICU stay days. In addition, daily body temperature (BT) and intracranial pressure (ICP) were recorded and the levels of TNF-α, IL-1β, IL-6, and S100B in cerebrospinal fluid (CSF) were also measured.

Materials and Methods

Subjects

A total of 53 patients with acute SAH were treated at China Medical University Hospital, Taichung, Taiwan from January 2007 and December 2007. Thirty-two patients who underwent craniotomy were included in the study. The inclusion criteria were the following: 1) SAH due to cerebral aneurysm rupture that was confirmed by sequential computed tomography angiography (CTA) scanning within 6 hours after the episode; 2) the neurological deficit was between grade 2 and 4 of Hunt and Hess (H&H) grade; 3) serum blood urea nitrogen (BUN) was ≦ 25 mg/ml, creatinine ≦ 1.8 mg/dl, and the creatinine clearance was ≧ 50 ml/min; 4) serum SGOT, SGPT, and alkaline phosphatase were less than three times the upper normal limit and the total bilirubin was less than 3 mg/dl; 5) serum haemoglobin was ≧8 g/dl, platelet counts ≧ $100\times10^3/\mu l$，white cell counts ≧ $2\times10^3/\mu l$，and the absolute neutrophils ≧1000/μl. The exclusion criteria were as follows: 1) patients with pregnancy; 2) age < 12 years or > 70 years; 3) H&H grade of 1 and 5; 4) patients or their families refuse participation in trial.

Study design

All the experimental procedures were according to the ethical principles dictated in the Declaration of Helsinki. The protocol of the trial was approved by the institutional review board of the China Medical University Hospital, Taichung City, Taiwan (DMR95：IRB80), and informed consent regarding the experimental procedures and purpose was obtained prior to the trial.

After undergoing an aneurysm clipping operation the patients were randomized by an on duty doctor who takes a lot of experimental group (EG) or control group (CG) from a dark box to either an EG which received complementary therapies of CM and modern standard treatment or a CG which received modern standard treatment only. Each group had 16 subjects. Because this study was a pilot study, there was no basis for calculating its power and sample size (Figure 1).

Standard treatment

Standard treatment of acute SAH according to the guidelines of the Stroke Council, American Heart Association[29] is based on clipping of the aneurysm as early as possible and the prevention of secondary insults to the brain. External ventricular drainage was performed routinely during aneurysm clipping. It was used not only to monitor the postoperative ICP but also for drainage of the intraventricular haemorrhage and was maintained for not more than 7 days to avoid related infection. All patients were intubated and placed on volume-controlled ventilation under sedation to maintain partial pressure of oxygen in arterial blood (PaO2) of at least 100 mm Hg and arterial carbon dioxide pressure or tension (PaCO2) of approximately 35-40 mm Hg after the operation. The endotracheal tube was not removed until the consciousness of the patient was clear and the ICP was stable. Hypertension, hyperperfusion, haemodilution and calcium-channel blocking agent (nimodipine) were started immediately after arrival in the ICU after surgery. ICP was treated by elevating the patient's head by raising one end of the bed, sedation, paralysis, and mannitol. Nutritional support was started as soon as possible and was maintained by administering adequate parenteral or enteral solutions. Oral acetaminophen was given regularly to prevent further pyrexia.

The complementary therapies of CM

The complementary therapies of CM were given every day continuously for 2 weeks after the patients started to take food on the second day after the surgical operation. Patients were mainly given the following four essential Chinese herbs: 1) *Astragalus menbranaceus* (Fisch) Bunge (Radix Astragalli, 12 g/day; Shaanxi, China); 2) *Gastrodia elata* Blume (Rhizoma Gastrodiae, 12 g/day; Sichuan, China); 3) *Acorus gramineus* Soland (Rhizoma Acori Graminei, 7.5 g/day; Sichuan, China), and 4) *Pheretima aspergillum* (E. Perrier) (Lumbricus, 12 g./day; Thailand). In addition, Chinese herbs such as *Paeonia suffruticosa* Andr (Cortex Moutan, 12 g/day; Zhejiang, China), Lonicera japonica Thunb (Flos Lonicerae, 19 g/day; Anhui, China), raw *Rehmannia glutinosa* Libosch (Radix Rehmaniae, 12 g/kg; Henan, China), and *Scutellaria baicalensis* Georgi (Radix Scutellariae, 12 g/kg; Hebei, China) were given when patients had fever or a heat phenomenon in TCM such as quickened radial pulse (more than 85 beats/min), tongue color was fresh red, etc. *Rheum palmatum* Linn (Radix et Rhizoma Rhei, 4 g/kg; Sichuan, China) and *Citrus aurantium* Linn (Fructus Aurantii Immaturus, 12 g/kg; Sichuan, China) were added when patients had no defecation for more than 3 days. The Chinese herbs were authenticated according to the characteristics and shape even histological section, and decocted by the Chinese herb specialist in the China Medical University Hospital. These herbs were mixed with 600 cc of water, and then decocted to 300 cc. Patients were given 100 cc of the solution of herbs three times a day.

Clinical characteristics and basic data recording

The age, gender, GCS scores, H&H grade and SAH grade of the patients were recorded on the day of admission.

Main outcome measure

GOS scores were assessed and recorded on the personal medical record in the outpatient door 3 months (±7 days) after admission by an evaluator who was blinded to the group. The GOS scores were divided into five grades from 1 to 5: score 1, death; score 2, vegetative state; score 3, severe disability; score 4, moderate disability; score 5, mild or no disability.[30] In addition, total admission days were used as an outcome measure including ICU stay days.

Secondary outcome measure

The Glascow Coma Scale (GCS) scores and H&H grade were recorded on the day of admission, and the GCS scores were also recorded on the day of discharge. The daily body temperature (BT), taken with an ear thermometer, and daily ICP were recorded. In addition, cytokine levels including IL-1β, IL-6, TNF-α, and S100 were measured in the cerebrospinal fluid on the 1st and 5th day after the operation.

Daily BT and ICP recordings

The BT and ICP were monitored every 2 hours continuously for 5 days after surgery. The average BT and ICP were calculated. The variation in BT was calculated (daily highest BT – average daily BT)^2 and the variation in ICP was calculated (daily highest ICP – average daily ICP)^2.

The measurement of cytokine levels

Three-milliliter samples of CSF were collected on the 1st and 5th days from the external ventricle drainage of the lateral ventricle after surgery. The samples were centrifuged for 20 minutes at 2000 rpm, and the supernatant was immediately stored at −80^{o}C until analysis. The levels of IL-1β, IL-6, and TNF-α were determined by using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Bender MedSystems, Inc., USA) and an ELISA reader (Dynex MRX, Virginia, USA). The sensitivity of the assay was typically 0.124 pg/ml for IL-1β, 0.094 pg/ml for IL-6, and 0.081 pg/ml for TNF-α. The S100B level in CSF was quantified by sandwich ELISA. The samples were analyzed in duplicate and compared with known concentrations. The lower limit of detection of the ELISA is 0.01 ng/ml. No cross-reactivity or interference with other related interleukins was observed. The data were represented in pg/ml and all assays were performed in duplicate.

Statistical Analysis

Student's t test for unpaired test and, whenever necessary, the Wilcoxon signed rank and repeated ANOVA were used to compare measurements. Data are expressed as means ± standard deviations. Spearman correlation coefficients were used to compare the relationships between the variations of daily BT and ICP and the concentrations of IL-1β, IL-6, TNF-α, and S100B. Statistical significance was set at $p < 0.05$.

Results

The analysis of basic data

The age, gender, GCS score on admission, H&H grade score on admission, and SAH grade score on admission were not significantly different between the EG and CG (all $p > 0.05$; Table 1).

Main outcome measures

The GOS score was assessed in all the 32 patients 3 months after admission. The average

GOS score was 3.7±1.4 in the EG which was significantly higher than the score of 3.0±1.7 in the CG ($p < 0.05$). A total of four patient's death due to intractable increased ICP in ICU, and the complication included pulmonary infection, urinary tract infection, and gastrointestinal tract hemorrhage etc., but no patient withdrew or adverse events were noted in the trial. The mortality rate during the stay in the ICU was 6.25% (1/16) in the EG which was similar to the rate of 18.8% (3/16) in the CG ($p > 0.05$). The mean number of ICU stay days was 16.8±8.1 for the CG which was significantly more than the 11.1±4.1 days for the EG ($p<0.05$). The total number of hospital stay days was 34.0±24.3 for the CG which was significantly more than the 25.2±24.5 days for the EG ($p < 0.05$).

Secondary outcome

The average GCS score at discharge was 12.3±2.5 for the EG which was significantly higher than the score of 10.3±2.9 for the CG ($p < 0.05$).

Effect of complementary therapies of CM on BT and ICP

The average daily BT and variation of daily BT, and the average daily ICP and variation of daily ICP (VDICP) from the 1st to 5th days after surgery were not significantly different between the EG and CG (all $p > 0.05$; Tables 2-3) except VDICP of day 4.

Effect of complementary therapies of CM on IL-1β, IL-6, TNF-α, and S100B in CSF

The difference between IL-1β levels on the 1st day and IL-1β levels on the 5th day was positively correlated with the average daily BT on the 1st, 4th, and 5th days after surgery in the EG (all $p < 0.05$; Table 4), whereas there was no correlation with average daily BT on the 2nd and 3rd days after surgery in the EG (both $p > 0.05$; Table 4). The difference between IL-1β levels on the 1st day and IL-1β levels on the 5th day had no correlation with the average BT on the 1st , 2nd, 3rd ,4th, and 5th days after surgery in the CG (all $p > 0.05$; Table 4).

The difference between IL-6 levels on the 1st day and IL-6 levels on the 5th day had no correlation with the average daily BT on the 1st, 2nd, 3rd ,4th, and 5th days after surgery in the EG and CG (all $p > 0.05$; Table 4),

The difference between TNF-α levels on the 1st day and TNF-α levels on the 5th day had no correlation with the average BT on the 1st , 2nd, 3rd ,4th, and 5th days after surgery in the EG and CG (all $p > 0.05$; Table 4),

The difference between S100B levels on the 1st day and S100B levels on the 5th day had no correlation with the average BT on the 1st, 2nd, 3rd ,4th, and 5th days after surgery in the EG and CG (all $p > 0.05$; Table 4).

Discussion

Our results indicated that complementary therapies of CM for patients with acute SAH may increase the GOS score 3 months after admission, and reduce the total number of admission days, including both ICU stay days, which suggests that complementary therapies of CM provide an advantage in outcome for such patients. Critically ill patients with SAH commonly have fever, a factor known to worsen neurologic injury due to vasospasm.[14] In these patients, fever and vasospasm may be both associated with the production and release of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α.[18-22] Increased protein levels of pro-inflammatory cytokines have been reported in brain tissues, cerebrospinal fluid, and blood of patients with SAH, traumatic brain injury, stroke, and other neurological conditions.[23,24]

Interleukin-1β is thought to play an important role in mediating inflammation and neuronal damage after traumatic brain injury, spontaneous SAH, and stroke by enhancing the inflammatory reactions via the release of other inflammatory mediators such as prostaglandins, collagenase, and phospholipase A_2.[12] Additionally, IL-1β has been implicated in apoptotic cell death,[13,14] leukocyte-endothelium adhesion,[15] blood-brain barrier disruption,[16] edema formation,[16,17] astrogliosis, and neovascularization.[18] Experimentally, intracerebroventricular administration of IL-1β is associated with marked stimulation of circulating IL-6 and TNF-α levels.[19,21] Inhibition of IL-1β has been shown to reduce the incidence of central pyrexia, vessel spasm, and early edema formation.[22,23] Our studies showed that complementary therapies of CM in patients with acute SAH did not significantly change the average daily BT or variation of daily BT, or the average daily ICP or variation of daily ICP except day 4 due to two patients death with increased ICP. The difference in IL-1β concentration between the 1st day and 5th day after surgery showed a positive correlation with daily BT on the 1st, 4th, and 5th day after surgery in the complementary therapies of CM group, whereas there were no similar results in the CG which did not receive complementary therapies of CM. These results suggest that complementary therapies of CM may decrease IL-1β concentration in CSF which reduces the inflammation and fever caused by SAH. Unfortunately, this tendency was not observed for IL-6, TNF-α, and S100B. More frequent checking of the concentration of cytokines and a longer observation period may be helpful for demonstrating a significant difference.

That *Gastrodia elata* and its component *vanillyl alcohol* may inhibit the production and scavengering of oxygen free radicals, and inhibit microglia activation in kainic acid-induced epileptic rats was shown in our previous studies.[26,31,32] A*astragaloside IV* is a component of *Astragalus membranaceus* that can reduce the cerebral infarction area induced by middle cerebral artery occlusion in rats, and this effect of *Aastragaloside IV* results from its anti-oxidative properties.[33] *Acorus graminueus* has the action of resolving phlegm to open orifices in TCM, and can enhance learning and memory.[34] *Lumbrokinase* is a component of *Pheretima aspergillum* (earthworm), and can meditate via antiplatelet activity, attenuating the calcium release from calcium storage, inhibiting intracellular adhesion molecular-1 (ICAM-1) expression to protect against cerebral ischaemia.[35] The *paeonol* component of *Paeonia suffruticosa* may reduce the cerebral infarction area and neurological deficit, and also has anti-oxidative action in cerebral ischaemia-reperfusion injured rat.[28] The component of *Lonicera japonica* may inhibit microglia activation to protect dopamingeric neurons from liopopolysaccaride (LPS)-induced injury,[36] and also may inhibit nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) to suppress inflammatory reaction in mouse alveolar macrophage.[37] *Catapol* is a component of *Rehmannia glutinosa* that may reduce lipid peroxidation and also may increase glutathione and superoxide dismutase activities in MPP^+-induced oxidative stress in mesencephalic neurons.[38] C*atapol* also can reduce the formation of intracellular reactive oxygen species in astrocytes with H_2O_2-induced oxidative stress.[39] The baicalin component of *Scutellaria baicalensis* can mediate via binding to chemokines to produce anti-inflammatory activity in human peripheral blood leucocytes,[40] and *baicalein* also can maintain brain mitochondrial homeostasis and function in rats with chronic cerebral hypoperfusion-induced oxidative damage.[41] *Rheum palmatum* is a laxative, and its emodin component can through the inhibition of AP-1 and NF-κB suppress matrix metalloproteinase in human cancer cells.[42] *Citrus aurantium* is qi-regulating and is medicinal for digesting, and it has antioxidant activity.[43] To sum up, the Chinese herbs taken together may produce anti-oxidation and ant-inflammation including the inhibiting generation and scavenging of oxygen free radicals, and the inhibition of IL-1β, suggesting that these action may improve functional recovery of SAH patients.

The present study was a pilot study and therefore there were some limitations as follows: 1) treatment with the complementary therapies of CM had to be agreed by the patients or their families, thus randomly assigning the patients to the CG or EG by a completely blind method was difficult; 2) the sample size was small; 3) there was no fixed CM formula. Future research using a randomized double-blind study design, an increased number of patients, and a fixed CM formula is needed.

In conclusion, TCM in patients with acute SAH is a worthy extension to treatment because they can increase GOS scores at 3 months after admission and also reduce total admission days including ICU stay days.

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Legend

Figure 1. Flowchart

Table 1. Clinical characteristics and basic data in acute subarachnoid hemorrhagic patients

	EG (n=16)	CG (n=16)	p
Age (years)	55.1±12.9	59.9±12.9	NS
Gender (female/male)	8/8	8/8	NS
GCS score in admission	9.6±4.8	8.5±4.4	NS
H&H grade in admission	2.9±1.2	3.3±1.2	NS
SAH grade in admission	2.1±0.9	2.6±0.9	NS

Data represent as Mean ± SD (standard deviation)；n: patients number；EG：experimental group, acute subarachnoid hemorrhagic patient with complementary therapies of Chinese Medicine; CG, control group, acute subarachnoid hemorrhagic patient without complementary therapies of Chinese medicine; GCS: Glasgow coma scale；H&H: Hunt & Hess；SAH: subarachnoid hemorrhage; NS: not significant.

Table 2. The averaged and variation daily body temperature changes in acute subarachnoid hemorrhagic patients

	ADBT		VDBT	
	EG	CG	EG	CG
Day 1	36.88±0.54	37.13±0.77	0.18±0.23	0.23±0.46
Day 2	37.19±0.46	37.26±0.54	0.13±0.19	0.21±0.42
Day 3	37.06±0.59	37.17±0.40	0.09±0.10	0.13±0.18
Day 4	37.25±0.64	37.31±0.56	0.12±0.14	0.12±0.17
Day 5	37.36±0.54	37.31±0.69	0.15±0.22	0.24±0.42

Data represent as Mean ± SD (standard deviation); EG：experimental group, acute subarachnoid hemorrhagic patient with complementary therapies of Chinese medicine; CG, control group, acute subarachnoid hemorrhagic patient without complementary therapies of Chinese medicine; ADBT: averaged daily body temperature; VDBT: variation of daily body temperature; Day 1: 1^{st} day after surgical operation; Day 2: 2^{nd} day after surgical operation; Day 3: 3^{rd} day after surgical operation; Day 4: 4^{th} day after surgical operation; Day 5: 5^{th} day after surgical operation; Wilcoxon signed rank test.

Table 3. The averaged and variation daily intracranial pressure in acute subarachnoid hemorrhagic patients

	ADICP		VDICP	
	EG	CG	EG	CG
Day 1	7.06±4.52	6.89±4.23	25.25±47.91	16.44±18.81
Day 2	9.16±4.40	11.00±8.62	5.91±10.55	7.24±15.14
Day 3	9.18±4.36	10.26±7.61	2.17±2.23	4.24±5.86
Day 4	9.78±6.03	10.10±7.23	1.70±3.75	13.06±22.22*
Day 5	7.93±2.66	10.71±8.05	4.17±9.79	5.96±9.07

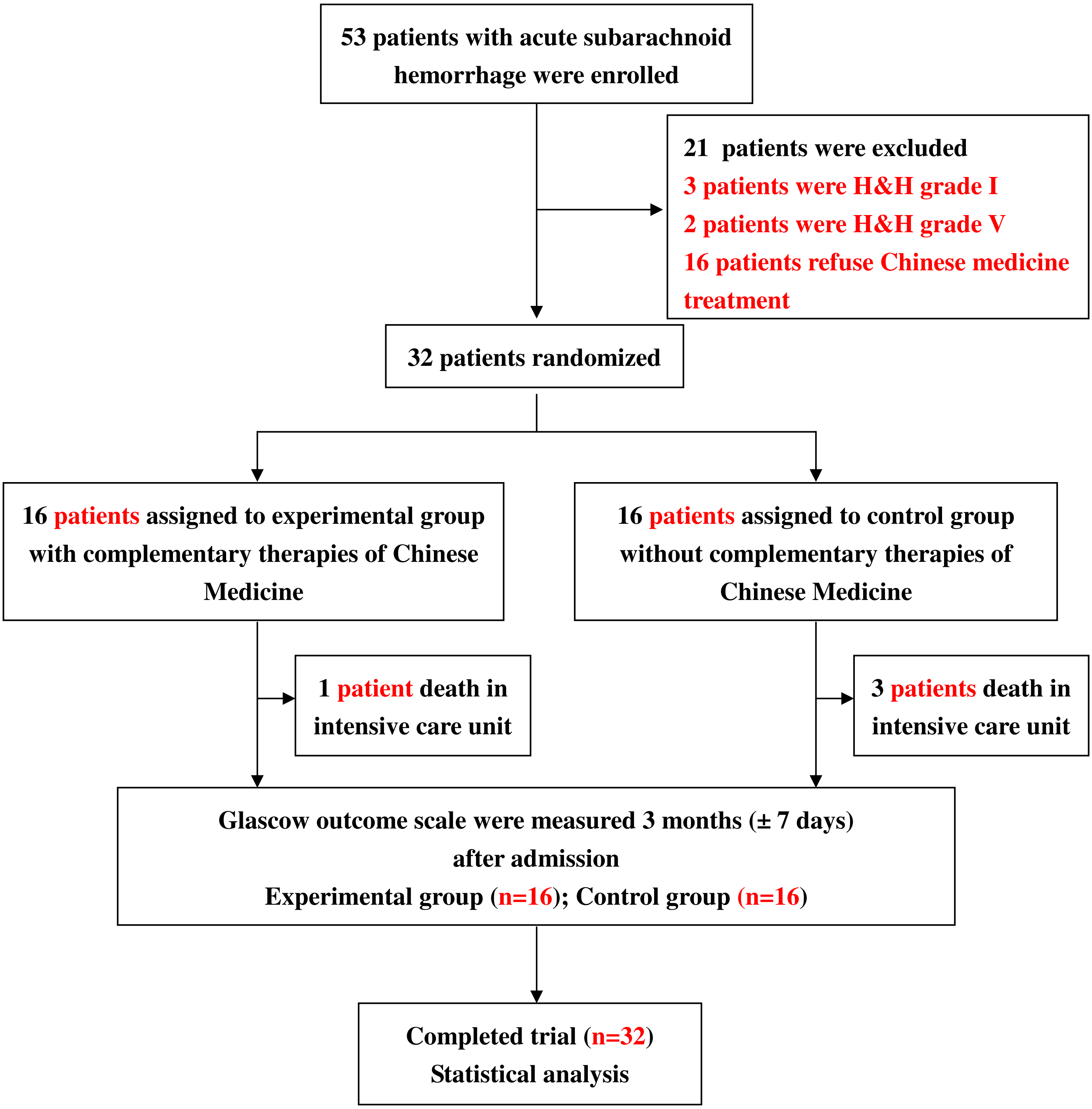
Data represent as Mean ± SD (standard deviation); EG：experimental group, acute subarachnoid hemorrhagic patient with complementary therapies of Chinese medicine; CG, control group, acute subarachnoid hemorrhagic patient without complementary therapies of Chinese medicine; ADICP: averaged daily intracranial pressure; VDICP: variation of daily intracranial pressure; Day 1: 1st day after surgical operation; Day 2: 2nd day after surgical operation; Day 3: 3rd day after surgical operation; Day 4: 4th day after surgical operation; Day 5: 5th day after surgical operation; Wilcoxon signed rank test;*$p < 0.05$ compared with EG..

Table 4: The relationship of IL-1β between averaged daily body temperatures in acute subarachnoid hemorrhage patients

		BT1	BT2	BT3	BT4	BT5
IL-1β Df	EG	0.59396*	0.12077	0.28698	0.56659*	0.56278*
	CG	-0.48266	-0.41090	-0.38263	-0.13824	-0.25460
IL-6 Df	EG	0.22727	-0.39091	-0.27273	0.10909	0.15490
	CG	0.00610	0.04863	0.52280	-0.10303	-0.53939
TNF-α Df	EG	0.08368	-0.16667	0.40000	0.41667	0.38494
	CG	0.35295	0.00000	0.05858	0.00000	0.30000
S100B Df	EG	0.31228	0.16783	0.31469	-0.03497	-0.04233
	CG	0.17956	0.26410	0.11538	0.26374	0.19257

EG：experimental group, acute subarachnoid hemorrhagic patient with complementary therapies of Chinese medicine; CG, control group, acute subarachnoid hemorrhagic patient without complementary therapies of Chinese medicine; IL-1β; Df: the difference of IL-1β concentration between 1^{st} and 5^{th} day; IL-6 Df: the difference of IL-6 concentration between 1^{st} and 5^{th} day; TNF-α Df: the difference of TNF-α concentration between 1^{st} and 5^{th} day; S100B Df: the difference of S100B concentration between 1^{st} and 5^{th} day; BT1: the average BT at the 1^{st} day after surgical operation; BT2: the average BT at the 2^{nd} day after surgical operation; BT3: the average BT at the 3^{rd} day after surgical operation; BT4: the average BT at the 4^{th} day after surgical operation; BT5: the average BT at the 5^{th} day after surgical operation；Spearman Correlation Coefficients; *$p < 0.05$.

Fig.1


53 patients with acute subarachnoid hemorrhage were enrolled
21 patients were excluded
3 patients were H&H grade I
2 patients were H&H grade V
16 patients refuse Chinese medicine treatment
32 patients randomized
16 patients assigned to experimental group with complementary therapies of Chinese Medicine
16 patients assigned to control group without complementary therapies of Chinese Medicine
1 patient death in intensive care unit
3 patients death in intensive care unit
Glascow outcome scale were measured 3 months (± 7 days) after admission
Experimental group (n=16); Control group (n=16)
Completed trial (n=32)
Statistical analysis