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External counterpulsation for acute ischaemic stroke (Review)

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[Intervention Review]

External counterpulsation for acute ischaemic stroke

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ABSTRACT

Background

External counterpulsation (ECP) may improve cerebral blood flow, and it has been proposed as a potential therapy for patients with ischaemic stroke.

Objectives

To assess the efficacy and safety of ECP for acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2011 Issue 2), MEDLINE (1948 to June 2011), EMBASE (1980 to June 2011), CINAHL (1982 to June 2011), AMED (Allied and Complementary Medicine) (1985 to June 2011), China Biological Medicine Database (CBM) (1978 to June 2011), Chinese National Knowledge Infrastructure (CNKI) (1979 to June 2011), Chinese Science and Technique Journals Database (VIP) (1989 to June 2011) and Wanfang Data (1984 to June 2011). We also searched ongoing trials registers, reference lists and relevant conference proceedings and contacted authors and manufacturers of external counterpulsation devices.

Selection criteria

Randomised controlled trials (RCTs) in which ECP (started within seven days of stroke onset) was compared with sham treatment or no treatment, or ECP plus routine treatment was compared with routine treatment alone, in patients with acute ischaemic stroke.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data, checked for adverse events data and contacted trialists for missing information.

Main results

We included two trials involving 160 patients. Numbers of death or dependent patients at the end of at least three months follow-up were not reported in either of the included trials. The outcome measure used in the included trials was only the number of participants with improvement of neurological impairment after treatment according to the Modified Edinburgh-Scandinavian Stroke Scale (MESSS) or self-making criteria. ECP was associated with a significant increase in the number of participants whose neurological impairment improved (risk ratio (RR) 1.75, 95% confidence interval (CI) 1.37 to 2.23). Only one trial reported no adverse events.

Authors' conclusions

The methodological quality of the included studies was poor, and reliable conclusions could not be drawn from the present data. High-quality and large-scale RCTs are needed.

PLAIN LANGUAGE SUMMARY

External counterpulsation for acute ischaemic stroke

Some studies have indicated that poor cerebral perfusion is related to unfavourable functional outcomes, precipitating strokes and other vascular events, which are often responsible for high mortality rates. External counterpulsation (ECP) is a non-invasive and acceptable method which is known to improve perfusion of the brain. It provides pressure to the calves, thighs and buttocks by means of air-filled cuffs. This helps to increase blood flow to the heart, brain and kidneys. This review identified two randomised controlled trials (RCTs) of ECP involving 160 participants with acute ischaemic stroke. There is no convincing evidence to support the routine use of ECP for the treatment of patients with acute ischaemic stroke. Further high-quality and large-scale RCTs are needed.

BACKGROUND

Description of the condition

Stroke is the second most common cause of death and a major cause of disability worldwide (Donnan 2008). Ischaemic stroke, which accounts for 80% of all strokes (Thrift 2001), is caused by a blockage in an artery that supplies blood to the brain, resulting in a deficiency in blood flow which is also the cause of permanent brain damage and long-term impairments. Despite the rapid progress in stroke prevention, an effective acute ischaemic stroke treatment with reliable evidence is still lacking, except for aspirin within 48 hours of stroke onset (Sandercock 2008), management in a stroke care unit (Stroke Unit Trialists' Collaboration 2007), thrombolysis with recombinant tissue plasminogen activator (in highly selected patients within 4.5 hours of stroke onset) (Adams 2007; Del Zoppo 2009; Wardlaw 2009) and decompressive surgery in patients with malignant middle cerebral artery (MCA) infarction (Vahedi 2007). Neuroprotection (Ginsberg 2009), Chinese herbal products (Wu 2007) and other therapies have been evaluated but their results have either been inconclusive or negative.

Description of the intervention

Some studies have indicated that poor cerebral perfusion is related to unfavourable functional outcomes, precipitating strokes and other vascular events, which are often responsible for high mortality rates (Ho 2006; Wong 2000; Wong 2003). As the main problem of ischaemic stroke is that the focal cerebral region cannot get enough blood, cerebral blood flow augmentation may be the first and most important target in acute ischaemic stroke management. External counterpulsation (ECP) is a non-invasive and acceptable method which is known to improve the perfusion of vital organs.

ECP uses an ECG-triggered diastolic pressure of approximately 250 mmHg to the calves, thighs and buttocks by means of air-filled cuffs. The diastolic augmentation of the blood flow and the simultaneously decreasing systolic afterload therefore increase the blood flow to the heart, brain and kidneys (Han 2008a).

How the intervention might work

The possible factors responsible for its clinical improvement are summarised as follows.

1. ECP can significantly increase blood flow in carotid, renal, hepatic and coronary arteries. These haemodynamic effects result in a rise in blood flow in multiple vascular beds, including the brain, kidneys, liver and myocardium (Applebaum 1997; Werner 1999).
2. ECP may help open the preformed collateral vessels to augment collateral perfusion by releasing shear-dependent vasomediators and augmenting arterial pressure. It has been verified that chronic exposure of the vascular bed to the augmented blood flow may increase vascular shear stress, and enhanced shear stress itself plays an important role in the maintenance of a functional endothelium (Niebauer 1996; Ozawa 2001; Soran 1999). Some studies have shown that increased shear stress can stimulate the release of a vasodilator, nitric oxide, and also inhibit the release of a vasoconstrictor, endothelial endothelin-1 (ET-1) (Akhtar 2006; Barsness 2001).
3. ECP may influence angiogenesis, which may also improve collateral perfusion. ECP may increase the endothelial shear stress, which is considered as a major stimulus for collateral development (Kersten 1999). Meanwhile, increased shear stress may upregulate the endothelial production of growth factors, such as vascular endothelial growth factor (VEGF), which plays a key role in angiogenesis (Gan 2000), thus angiogenesis is promoted by ECP.

Why it is important to do this review

ECP has been approved for use in angina, myocardial infarction, congestive heart failure and cardiogenic shock because it augments blood flow to cardiac and systemic circuits (Bonetti 2003; Lawson 2002). It may improve cerebral blood flow, so it has been proposed as a potential therapy for patients with brain ischaemia (Han 2008a). Although there are a few published studies about the clinical efficacy of ECP in patients with ischaemic stroke, the potential therapeutic effect is controversial. The aim of this review is to systematically analyse all the randomised controlled trials (RCTs) of ECP for acute ischaemic stroke in order to provide the best available evidence for clinical practice and further research planning for stroke treatment.

OBJECTIVES

To assess the efficacy and safety of ECP for acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, irrespective of blinding, publication status or language, comparing ECP therapy with sham therapy or no therapy, were eligible for inclusion. We excluded trials in which the authors reported only laboratory parameters.

Types of participants

Trials that included patients of any age or sex with acute ischaemic stroke (within seven days of onset) were eligible. The clinical definition of ischaemic stroke is that of the World Health Organization criteria (Hatano 1976) with computerised tomography (CT) or magnetic resonance imaging (MRI) scanning to exclude haemorrhagic stroke.

Types of interventions

We included trials evaluating ECP in patients with ischaemic stroke, regardless of the frequency, intensity or the duration of treatment. The control interventions were sham treatment or no treatment. We also included trials where the addition of ECP to another treatment was compared with the other treatment alone.

Types of outcome measures

Primary outcomes

Death or dependency at the end of long-term follow-up (at least three months). Dependency is defined as a Barthel Index (BI) score less than or equal to 60, a modified Rankin Scale (mRS) of grade 3 to 5, or the trialists' own definition.

Secondary outcomes

1. Death from all causes within the first two weeks of treatment and by the end of the scheduled treatment period.
2. Improvement of neurological impairment (e.g. National Institute of Health Stroke Scale (NIHSS), Canadian Neurological Scale (CNS), European Stroke Scale (ESS), Scandinavian Stroke Scale (SSS) or Chinese Stroke Scale (CSS), etc) at the end of the scheduled treatment.
3. Improvement of activities of daily living (ADL) (e.g. BI, mRS or trialists' own definition) at the end of long-term follow-up.
4. Adverse effects of the intervention (e.g. skin abrasion, low back pain and muscle ache).

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

Electronic searches

We searched the following databases:

- Cochrane Stroke Group Trials Register (which was last searched by the Managing Editor in June 2011);
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2011 Issue 2) (Appendix 1);
- MEDLINE (1948 to June 2011) (Appendix 2);
- EMBASE (1980 to June 2011) (Appendix 3);
- CINAHL (1982 to June 2011) (Appendix 4);
- AMED (Allied and Complementary Medicine) (1985 to June 2011) (Appendix 5);
- The China Biological Medicine Database (CBM) (1978 to June 2011);
- The Chinese National Knowledge Infrastructure (CNKI) (1979 to June 2011);
- Chinese Science and Technique Journals Database (VIP) (1989 to June 2011); and
- Wanfang Data (http://www.wanfangdata.com/) (1984 to June 2011).

The Cochrane Stroke Group Trials Search Co-ordinator developed the search strategies for CENTRAL, MEDLINE, EMBASE, CINAHL and AMED and we adapted the MEDLINE search strategy for the other databases.

Searching other resources

In an effort to identify further published, unpublished and ongoing studies we:

1. searched the following ongoing trials and research registers (which was last searched in June 2011):
   a. ClinicalTrials.gov (http://www.clinicaltrials.gov/);
   b. Current Controlled Trials (http://www.controlled-trials.com);
   c. Stroke Trials Registry (http://www.strokecenter.org/trials/);
   d. International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
   e. Chinese Clinical Trials Registry (http://www.chictr.org/(S(chtp1eftsefc1afxrfrpdp55))/Default.aspx);
2. searched databases of conference abstracts:
   a. Conference Proceedings Citation Index Science (CPCI-S) (1990 to June 2011);
   b. China Medical Academic Conferences (CMAC) in Chinese Medical Current Contents (CMCC) (1995 to June 2011);
3. searched reference lists from relevant articles and reviews;
4. contacted authors of relevant trials;
5. contacted manufacturers of external counterpulsation devices (Chongqing PSK-Health Sci-Tech Development Co Ltd, June 2011); and
6. used Science Citation Index Cited Reference Search for forward tracking of relevant references.

We searched for trials in all languages and arranged translation of relevant articles published in languages other than English and Chinese.

Data collection and analysis

Selection of studies

Two review authors independently scanned the titles, abstracts and keywords of records obtained from the electronic searches and excluded those that were obviously irrelevant. We obtained the full text of the remaining articles and selected those studies that met the selection criteria outlined previously. We resolved any disagreements through discussion and, when necessary, we consulted with a third review author (Ming Liu). If it had not been possible to resolve a disagreement, we planned to add the study to those awaiting assessment and to contact the study authors for clarification.

Data extraction and management

Two review authors independently extracted data on methods, patients, interventions, outcomes and results by using a data extraction form. The same two review authors cross-checked all extracted data and resolved any disagreements through discussion. If consensus could not be reached, we asked a third review author (Ming Liu) to make a final decision. For dichotomous outcomes, we extracted the number of participants experiencing the event and the total number of participants in each arm of the trial. For continuous outcomes, we extracted the mean value and standard deviation for the changes in each arm of the trial along with the total number in each group. When necessary, we contacted the study authors for additional unpublished data.

Assessment of risk of bias in included studies

We assessed the methodological quality of selected studies as described in section 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We scored each of the following points as 'low risk', 'high risk' or 'unclear risk' of bias and reported them in the 'Risk of bias' tables.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Other bias.

On the basis of these criteria, we divided studies into the following three categories.

1. A - all quality criteria met: low risk of bias.
2. B - one or more of the quality criteria only partly met: moderate risk of bias.
3. C - one or more criteria not met: high risk of bias.

Two review authors independently evaluated all the studies. They resolved any disagreements through discussion. If consensus could not be reached, they asked a third review author (Ming Liu) to make a final decision.

Measures of treatment effect

We expressed results for dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI), and expressed results for continuous outcomes as mean difference (MD) with 95% CI (if the same scale for each trial was available) or standardised mean difference (SMD) with 95% CI (if different scales were used).

Unit of analysis issues

For studies with non-standard designs (e.g. cross-over trials, cluster-randomised trials), we planned to manage the data according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). For example, if we had found any cross-over trials, we would only have analysed the data from the first period.

Dealing with missing data

If data were missing, we contacted the investigators for additional information. If some data remained unavailable, we considered both best-case and worst-case scenarios.

Assessment of heterogeneity

We determined heterogeneity according to the I^2 statistic.

Assessment of reporting biases

We used the funnel plot method (Egger 1997).

Data synthesis

We performed statistical analysis using the Cochrane Review Manager software, RevMan 5.1 (RevMan 2011) and performed all analyses in accordance with the intention-to-treat method. We reported the results as RR with 95% CI for dichotomous data and as MD or SMD with 95% CI for continuous data. We used the random-effects model to combine individual results. If there were no suitable studies, we provided a narrative summary of the study results.

Subgroup analysis and investigation of heterogeneity

If appropriate data were available, we intended to undertake subgroup analysis according to:

1. different times to the start of ECP therapy;
2. different intensity of ECP therapy; and
3. different duration of ECP therapy.

We quantified inconsistency across studies using the I^2 statistic.

Sensitivity analysis

We re-analysed the data excluding studies:

- with inadequate allocation concealment;
- not using sham therapy; and
- not using a blind rater to evaluate outcomes.

RESULTS

Description of studies

Results of the search

From a total of 1582 articles generated by the electronic searches and handsearches, we excluded 473 duplicates, 835 irrelevant references by reading the title and 258 references by reading the abstract or text. We identified 16 potentially eligible trials of which two completed trials (Han 2000; Wei 1995) and two ongoing trials (Guluma 2009; Wong 2007) met the inclusion criteria for this review. As for the remainder of the 16 trials identified, we excluded five trials (Han 2008b; Meng 2000; Sun 1989; Xu 1989; Zhang 2003) because they enrolled some patients with ischaemic stroke who were beyond seven days from onset, three trials (Cen 1994; Li 1997; Liu 2003) as they were not RCTs, another three trials (Li 2005; Yang 1996; Zhang 2001) because the comparison in each trial was inappropriate, and one trial (Gao 2009) on account of the inconsistent data in the text.

Included studies

Both included trials (Han 2000; Wei 1995) were conducted in China and published in Chinese journals. A total of 160 participants were enrolled in the two studies and the age of participants ranged from 46 to 80 years. One trial (Han 2000) only included males, the other (Wei 1995) included more males than females. Both of the included trials reported the inclusion criteria but did not report exclusion criteria. In one trial (Wei 1995), all patients were enrolled within the first 48 hours of stroke onset; in the other one (Han 2000), all patients were enrolled within the first 72 hours of stroke onset. The stroke severity of the participants were similar between treatment group and control group in each trial.

In the treatment groups of both trials, ECP was applied one hour once daily with a therapeutic pressure (about 290 to 330 mmHg). In both the treatment group and the control group of each trial, the same routine therapy (medicine or acupuncture, or both) was used. One trial reported the treatment period of ECP was 24 days (Wei 1995) while the other trial (Han 2000) did not mention the duration of treatment. Details of routine therapy are reported in the Characteristics of included studies table.

One trial (Wei 1995) evaluated the effect of ECP at the end of treatment on the number of participants with improvement of neurological impairment according to more than 45% decrease of Modified Edinburgh-Scandinavian Stroke Scale (MESSS) score. The other trial (Han 2000) applied a measurement of neurological impairment that was similar to MESSS but defined by the trialists themselves. None of the participants in either of the trials were followed up after treatment was discontinued. No deaths were reported in either trial. Assessment of quality of life was not undertaken in either of the trials. Only one trial (Han 2000) reported no adverse events.

All information of included trials is presented in the Characteristics of included studies table.

As for the two ongoing trials, one (Wong 2007) was conducted in China, the other (Guluma 2009) in the USA. For details of the ongoing trials, see Characteristics of ongoing studies table.

Excluded studies

The reasons for excluding 12 trials are given in the Characteristics of excluded studies table.

Risk of bias in included studies

Allocation

The two included trials reported 'randomly allocating' participants but the method of randomisation was not described. Meanwhile, no trial stated the method of allocation concealment. Thus, we graded random sequence generation and allocation concealment for these trials as unclear risk of bias.

Blinding

No trial used sham ECP (placebo) as the control. None of the investigators stated the method of blinding, so we did not know what kind of blinding method for participants and outcome assessors was used in these included trials. We assessed blinding as unclear risk of bias.

Incomplete outcome data

No patients were lost to follow-up. None of the included trials stated an intention-to-treat analysis. This we assessed as low risk of bias.

Selective reporting

No trial protocol was available, and we were not sure of any selective reporting of data. Therefore, there was insufficient information for us to make a judgement on selective reporting. We assessed this as unclear risk of bias.

Other potential sources of bias

We were not sure of any potential publication bias, however, this could not be investigated by using a funnel plot as only two trials were included.

Effects of interventions

Primary outcome measures

Death or dependency at the end of long-term follow-up (at least three months)

Neither trial observed the long-term effect of ECP on death or dependency at the end of follow-up.

Secondary outcomes measures

Death from all causes within the first two weeks of treatment and by the end of the scheduled treatment period

No death was reported within the first two weeks of treatment or by the end of the scheduled treatment period.

Improvement of neurological impairment at the end of the scheduled treatment

The outcomes measured after treatment were assessed according to MESSS or similar to MESSS in both trials. Meta-analysis of the two trials, which used a dichotomous outcome variable, showed that a significantly higher proportion of participants treated with ECP had an improvement of their neurological impairment at the end of treatment compared with the control participants (RR 1.75, 95% CI 1.37 to 2.23) (See Analysis 1.1).

Improvement of ADL at the end of long-term follow-up

Assessment of improvement of ADL was not undertaken in either trial.

Adverse effects

Only one trial (Han 2000) reported no adverse effects.

Subgroup analysis

Effects in patients with different times to the start of ECP therapy

Neither of the two trials reported the accurate starting time of treatment. Therefore, we could not perform this subgroup analysis.

Effects in patients with different intensity of ECP therapy

The intensity of ECP therapy was similar (about 290 to 330 mmHg one hour once daily) in both included studies. Therefore, it was not possible to do a subgroup analysis for different intensity of ECP therapy.

Effects in patients with different duration of ECP therapy

Only one trial stated the duration of ECP therapy, thus it was not appropriate data to perform a subgroup analysis.

Sensitivity analysis

Excluding studies with inadequate allocation concealment

The method of allocation concealment was unclear in both included studies. Therefore, such sensitivity analyses could not be done. In future, investigators of RCTs should describe the methods of allocation concealment in detail when the trial results are published.

Excluding studies not using sham therapy

No study used sham therapy in the control group. To measure the effect of ECP for ischaemic stroke objectively, sham therapy should be used in the control group in future RCTs.

Excluding studies not using a blinded rater to evaluate outcomes

Neither trial stated whether a blinded rater was used to evaluate outcomes. Thus, there were no adequate data to conduct sensitivity analysis.

DISCUSSION

Summary of main results

We included two RCTs (including 160 participants) of ECP for acute ischaemic stroke. The quality of these trials was generally poor. There is no convincing evidence to support the routine use of ECP for the treatment of patients with acute ischaemic stroke.

Neither of the trials reported the primary outcome (death or dependency at the end of long-term follow-up) for this review. Both trials only evaluated the effect of ECP at the end of treatment on the number of participants with improvement of neurological impairment. Meta-analysis of the two trials, which used a

dichotomous outcome variable, showed that a significantly higher proportion of participants treated with ECP had an improvement of their neurological impairment at the end of treatment period compared with the control participants (RR 1.75, 95% CI 1.37 to 2.23). Only one trial reported no adverse effects.

Overall completeness and applicability of evidence

The methodological quality of the included studies was poor, and reliable conclusions could not be drawn from the present data.

Several studies have certified that ECP was safe and feasible for patients with ischaemic stroke. Some key points of ECP treatment for patients with ischaemic stroke should be appreciated in future studies as follows.

Subtype of ischaemic stroke

Han et al (Han 2010) have indicated that it is important to identify the subtype of patients with ischaemic stroke who may benefit most from ECP treatment. In this review, we do not have sufficient data to analysis the effect of ECP for different subtypes of ischaemic stroke. Therefore, there is not enough evidence to prove which subtype of patients with ischaemic stroke might benefit most. More RCTs comparing ECP for different subtypes of ischaemic stroke are necessary to address this question.

Time window, intensity and duration of ECP treatment

We planned to carry out a subgroup analysis of ECP effects in patients with different starting times of treatment. However, no trial reported the accurate time of treatment being started. Some salvageable brain tissue may exist up to eight to 24 hours from symptom onset, while availability of a low-risk non-invasive intracranial blood flow augmentation device would provide a treatment option to a large number of patients with ischaemic stroke (Alexandrov 2008), so it is important to demonstrate whether there is a specific time window of ECP for treating patients.

We also planned to do some subgroup analyses of the effects on patients of different intensity or duration of ECP. However, the intensity of ECP was the same in both included trials, and only one trial stated the duration of ECP treatment. To the best of our knowledge, no clinical study or even animal model assessment has ever been carried out to explore whether ECP therapy has a different therapeutic effect under a different intensity or duration of treatment for patients with acute ischaemic.

As a result, more high-quality, large-scale RCTs are needed to address which time window, intensity and duration of ECP treatment are optimal for patients with ischaemic stroke.

Age

Most clinical trials of main therapies exclude patients over 80 years old (Wenger 2006), for example, most of the large trials on thrombolysis such as ECASS-3 (Hacke 2008) and DIAS-2 (Hacke 2009). But, some studies have suggested that age alone should not preclude very elderly patients from participating in clinical trials (Wang 2011). In this review, the age of the participants varied between 46 and 80 years and there is no information on ECP therapy on elderly patients with ischaemic stroke. Therefore, further RCTs should enrol patients over 80 years.

Quality of the evidence

The evidence summarised in this review comes from two small and low-quality studies in which the total number of participants was 160. A robust conclusion cannot be drawn about the effectiveness of ECP for acute ischaemic stroke. Key methodological limitations of the included studies and recommendations for future trials are detailed below (see Implications for research).

Potential biases in the review process

We are sure that we have identified the existing large trials relevant to our question. However, we cannot deny the possibility that there are additional trials which are unpublished or published in sources not covered by our search. This may lead to some biases.

Agreements and disagreements with other studies or reviews

We did not find any other studies or reviews of ECP for acute ischaemic stroke.

AUTHORS' CONCLUSIONS

Implications for practice

This review does not provide convincing evidence to support the routine use of ECP for the treatment of patients with acute ischaemic stroke.

Implications for research

This review suggests that ECP may improve neurological impairment after acute ischaemic stroke. High-quality, large-scale RCTs are needed to confirm or refute these results. Future trials should overcome the limitations of the trials presented in this review.

The following features should be addressed in future studies:

- adequate random sequence generation and allocation concealment;
- sham therapy (placebo) control;
- blinding of investigator, participants and outcome assessors;
- use of internationally accepted scales and endpoint measurements of primary outcome measurements at long-term follow-up should be made;
- adverse events should be critically assessed;
- description of withdrawal and use of intention-to-treat analysis;
- reports of the trials should conform to the recommendations of the CONSORT statement.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Han 2000

Methods	RCT Method of randomisation: not stated Allocation concealment: not stated Blinding: not stated ITT analysis: not stated Losses to follow-up: none
Participants	Country: China 94 participants with acute ischaemic stroke within 72 hours (46 treatment, 48 control) Sex: all males Age: 46 to 80 years Comparability: age and stroke severity similar

Han 2000 *(Continued)*

Interventions	Treatment: ECP 1 hour once daily with therapeutic pressure (about 290 mmHg) plus compound danshen injection 20 ml once daily plus hydroxyethyl starch 500 ml once daily plus acupuncture Control: compound danshen injection 20 ml once daily plus hydroxyethyl starch 500 ml once daily plus acupuncture
Outcomes	Number of participants with neurological improvement (as defined by the trialists; similar to MESSS) at the end of the treatment period
Notes	Duration of ECP therapy: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation was reported but the method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available, and we were not sure of any selective reporting of the results
Other bias	Unclear risk	There was Insufficient information to assess whether an important risk of bias exists

Wei 1995

Methods	RCT Method of randomisation: not stated Allocation concealment: not stated Blinding: not stated ITT analysis: not stated Losses to follow-up: none
Participants	Country: China 66 participants with acute ischaemic stroke within 48 hours (33 treatment, 33 control); all had brain CT scan proven

Wei 1995 *(Continued)*

	Sex: treatment: 30 males, 3 females; control: all males Age: treatment: 55 to 75 years, 62.3 ± 4.6 years; control: 48 to 80 years, 63 ± 5.2 years Comparability: stroke severity similar
Interventions	Treatment: ECP 1 hour once daily with therapeutic pressure (about 290 to 330 mmHg) for 24 days plus dextran 40 and venoruton for 28 days Control: dextran 40 and venoruton for 28 days
Outcomes	Number of participants with neurological improvement (MESSS score decrease > 45%) at the end of the treatment period (28 days)
Notes	Duration of ECP therapy: 24 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation was reported but the method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available, and we were not sure of any selective reporting of the results
Other bias	Unclear risk	There was Insufficient information to assess whether an important risk of bias exists

CT: computerised tomography
ECP: external counterpulsation
ITT: intention-to-treat
MESSS: Modified Edinburgh-Scandinavian Stroke Scale
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cen 1994	Quasi-RCT

Study	Reason for exclusion
Gao 2009	The data of this trial was inconsistent in the text
Han 2008b	Some eligible patients over 7 days from onset
Li 1997	Not RCT
Li 2005	The comparison was inappropriate: ECP + ligustrazine injection + naoxing decoction versus nimodipine tablets + decoction placebo
Liu 2003	Quasi-RCT
Meng 2000	Some eligible patients over 7 days from onset
Sun 1989	Some eligible patients over 7 days from onset
Xu 1989	Some eligible patients over 7 days from onset
Yang 1996	The comparison was inappropriate: ECP versus danshen injection
Zhang 2001	The comparison was inappropriate: ECP versus dextran 40 + danshen injection
Zhang 2003	Some eligible patients over 7 days from onset

ECP: external counterpulsation
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Guluma 2009

Trial name or title	A randomised, controlled phase 1 study of external counterpulsation as a treatment for acute ischaemic stroke
Methods	RCT Blinding: single blind (subject) Intervention model: parallel assignment Placebo control
Participants	Country: USA Estimated enrolment: 40 Ages eligible for study: 18 to 85 years Genders eligible for study: both Inclusion criteria: • Adults between the ages of 18 and 85, inclusive • Symptoms consistent with acute ischaemic stroke, with a measurable neurological deficit at presentation • Ability to initiate external counterpulsation within 48 hours of stroke onset • No evidence of haemorrhage on CT scan or MRI

Guluma 2009 *(Continued)*

- MCA distribution stroke: a total or partial anterior circulation infarct (TACI or PACI by Oxfordshire criteria) consistent with MCA distribution ischaemia, or a lacunar stroke felt by the investigator to possibly involve a deep perforating branch in the MCA territory (LACI by Oxfordshire criteria)

Exclusion criteria:

- Rapidly resolving stroke symptoms consistent with a transient ischaemic attack
- Severe stroke defined as an NIHSS > 22
- Intracranial haemorrhage (SAH, EDH, SDH, IPH, haemorrhagic conversion) on CT scan
- Brain tumour or brain abscess on CT scan or MRI
- Presentation consistent with SAH (such as a sudden, severe thunderclap headache, or an associated third nerve palsy)
- History of cerebral aneurysm, AVM, or haemorrhagic stroke
- Either treatment or planned treatment of current stroke with standard thrombolytic therapy (intravenous or intra-arterial) or neurothrombectomy
- History of lower limb amputation above the ankle
- History of untreated aortic dissection
- History or suspicion of thoracic or abdominal aortic aneurysm
- Known significant anomaly of the heart, aorta, or great vessels that would be complicated by elevated diastolic pressures
- BP > 180/100 that remains so after minimal treatment (such as 1 or 2 doses of an antihypertensive agent, or as determined by the investigator)
- History of non-trivial aortic regurgitation, or any symptomatic valvular heart disease determined by the investigator to be at risk of worsening on ECP
- Significant symptomatic congestive heart failure (orthopnoea, CHF-related dyspnoea, or rales and jugular venous distention on exam) or a left ventricular ejection fraction known to be < 30%
- Diagnosis of significant lower extremity peripheral vascular occlusive disease (PVOD), or symptomatic PVOD as determined by the investigator (especially symptoms of claudication)
- Phlebitis, stasis ulcer, severe varicosities
- Diagnosis of DVT within the past month, or current symptoms strongly suggestive of new DVT, such as asymmetric calf or leg swelling, discomfort, or erythema (to be evaluated by screening duplex)
- Pacemaker or automated implanted defibrillator (AICD)
- A cardiac dysrhythmia (such as atrial fibrillation or atrial flutter, or frequent premature ventricular contractions (PVCs) or premature atrial contractions (PACs) as determined by the investigator) that would interfere with ECP triggering
- Pregnancy (as determined by a urine pregnancy test in females of child-bearing age)
- Known coagulopathy, thrombocytopenia with platelet count < 100,000, or taking warfarin with an INR > 2.0
- History positive for chronic low back pain, radiculopathy suggestive of herniated lumbar disc, or related surgery
- Known collagen vascular disease
- Obesity to a degree (as determined by the investigator) that would prevent proper placement and/or activation of counterpulsation cuffs
- Any psychological, social, or legal condition that would interfere with the ability of the patient or his or her surrogate to give Informed Consent and/or his or her capacity to comply with all study requirements, including the necessary time commitment
- An inadequate temporal window for TCD insonation
- Currently involved or have been involved in a clinical trial within the last 30 days

Interventions	Treatment: ECP at a full pressure: a 1-hour treatment of ECP at full pressure, which will be applied in a tiered, dose-escalating manner, starting at 200 mmHg and increasing up to 300 mmHg based on assessments made Control: ECP at sham-pressure: a 1-hour treatment of ECP at an inactive pressure, which will be applied at 75 mmHg and kept there for the hour while assessments are made

Guluma 2009 *(Continued)*

Outcomes	Primary outcome measures: • Feasibility and tolerability of ECP; time frame: during 1 hour of treatment; designated as safety issue: no • Safety (including endpoints such an increase NIHSS during or immediately after ECP, and acute haemorrhage on repeating imaging, serious adverse events related to ECP, mortality); time frame: 30 days; designated as safety issue: yes Secondary outcome measures: • Acute change in NIHSS during or immediately after ECP; time frame: within the 1-hour treatment period and immediately after treatment; designated as safety issue: no • NIHSS at 7 days and 30 days post-randomisation; time frame: 30 days; designated as safety issue: no • Lesion size on day 30 head CT; time frame: 30 days; designated as safety issue: no
Starting date	December 2009
Contact information	ClinicalTrials.gov identifier: NCT00983749 Principal Investigator: Kama Z Guluma MD, University of California, San Diego, USA
Notes	Estimated study completion date: December 2011 Duration of follow-up: 30 days

Wong 2007

Trial name or title	A multi-centre, randomised, controlled study of external counterpulsation for patients with recent atherosclerotic stroke
Methods	RCT Blinding: open label Intervention model: parallel assignment
Participants	Country: China Estimated enrolment: 250 Ages eligible for study: not less than 18 years Genders eligible for study: both Inclusion criteria: • Participant is aged not less than 18 • Participant is presented with clinical diagnosis of ischaemic stroke according to the WHO criteria • Recent ischaemic stroke is within 7 days of symptom onset • Participant is found to have motor deficit as a result of stroke • Participant has brain CT performed and results confirmed no evidence of intracerebral haemorrhage • NIHSS is between 4 and 16 inclusive • Pre-stroke mRS 0 to 1 • Evidence of large artery occlusive disease. If no diagnostic procedure is done before randomisation, neuroimaging should be done within 3 days of randomisation

Wong 2007 *(Continued)*

	• Participant or his/her legally acceptable representative is willing to provide written informed consent Exclusion criteria: • Participant is aged less than 18 • Participant has evidence for cardioembolic stroke such as atrial fibrillation and rheumatic heart disease • Participant has evidence for haemorrhage on brain CT • Participant has a history of intracerebral haemorrhage • Participant has evidence for AVMs, AV fistula or aneurysm • Participant has active malignancy • Participant has no definite motor deficit • Participant has a NIHSS of less than 4 or greater than 16 • Participant has sustained hypertension (systolic >180 mmHg or diastolic > 100 mmHg) • Participant is unlikely to be followed up at Week 12 • Participant has co-existing systemic diseases: renal failure (creatinine > 300 µmol/L, if known), cirrhosis, severe dementia or psychosis • Participant has brain tumour or other significant non-ischaemic brain lesion on CT • Participant has thrombocytopenia (platelet count < 100,000/mm^3, if known) • Participant is a pregnant female, a breast-feeding mother, is planning pregnancy during the course of the trial or has a positive urine pregnancy test immediately prior to randomisation • Participant is participating in another clinical trial within 30 days before randomisation • Participant or his/her legally acceptable representative is unwilling to provide written informed consent
Interventions	Treatment: external counterpulsation 35 x 1-hour sessions over a 7-week period
Outcomes	Primary outcome: • Combined endpoint ("good outcome") at 12 weeks defined as the overall surviving patients with mRS 0 to 2 (i.e. bad outcome as death or mRS 3 to 5) Secondary outcome: • NIHSS at end of week 7 and 12; difference of NIHSS between baseline and week 12; mRS at week 7 and 12 (0 to 1 as "good outcome"); Barthel Index at week 7 and 12
Starting date	1 May 2007
Contact information	Registration number: ChiCTR-TRC-09000706 Dr Ka Sing Wong, Department of Medicine and Therapeutics, Hong Kong, SAR, China Tel: 2632-3471 Email: ks-wong@cuhk.edu.hk
Notes	Duration of follow-up: 12 weeks

AICD: automated implanted defibrillator
AVM: arteriovenous malformation
BP: blood pressure
CHF: congestive heart failure
CT: computerised tomography
DVT: deep venous thrombosis
ECP: external counterpulsation
EDH: extradural haemorrhage

INR: International Normalised Ratio
IPH: intraparenchymal haemorrhage
LACI: lacunar infarction
MCA: middle cerebral artery
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
PACI: partial anterior circulation infarct
PVOD: peripheral vascular occlusive disease
RCT: randomised controlled trial
SAH: subarachnoid haemorrhage
SDH: subdural haemorrhage
TACI: total anterior circulation infarct
TCD: transcranial doppler
WHO: World Health Organization

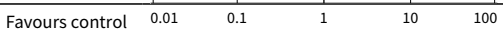
DATA AND ANALYSES

Comparison 1. ECP versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of neurological impairment at the end of the scheduled treatment (dichotomous)	2	160	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.37, 2.23]

Analysis 1.1. Comparison 1 ECP versus control, Outcome 1 Improvement of neurological impairment at the end of the scheduled treatment (dichotomous).

Study or subgroup	ECP n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Han 2000	40/46	25/48		68.09%	1.67[1.24,2.24]
Wei 1995	27/33	14/33		31.91%	1.93[1.26,2.96]
Total (95% CI)	**79**	**81**		**100%**	**1.75[1.37,2.23]**
Total events: 67 (ECP), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=4.52(P<0.0001)					



APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1.MeSH descriptor cerebrovascular disorders this term only
#2.MeSH descriptor basal ganglia cerebrovascular disease this term only
#3.MeSH descriptor brain ischemia explode all trees
#4.MeSH descriptor carotid artery diseases this term only
#5.MeSH descriptor carotid artery thrombosis this term only
#6.MeSH descriptor intracranial arterial diseases this term only

#7.MeSH descriptor cerebral arterial diseases this term only
#8.MeSH descriptor intracranial embolism and thrombosis explode all trees
#9.MeSH descriptor stroke explode all trees
#10.(ischaemic in Title, Abstract or Keywords or ischemic in Title, Abstract or Keywords)
#11.(stroke* in Title, Abstract or Keywords or apoplex* in Title, Abstract or Keywords or (cerebral in Title, Abstract or Keywords and vasc* in Title, Abstract or Keywords) or cerebrovasc* in Title, Abstract or Keywords or cva in Title, Abstract or Keywords or attack* in Title, Abstract or Keywords)
#12.(#10 and #11)
#13.(brain in Title, Abstract or Keywords or cerebr* in Title, Abstract or Keywords or cerebell* in Title, Abstract or Keywords or vertebrobasil* in Title, Abstract or Keywords or hemispher* in Title, Abstract or Keywords or intracran* in Title, Abstract or Keywords or intracerebral in Title, Abstract or Keywords or infratentorial in Title, Abstract or Keywords or supratentorial in Title, Abstract or Keywords or (middle in Title, Abstract or Keywords and cerebr* in Title, Abstract or Keywords) or mca* in Title, Abstract or Keywords or (anterior in Title, Abstract or Keywords and circulation in Title, Abstract or Keywords))
#14.(ischemi* in Title, Abstract or Keywords or ischaemi* in Title, Abstract or Keywords or infarct* in Title, Abstract or Keywords or thrombo* in Title, Abstract or Keywords or emboli* in Title, Abstract or Keywords or occlus* in Title, Abstract or Keywords or hypoxi* in Title, Abstract or Keywords)
#15.(#13 and #14)
#16.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #12 or #15)
#17.MeSH descriptor counterpulsation this term only
#18.MeSH descriptor assisted circulation this term only
#19.(counterpulsation in Title, Abstract or Keywords or "counter pulsation" in Title, Abstract or Keywords or counter-pulsation in Title, Abstract or Keywords or ECP in Title, Abstract or Keywords or EECP in Title, Abstract or Keywords or "diastolic augmentation" in Title, Abstract or Keywords or counterpressure in Title, Abstract or Keywords or "counter pressure" in Title, Abstract or Keywords or CardiAssist in Title, Abstract or Keywords)
#20.(augment* in Title, Abstract or Keywords or assist* in Title, Abstract or Keywords)
#21.(perfusion in Title, Abstract or Keywords or "blood flow" in Title, Abstract or Keywords or circulation in Title, Abstract or Keywords)
#22.(#20 and #21)
#23.(#17 or #18 or #19 or #22)
#24.(#16 and #23)

Appendix 2. MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. assisted circulation/ or counterpulsation/
6. (counterpulsation or counter pulsation or counter-pulsation or ECP or EECP or diastolic augmentation or counterpressure or counter pressure or CardiAssist).tw.
7. ((augment$ or assist$) adj5 (perfusion or blood flow or circulation)).tw.
8. 5 or 6 or 7
9. 4 and 8

Appendix 3. EMBASE (Ovid) search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/
2. stroke patient/ or stroke unit/
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
5. 1 or 2 or 3 or 4
6. assisted circulation/ or counterpulsation/
7. (counterpulsation or counter pulsation or counter-pulsation or ECP or EECP or diastolic augmentation or counterpressure or counter pressure or CardiAssist).tw.
8. ((augment$ or assist$) adj5 (perfusion or blood flow or circulation)).tw.
9. 6 or 7 or 8
10. 5 and 9

Appendix 4. CINAHL (Ebsco) search strategy

S16 .S9 and S15
S15 .S10 or S11 or S14
S14 .S12 and S13
S13 .TI (perfusion or blood flow or circulation) or AB (perfusion or blood flow or circulation)
S12 .TI (augment* or assist*) or AB (augment* or assist*)
S11 .TI (counterpulsation or counter pulsation or counter-pulsation or ECP or EECP or diastolic augmentation or counterpressure or counter pressure or CardiAssist) or AB (counterpulsation or counter pulsation or counter-pulsation or ECP or EECP or diastolic augmentation or counterpressure or counter pressure or CardiAssist)
S10 .(MH "Assisted Circulation") OR (MH "Counterpulsation")
S9 .S1 or S2 or S5 or S8
S8 .S6 and S7
S7 .TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)
S6 .TI (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebr* or mca* or anterior circulation) or AB (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebr* or mca* or anterior circulation)
S5 .S3 and S4
S4 .TI (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva or attack*) or AB (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva or attack*)
S3 .TI (ischemi* or ischaemi*) or AB (ischemi* or ischaemi*)
S2 .(MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Carotid Artery Diseases") OR (MH "Carotid Artery Thrombosis") OR (MH "Cerebral Ischemia+") OR (MH "Intracranial Arterial Diseases") OR (MH "Cerebral Arterial Diseases") OR (MH "Intracranial Embolism and Thrombosis+") OR (MH "Stroke")
S1 .(MH "stroke patients") or (MH "stroke units")

Appendix 5. AMED (Ovid) search strategy

1. cerebrovascular disorders/ or cerebral infarction/ or cerebral ischemia/ or cerebrovascular accident/ or stroke/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. 1 or 2 or 3
5. (counterpulsation or counter pulsation or counter-pulsation or ECP or EECP or diastolic augmentation or counterpressure or counter pressure or CardiAssist).tw.
6. ((augment$ or assist$) adj5 (perfusion or blood flow or circulation)).tw.
7. 5 or 6
8. 4 and 7

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: Sen Lin, Ming Liu, Bo Wu, Zilong Hao
- Develop a search strategy: Sen Lin, Ming Liu, Bo Wu, Zilong Hao
- Search for trials: Sen Lin, Bo Wu
- Obtain copies of relevant references: Sen Lin, Bo Wu, Zilong Hao
- Trials selection: Sen Lin, Jie Yang, Ming Liu
- Data extraction and data entry: Sen Lin, Wendan Tao
- Analysis, writing the final review and interpreting the results: Sen Lin, Ming Liu, Bo Wu, Zilong Hao
- The review will be updated by Sen Lin, Bo Wu

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Cerebrovascular Circulation; Brain Ischemia [physiopathology] [*therapy]; Counterpulsation [*methods]; Randomized Controlled Trials as Topic [standards]; Stroke [physiopathology] [*therapy]; Treatment Outcome

MeSH check words

Humans