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[Intervention Review]

Enhanced external counterpulsation for chronic angina pectoris

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ABSTRACT

Background

Cardiovascular disease is a major cause of death in developed and developing countries. Refractory stable angina pectoris is, in general, inadequately responsive to conventional medical therapy.

Enhanced external counterpulsation is a non-invasive treatment for patients with refractory angina and involves the placing of compressible cuffs around the calves and lower and upper thighs. These are inflated sequentially so that during early diastole they help propel blood back to the heart and when deflated at end of diastole allow the blood vessels to return to their normal state. It is claimed that enhanced external counterpulsation can help reduce aortic impedance and thereby alleviate some of the symptoms of angina.

Objectives

To assess the effects of enhanced external counterpulsation therapy in improving health outcomes for patients with chronic stable or refractory stable angina pectoris.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (2008, Issue 1), MEDLINE (1966 to February 2008), EMBASE (1980 to February 2008), LILACS via BIREME (to February 2008) and ISI Science Citation Index on Web of Science (to February 2008). No language restrictions were applied.

Selection criteria

Randomized controlled trials and cluster-randomized trials comparing enhanced external counterpulsation therapy to sham treatment in adults, aged over 18 years, with chronic stable and stable refractory angina pectoris graded Canadian Cardiovascular Society Class III to IV at baseline.

Data collection and analysis

Two authors independently screened papers, extracted trial details and assessed risk of bias.

Main results

One trial (139 participants) was included in this review. Poor methodological quality, in terms of trial design and conduct, incompleteness in reporting of the review's primary outcome, limited follow up for the secondary outcomes and subsequent flawed statistical analysis, compromised the reliability of the reported data.

Authors' conclusions

We found one relevant trial which failed to address the characteristics of interest satisfactorily, in terms of severity of angina, for the participants in this review. Participants with the most severe symptoms of angina were excluded, therefore the results of this study represent only a subsection of the broader population with the disorder, are not generalizable and provide inconclusive evidence for the effectiveness of enhanced external counterpulsation therapy for chronic angina pectoris.

PLAIN LANGUAGE SUMMARY

Does enhanced external counterpulsation reduce symptoms of chronic and refractory angina pectoris?

Angina pectoris is a form of cardiovascular disease. Symptoms include episodic tightness in the chest accompanied by pain in the jaw, back, shoulder or arm and normally last for between 1 to 5 minutes. Angina is classified according to its severity and may be treated with drugs, lifestyle modifications, education and counselling. Refractory angina is a form of angina that does not respond well to conventional treatments and patients experience limitations in their ability to undertake physical activity.

Enhanced external counterpulsation is a treatment that involves placing cuffs around the legs of a patient, which when inflated assist blood to return to the heart and as the cuffs deflate allow blood vessels to return to normal. It is believed that this treatment may alleviate some of the symptoms of angina. Treatment consists of one hour daily sessions for a period of up to seven weeks and is performed in a medically supervised environment.

This review studied the effectiveness and safety of enhanced external counterpulsation in improving health outcomes for patients aged 18 years or over with chronic stable and refractory angina (graded Canadian Cardiovascular Society angina class III to IV). The review compared outcomes in patients treated with enhanced external pulsation to patients treated with a sham treatment. Searches found over 300 potentially eligible studies however only one study met most of the inclusion criteria. The study used in the review involved 139 participants in the United States. Participants in the study were treated with hour long sessions, either once or twice daily of active enhanced external counterpulsation or inactive enhanced external counterpulsation (sham). Limited data was available on the health related outcomes of patients participating in the study; however health related quality of life outcomes were larger in the enhanced external counterpulsation patients than patients receiving the inactive (sham) treatment; but the improvement was only significant in three of nine parameters. Angina pain counts decreased in the patients receiving enhanced external counterpulsation and this result was statistically significant.

55% of patients receiving treatment reported adverse events compared to 26% in the control group with approximately half of these events considered as device-related. Adverse events reported included leg and back pain and skin abrasions.

The review found that there is a lack of reliable and conclusive evidence that enhanced external counterpulsation can improve symptoms of angina in patients with chronic stable or refractory forms of the condition.

BACKGROUND

Prevalence and aetiology

Cardiovascular disease is a major cause of death in developed and developing countries, accounting for 29% of the 56 million deaths annually worldwide, of which 12% are attributable to coronary artery disease or ischaemic heart disease (WHO 2002). Ischaemic heart disease affects the heart by restricting or blocking the flow of blood around it, resulting in lack of oxygen to the heart muscle and causing the classic pain of angina pectoris. It has been estimated to affect more than 250,000 patients each year in developed countries (Mannheimer 2002). Atherosclerosis (hardening of the arteries), in conjunction with a gradual narrowing of the coronary arteries as a result of plaque deposits in the artery walls, is the principal cause of ischaemic heart disease. It is a chronic process that begins during adolescence and leads to progressive disability and a reduction in the quality of life of affected individuals.

Symptoms and diagnosis

Angina is an episodic clinical condition typified by symptoms of intense tightness or heavy pressure in the chest, and pain in the jaw, shoulder, back or arm. Stable angina is defined as chest pain or discomfort that follows a consistent pattern and does not change in severity, duration, time of appearance, or the setting in which it occurs. It typically lasts one to five minutes and may be caused by periods of exertion or emotional stress. It is relieved by rest and the episodes are usually predictable (Gill 1999).

Refractory stable angina pectoris is characterized by symptoms that are in general inadequately responsive to conventional medical therapy. Patients with this form of angina have marked limitation of ordinary physical activity, may be unable to perform any ordinary physical activity without discomfort and are either unsuitable for, or unwilling to undergo, revascularization surgery (Mannheimer 2002).

Objective evidence of ischaemia is normally demonstrated by exercise treadmill testing, stress imaging studies and coronary arteriography (Kim 2002).

Classification of symptoms

The Canadian Cardiovascular Society (CCS) has established a classification system for the grading of angina (Campeau 1976).

- Grade I angina occurs with strenuous, rapid or prolonged exertion.
- Grade II angina is associated with slight limitation of ordinary activity, e.g. walking more than two blocks, climbing stairs, or under emotional stress.
- Grade III angina is associated with marked limitation of ordinary physical activity, e.g. walking one or two blocks on the level or climbing one flight of stairs.
- Grade IV is associated with inability to carry on any physical activity without discomfort; anginal syndrome may be present at rest.

Treatment options and management of angina

Cardiac rehabilitation for patients with angina pectoris is intended firstly to reduce the likelihood of further cardiac events and secondly to reduce symptoms of myocardial ischaemia and improve functional capacity. A range of treatment options is available: drug therapy (e.g. beta-blockers, calcium channel blockers, nitrates); lifestyle modifications (weight loss, smoking cessation, exercise programs); and education and counseling (SIGN 2007). More invasive procedures for patients with refractory angina who are unable to undergo conventional revascularization procedures might include percutaneous myocardial laser revascularization (PMR) and spinal cord stimulation (SCS), each of which carries a risk of complications (Kim 2002; Lanza 2007; Mannheimer 2002).

Enhanced external counterpulsation

In view of its non-invasive approach keen interest has been shown in the use of enhanced external counterpulsation in patients with refractory angina (persisting unsatisfactory control of anginal symptoms with medication). This technique involves the placing of compressible cuffs around the patient's calves and lower and upper thighs. These are then inflated sequentially such that during early diastole they help propel blood back to the heart and when deflated at end of diastole allow the blood vessels to return to their normal state. It is claimed that, in this way, enhanced external counterpulsation can help reduce aortic impedance in addition to improving coronary perfusion pressure and flow, and increasing collateralization, thereby providing a measure of lasting effect which can alleviate some of the symptoms of angina.

Continuous monitoring during treatment is via a finger plethysmogram and electrocardiogram (ECG) which are connected to a control and display console. Treatment is conducted by a trained technician in a medically supervised environment and consists of one-hour daily sessions for a period of up to seven weeks. Although the precise mode of action of this treatment is unclear several explanations have been suggested and include enhanced diastolic flow, the possible collateralization of coronary vessels and an improvement in endothelial function (Cohn 2006).

The effectiveness of this intervention for patients with refractory angina and heart failure has been investigated in a number of international studies over the last 20 years and more recent reports have sought to review this evidence (BCBSA 2002; MAS 2006).

OBJECTIVES

To evaluate the effectiveness and safety of enhanced external counterpulsation therapy in improving health outcomes for patients with chronic stable or refractory stable angina pectoris.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) including cluster-randomized trials.

Types of participants

Patients aged 18 years or over and of either gender with chronic stable and stable refractory angina pectoris, evaluated by clinical assessment and graded (Canadian Cardiovascular Society (CCS) angina class III to IV at baseline). We intended to include studies in which participants had previously undergone revascularization

surgery providing the distribution of participants was equal in both treatment and control groups.

Types of interventions

Enhanced external counterpulsation compared to sham treatment. The minimum follow up for this intervention was six months after completion of the last cycle of treatment.

Types of outcome measures

Primary outcomes

1. Health-related quality of life (HRQoL) parameters from baseline to the end of treatment or baseline to 12 months after treatment, assessed by any validated cardiac disease specific or generic instrument.

Secondary outcomes

1. Anginal pain: frequency of episodes, severity (expressed as scores obtained through any validated patient reported outcomes instrument, either generic or cardiac specific), duration of episode.
2. Nitroglycerin usage: frequency and dosage.
3. Limitation of normal physical activity including measures of endurance (exercise duration), i.e. exercise treadmill testing, expressed as between treatment group changes in exercise duration from baseline to post-treatment. Alternatively, to an electrophysiologic endpoint (> 1 mm ST segment depression).

Costs

We noted any economic data which were reported in any of the included studies.

Adverse effects

We noted any specific adverse effects related to any clinically diagnosed reactions to the active intervention, as reported in any of the included studies.

Search methods for identification of studies

Electronic searches

The following databases were searched on 29 February 2008: all databases in *The Cochrane Library* (2008, Issue 1) including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to February 2008), EMBASE (1980 to February 2008), the LILACS (Clinical Trials) database via the BIREME platform and ISI Science Citation Index on Web of Science.

The MEDLINE search strategy was combined with phases 1 and 2 of the Cochrane Sensitive Search Strategy for Randomized Controlled Trials (RCTs) as published in Appendix 5b.2 of the *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6* (updated September 2006) (Higgins 2006). Strategies were designed for each database, based on the search strategy developed for MEDLINE but revised appropriately for each database (see Appendix 1).

Searching other resources

We cross-checked the reference lists of potentially relevant clinical trials and examined the review authors' personal databases of trial reports to try to identify any additional trials. We made attempts to contact the investigators in several of the identified studies by electronic mail to ask for further trial details and information about any additional published or unpublished trials.

Although there were no language restrictions on included studies we did not identify any relevant non-English papers.

The authors of three studies were contacted for further information: Arora 1999 missing quality of life data (no response); May 2007 to clarify trial details and to ask for information about any future trials; and Loh 2006 , excluded at the abstract stage, but as this was a more recent study we contacted the authors for information about any missed or planned RCTs. They will contact us in the future about a planned study.

Data collection and analysis

Selection of studies

Two authors, Amani Al Hajeri (AAH) and Zbys Fedorowicz (ZF), independently assessed the abstracts of studies resulting from the searches. We obtained full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision. These two authors assessed the full text papers independently and resolved any disagreement on the eligibility of included studies through discussion and consensus, or if necessary through a third party (Bruce Manzer (BM)). After assessment, the authors eliminated from further review any remaining studies that did not match the inclusion criteria and noted the reasons for their exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

Two authors (ZF and BM) collected study details and outcomes data independently, using a predetermined form designed for this purpose. We entered study details into the 'Characteristics of included studies' table in RevMan 5 (RevMan 2008). The authors only included data if there was an independently reached consensus; we resolved any disagreements by consulting with a third author (Fawzi Amin (FA)).

We extracted the following details:

Study methods

1. Method of allocation.
2. Masking of participants, investigators and outcomes assessment.
3. Exclusion of participants after randomization and proportion of losses at follow up.

Participants

1. Country of origin.
2. Sample size.
3. Age.
4. Sex.
5. Inclusion and exclusion criteria.

Intervention

1. Duration and length of time in follow up.

Control

1. Duration and length of time in follow up.

Outcomes

1. Primary and secondary outcomes described in the 'Types of outcome measures' section.

The authors planned to use this information to help assess heterogeneity and the external validity of any included trials.

Assessment of risk of bias in included studies

Each review author then graded the selected study independently according to the criterion grading system described in the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0.0 (updated February 2008) (Higgins 2008).These authors compared the gradings and discussed and resolved any inconsistencies in the interpretation of inclusion criteria and their significance to the selected study. We assessed the following parameters of methodological quality and used them to help in evaluating the risk of bias within this study.

(1) Sequence generation

We graded this criterion as yes (adequate) or unclear. Adequate methods of randomization included; computer generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice.

(2) Allocation concealment

The authors graded this as yes (adequate), unclear or no (inadequate). Adequate methods of allocation concealment included either central randomization or sequentially numbered sealed opaque envelopes. We considered this criterion inadequate if there was an open allocation sequence and the participants and trialists could foresee the upcoming assignment.

(3) Blinding of participants, investigators and outcomes assessment

We assessed blinding using the following criteria (detection and performance bias):

1. blinding of participants (yes/no/unclear);
2. blinding of caregiver (yes/no/unclear);
3. blinding of outcome assessment (yes/no/unclear); and
4. blinding not feasible.

(4) Handling of withdrawals and losses

The authors graded this as yes (adequate), unclear and no (inadequate) according to whether there was a clear description given of the difference between the two groups of losses to follow up (attrition bias).

We categorized risk of bias in the included study according to the following:

A - low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met;
B - moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were partly met; or
C - high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Assessment of heterogeneity

Only one trial was included in this review and thus no assessment of heterogeneity was carried out, but if further trials are identified and included in future updates then the following methods will be used.

We will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included studies.

We will assess statistical homogeneity using a Chi^2 test and use the I^2 statistic to quantify inconsistency across any included studies. The I^2 test describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) and where a value greater than 50% may be considered substantial heterogeneity (Higgins 2003).

Assessment of reporting biases

If further trials are identified for inclusion in this review, we will assess publication bias according to the recommendations on testing for funnel plot asymmetry as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (Higgins 2008), and explore these in the Discussion if appropriate.

Data synthesis

Only a single trial was identified for inclusion in this review, but in view of the paucity of data for participants categorised Class III and the absence of any data for Class IV, the incompleteness of data for the relevant primary outcome and the uncertain reliability of the data reported for the secondary outcomes for this review, we entered no data into the RevMan analysis. For future updates of this review, or when further studies are identified, the following methods of data management will apply.

We will analyse the data using RevMan 5 and report the results according to Cochrane Collaboration criteria.

We will calculate the mean difference (MD) and 95% confidence intervals (CI) for continuous data obtained from visual analogue scales. We will calculate risk ratios (RR) and their 95% confidence intervals for all dichotomous data.

We will pool results of clinically and statistically homogeneous trials to provide estimates of the efficacy of the interventions only if the included studies have similar interventions received by similar participants. We will calculate number needed to treat to benefit (NNTB) and number needed to treat to harm (NNTH) for the whole pooled estimates.

For the synthesis and meta-analysis of any quantitative data we will use either the fixed-effect or random-effects models. If it is established that there is significant heterogeneity between the studies we will use the random-effects model.

In the event that there are insufficient clinically homogeneous trials for this intervention or insufficient study data that can be pooled we will conclude the review with a narrative synthesis.

Sensitivity analysis

If there are sufficient included studies we plan to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment, unclear or inadequate blinding of outcomes assessment and completeness of follow up.

RESULTS

Description of studies

Results of the search

After removal of duplicates, the search results produced 318 references to potentially eligible studies. After examination of the titles and abstracts of these references, we eliminated 288 and excluded them from further review. We obtained full text copies of the remaining 30 references and subjected them to further evaluation. We examined the bibliographical references of all of the studies but these did not provide any additional citations to potentially eligible trials.

We arranged to translate Yu 2006 from the Swedish to the English language and subsequently excluded this study, noting the reasons for its exclusion. The search results included two health technology assessment reports (BCBSA 2002; MAS 2006) which we examined and as they provided no additional RCTs over and above those all readily identified as potentially eligible we subsequently eliminated them from further evaluation.

After discussion between the review authors we resolved any remaining uncertainties on the eligibility of any of the studies by consensus and subsequently eliminated all except one (Arora 1999) of the remaining studies, noting the reasons for their exclusion in the 'Characteristics of excluded studies' table.

Included studies

Only one study, involving 139 participants, was included in this review (Arora 1999). A follow-up paper examined quality of life in a subset of the participants at one year after completion of treatment.

Characteristics of the trial setting and investigators

This was a multi-centre, prospective, randomized controlled trial conducted in seven university hospital medical centers in the US and was funded by a grant from Vasomedical, Inc., Westbury, New York, a manufacturer of the principal equipment used in this trial. The investigators did not declare any potential conflicts of interest. The providers and assessors of the treatments were research staff at the medical centers.

Characteristics of the participants

Only adults (21 to 81 years) with symptoms consistent with the Canadian Cardiovascular Society (CCS) classification of angina levels I, II or III, documented evidence of CAD and with an exercise treadmill test (ETT) positive for ischemia were recruited for this trial.

The trial excluded participants with unstable angina, overt congestive cardiac failure, with a pacemaker or implantable defibrillator, deep vein thrombosis, bleeding diatheses and warfarin use, those who have had myocardial infarction (MI) or undergone coronary artery bypass grafting (CABG) in the preceding three months or cardiac catheteriszation in the previous two weeks, those unable to undergo a treadmill test or if they were those enrolled in other cardiac rehabilitation programmes, were excluded.

Participants in this study that matched the relevant criteria for this review consisted only of those categorizsed as Class III: 15/66 (22.7%) in the sham group, and 17/71 (23.9%) in the active counterpulsation group. Those designated Class IV were excluded. A baseline exercise treadmill test (ETT), medical history and clinical examination were performed four weeks prior to treatment.

Characteristics of the interventions

Patients received hour-long sessions, once or twice daily, of active counterpulsation or inactive counterpulsation (sham) treatment for 35 hours over a four to seven -week period. Nitroglycerin (NTG) medication was permitted as and when required.

Characteristics of outcome measures

Health-related quality of life

Limited data for the primary outcome of this review, of health related quality of life (HRQoL), obtained from self- completed questionnaires (Medical Outcomes Study 36-Item Short Form Health Survey, Quality of Life Index-Cardiac Version III) at baseline, at the end of treatment and at 12 months, were available in a subsequent report of the trial.

Anginal pain counts

The frequency of self-reported anginal episodes was calculated by taking the average over three successive treatment days. Baseline data were calculated and represented by the number of episodes during the first three treatment sessions. Data were computed as percentage change in anginal counts, and differences between baseline and the end of treatment. Anginal counts were categorized according to levels of improvement at 50%, 25% to 49% or 0% to 24% and levels of deterioration at 1% to 25%, 26% to 50% or 51% to 100%.

Nitroglycerin usage

The number of nitroglycerin tablets taken in the 24-hour period prior to any treatment session, was calculated as the average on-demand usage.

Exercise duration

Exercise treadmill tests were conducted one week after completion of treatment with no further follow up. Duration of exercise was measured from initiation to the beginning of recovery. Time to ST segment depression: exercise initiation to horizontal/down sloping ST depression ≥ 1 mm, 80ms after the J point persisting for three beats.

Costs

No costs were reported.

Adverse events

Adverse events related to the device were reported in both groups. It was found that 39 (55%) of the treated group reported adverse events compared to 17 (26%) in the control group (P = 0.001). Ten of the 25 events reported by the 17 patients in the control

group were considered device-related, involving either the skin, lower legs or back. Thirty-seven of the 70 events reported by the 39 patients in the treated group were considered device-related. The remaining complaints in each group were considered minor and not directly related to treatment . Leg discomfort was reported in 11.6 ± 22.7% of sham sessions and 4.9 ± 18.7% of enhanced external counterpulsation (EECP) sessions (P = 0.06). Although 47 of the 95 events reported by both groups combined were considered device-related, only five patients withdrew from the study due to leg complaints (e.g. pain, abrasion).

Further details of this trial are available in the 'Characteristics of included studies' table.

Risk of bias in included studies

As more than one of the criteria used in the assessment of risk of bias were not met the included study was assessed as having a high risk of bias.

See the 'Risk of bias' table in the 'Characteristics of included studies'.

Effects of interventions

Primary outcomes

Health-related quality of life

The improvement in health-related quality of life was larger in the enhanced external counterpulsation (EECP) group than in the sham group. However, the difference was only significant in three out of nine parameters.

The response rate in these self-administered assessments (54% (71) (n = 35 sham treatment - 31% Class III; n = 36 EECP - 6% Class III)) was poor and skewed towards the sham treatment group. This precludes the use of the data, which have not been included in a RevMan analysis.

Secondary outcomes

Anginal pain counts

In the intention-to-treat analysis, angina counts were 0.76 ± 0.15 at baseline and 0.55 ± 0.27 post-treatment in the active-counterpulsation (CP) group. In the inactive-CP group, angina counts were 0.76 ± 0.13 at baseline and 0.77 ± 0.2 post-treatment. The difference between groups in the change in angina counts from baseline to post-treatment showed a trend to statistical significance (adjusted mean active CP: 20.11 ± 0.21 versus inactive CP: 0.13 ± 0.22; P < 0.09). In patients who completed 34 sessions, angina counts were 0.72 ± 0.14 at baseline and 0.57 ± 0.38 post-treatment in the active-CP group. In the inactive-CP group, angina counts were 0.77 ± 0.14 at baseline and 0.76 ± 0.22 post-treatment. The difference between groups in the change in angina counts from baseline was statistically significant (adjusted mean active CP: -0.033 ± 0.27 versus inactive CP: 0.15 ± 0.27; P < 0.035). A similar number of patients in each group showed a 0% to 25% level of improvement, but more patients reported a > 50% improvement in angina frequency, and fewer worsened in the active-CP group compared with the inactive-CP group (P < 0.05).

Nitroglycerin usage

In the intention-to-treat analysis, nitroglycerin usage was 0.47 ± 0.13 at baseline and 0.19 ± 0.07 post-treatment in the active-CP group. In the inactive-CP group, nitroglycerin usage was 0.51 ± 0.15 at baseline and 0.45 ± 0.19 post-treatment. The difference between groups in change in nitroglycerin usage from baseline to post-treatment was not significant (adjusted mean active CP: 20.32 ± 0.12 versus inactive CP: 20.10 ± 0.12; P < 0.1). In patients who completed 34 sessions, nitroglycerin usage was 0.39 ± 0.11 at baseline and 0.12 ± 0.04 post-treatment in the active-CP group. In the inactive-CP group, nitroglycerin usage was 0.56 ± 0.17 at baseline and 0.43 ± 0.21 post-treatment. The difference between groups in this parameter from baseline to post-treatment was not significant (adjusted mean: active CP: 20.32 ± 0.15 versus inactive CP: 20.19 ± 0.14; P < 0.1).

The report was unclear as to the precise number of Class III participants providing data for these outcomes. The validity and interpretability of the reported data were also compromised by inappropriate statistical analyses which further restricted their usefulness for these outcomes in our review, and they have therefore not been entered into a meta-analysis.

Exercise duration

There was a significant number of drop-outs and an intention-to-treat analysis of the data was therefore not carried out.

Adverse effects

Device related events were reported in both the EECP group and in the sham group and included leg and back pain and skin abrasions. A number of events which were considered non-device related were reported but the investigators did not clarify how these were determined.

DISCUSSION

Conventional approaches to the treatment of chronic angina include drug therapy, lifestyle modifications and revascularization techniques, the limitations of which are clearly acknowledged. Enhanced external counterpulsation (EECP) as an alternative and non-invasive modality should crucially seek to address at least some of the goals of treatment in chronic stable angina, notably an improvement in quality of life, a reduction in the incidence of myocardial infarction and a decrease in the number and severity of anginal episodes for the individual. The assessment of risk of bias of the one included study was consistent with that in other reports and somewhat disappointingly and singularly reflected its inability to provide reliable high-level evidence for the effectiveness of this intervention for patients with chronic angina pectoris, or to support its routine use.

The Blue Cross and Blue Shield Association Medical Advisory Panel (BCBSA 2002) stated that the evidence supporting the role of EECP as an effective treatment for heart failure is lacking in both quantity and quality, and the Ontario Medical Advisory Secretariat also concluded that there is insufficient evidence to support the effectiveness and safety of EECP treatment for patients with refractory stable Grade III to IV angina (Canadian Cardiovascular Society (CCS)) or heart failure (MAS 2006).

Identification of potential improvements in clinical care should be made through well-designed randomized clinical trials and their

findings should apply to a wider population than those included in the trial reported here. To minimize the effects of selection bias, trialists should aim to enrol a broad but representative cross-section of patients from the population of interest. The numerous exclusion criteria, in addition to the lack of participants classified as CCS Grade IV, in the included study restricted the eligible patient population and further diminished the generalizability of the findings of the intervention under evaluation.

AUTHORS' CONCLUSIONS

Implications for practice

Policy makers and healthcare providers need to be able to assess the generalizability of clinical trials carefully before applying their findings. The absence of participants within the study population of the included trial with characteristics relevant to the broader population of those with the disorder of interest therefore somewhat limited this trial's external validity and generalizability and it is most probable, therefore, that its results cannot be extrapolated to, and are of limited relevance to, patients with the severest symptoms of chronic angina pectoris.

Implications for research

There is a lack of reliable and conclusive evidence that enhanced external counterpulsation therapy can improve symptoms of angina and other relevant health outcomes for patients with chronic stable or refractory stable angina pectoris. In view of the continuing interest in this procedure as a treatment option further research to address the remaining uncertainties is justified.

Future research should focus on well-designed randomized controlled trials, with more consistent follow up and outcomes assessment, clearer reporting of trial details, plausible statistical analysis of data and conformity with the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arora 1999

Methods	Randomized, parallel group, multi-centre trial in the US from May 1995 to May 1997 Randomization in blocks of 10, equal assignment to treatment/control at each center Baseline ETT 4 weeks prior to treatment All medications unchanged Description of withdrawals: flow chart
Participants	RANDOMIZED: N = 139 (EECP 72, SHAM 67) all male. Withdrawals prior to treatment: 1 in each group (N = 137) WITHDRAWALS: In the EECP group 9 out of 12 withdrawn because of adverse events (9/12) and 3 out of 12 withdrawn for other reasons (3/12). In the SHAM group only 1 withdrawal from adverse events (1/1). COMPLETED TRIAL: N = 124: EECP 59; SHAM 65 Age: 53 to 73 (median 63) Race: 75% white, remainder black, Hispanic, Asian and other BASELINE CHARACTERISTICS: Canadian Cardiovascular Society classification (CCS) I: 26.3%; II: 50.4%; III: 23.3%. Previous CABG: 42.2% Medication: NTG = 80.4%; ASA = 89.1%; CCB = 58.3%; BB = 73.9%; lipid-lowering agents = 56% INCLUSION CRITERIA: 21 to 81 years; CCS I, II or III; documented evidence of CAD; ETT positive for ischaemia EXCLUSION CRITERIA: MI or CABG in the preceding 3 months; cardiac catheterization in preceding 2 weeks; unstable angina; overt congestive heart failure or a left ventricular ejection fraction ≤ 30%; significant valvular heart disease; BP > 180/100 Hg; permanent pacemaker or implantable defibrillator; non-bypassed L main stenosis > 50%; pregnant women or of childbearing potential; inability to undergo treadmill testing
Interventions	35 1-hour sessions (once or twice/day) of active counterpulsation (72) or inactive counterpulsation (67) over a 4 to 7-week period. Cuff pressure: active (300 mm Hg), inactive (75 mm Hg).
Outcomes	Self-reported anginal pain counts: frequency of episodes/day. Difference (% change) baseline to end of treatment categorised as: improvement 50%, 25% to 49%, 0% to 24%; worse 1% to 25%, 26% to 50%, 51% to 100%. Exercise duration: ETT solely 1 week post-treatment, no further follow up. Duration of exercise measured from initiation to beginning of recovery. Data availability: EECP 57 (79%), SHAM 58 (87%). No ITT analysis. Time to ST segment depression: exercise initiation-horizontal/down sloping ST depression ≥1 mm, 80 ms after J point persisting for 3 beats No ITT analysis

Arora 1999 *(Continued)*

	NTG usage: documented as the 24-hour period prior to treatment session Adverse events noted
Notes	Study sponsors: Vasomedical Inc., Westbury, New York

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "When an eligible patient was identified at a study center, his or her characteristics were communicated to the Study Coordinator at the Core Laboratory...eligible subjects were assigned at random...random codes generated in blocks of 10, with whole blocks assigned to one center". Comment: central allocation by a third party
Allocation concealment (selection bias)	Low risk	Quote: "Assignment was transmitted only to personnel administering EECP at each study center" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants: Quote: "...to prevent subjects from recognizing any observable differences between sham and active treatment, appointments were scheduled so as to minimize any opportunities for study subjects in one group to discuss their experience with others" Comment: the blinding of participants may have been compromised by the impossibility of blinding the healthcare providers Healthcare providers: Comment: not possible to blind Outcome assessors & data analysts: Quote: "Study personnel involved in collecting and processing data at the study centers and at the Core Laboratory remained blinded for the duration of the study" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear drop-outs and overall inconsistencies and lack of clarity in reporting and presentation of data. Missing data: only 71 (54%) of the participants in Arora 1999 provided data for the primary outcome of Health-related quality of life in the 12-month follow up reported in a separate paper.
Selective reporting (reporting bias)	Unclear risk	Lack of ITT analysis for 2 principal endpoints which were secondary outcomes for this review
Other bias	Unclear risk	Quote: "This study was funded by a grant from Vasomedical Inc., Westbury, New York", the supplier of equipment used in the study. The authors did not declare or report any potential conflicts of interest.

ASA = Aspirin
BB = Beta blockers
BP = Blood pressure
CABG = Coronary artery bypass grafting
CAD = Coronoary artery disease
CCB = Calcium channel blockers
CCS = Canadian Cardiovascular Society

EECP = enhanced external counterpulsation
ETT = exercise treadmill test
ITT = intention-to-treat analysis
MI = myocardial infarction
NTG = nitroglycerin

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

Study	Reason for exclusion
Abrams 2005	Clinical vignette; non-RCT
Arora 2002	Abstract, reviewing results from International EECP Patient Registry
Banas 1972	Non-RCT
Banas 1973	Non-RCT
Barsness 2001	Non-RCT; non-controlled study. International EECP Patient Registry (IEPR).
Bazaz 2001	Abstract for poster presentation reviewing results from International EECP Patient Registry
BCBSA 2002	Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) report, no additional RCTs identified
Beller 2002	Review, no additional RCTs identified
Campbell 2006	Observational study
Clapp 1974	Reference unobtainable
Cohn 1999	Review, no additional trials identified in the references
Cohn 2006a	Review, no additional trials identified in the references
Conti 2006	Review, no additional RCTs identified
Dery 2004	Review, no additional trials identified
Holmes 2002	Review, no additional trials identified in the references
Kennard 2002	International EECP Patient Registry (IEPR)
Kim 2002a	Review, no additional trials identified in the references
Kronhaus 2004	Non-RCT
Lawson 1997	Report of EECP Consortium; nonRCT, multicentre cohort study
Manchanda 2007	Review, no additional trials identified in the references
MAS 2006	Health Technology Policy Assessment for the Ontario Ministry of Health, no additional trials identified in the references
May 2007	Review (Danish), no additional trials identified (contact with Investigators)
Scheidt 2005	Review, no additional RCTs identified

Study	Reason for exclusion
Shavelle 2007	Review, no additional trials identified in the references
Shea 2005	Review, no additional trials identified in the references
Yu 2006	Review (Swedish), no additional trials (translated by Dr J. Jilek)

EECP = enhanced external counterpulsation
HRQoL = health-related quality of life
RCT = randomized controlled trial

APPENDICES

Appendix 1. Search strategies

The Cochrane Library

#1 MeSH descriptor coronary disease explode all trees
#2 MeSH descriptor myocardial ischemia this term only
#3 angina* in All Text
#4 (coronary in All Text near/3 disease* in All Text)
#5 (myocardial in All Text and ischemia in All Text)
#6 (#1 or #2 or #3 or #4 or #5)
#7 MeSH descriptor counterpulsation this term only
#8 counterpulsation in All Text
#9 counter next pulsation in All Text
#10 EECP in All Text
#11 ECP in All Text
#12 counterpressure in All Text
#13 counter next pressure in All Text
#14 (#7 or #8 or #9 or #10 or #11 or #12 or #13)
#15 (#6 and #14)

MEDLINE (on Ovid) 1966 to present

1 exp Coronary Disease/ (144132)
2 exp Angina Pectoris/ (34897)
3 Myocardial Ischemia/ (23881)
4 angina.tw. (35162)
5 (coronary adj3 disease$).tw. (75175)
6 or/1-4 (194402)
7 Counterpulsation/ (478)
8 EECP.tw. (127)
9 ECP.tw. (2144)
10 (external adj5 counterpulsation).tw. (227)
11 (external adj5 counter pulsation).tw. (8)
12 counterpressure.tw. (148)
13 counter pressure.tw. (101)
14 or/7-13 (2918)
15 6 and 14 (227)
16 randomized controlled trial.pt. (248340)
17 controlled clinical trial.pt. (76350)
18 Randomized controlled trials/ (52334)
19 random allocation/ (59709)
20 double blind method/ (94724)
21 single-blind method/ (11622)
22 or/16-21 (419127)
23 exp animal/ not humans/ (3253392)
24 22 not 23 (392624)

25 clinical trial.pt. (440652)
26 exp Clinical Trials as Topic/ (198184)
27 (clin$ adj25 trial$).ti,ab. (140482)
28 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab. (91426)
29 placebos/ (26640)
30 placebo$.ti,ab. (106901)
31 random$.ti,ab. (396364)
32 research design/ (51042)
33 or/25-32 (886878)
34 33 not 23 (822975)
35 24 or 34 (844895)
36 15 and 35 (61)

EMBASE (on Ovid) 1980 to 2008 Week 08

1 Ischemic Heart Disease/ (54556)
2 exp Angina Pectoris/ (36797)
3 exp Coronary Artery Disease/ (77390)
4 Ischemic Heart Disease/ (54556)
5 angina.tw. (28734)
6 (coronary adj3 disease$).tw. (66560)
7 or/2-6 (165708)
8 Counterpulsation/ (761)
9 EECP.tw. (125)
10 ECP.tw. (2034)
11 (external adj5 counterpulsation).tw. (178)
12 (external adj5 counter pulsation).tw. (5)
13 counter pressure.tw. (77)
14 Counterpressure.tw. (95)
15 or/8-11 (2816)
16 7 and 15 (293)
17 clinical trial/ (492609)
18 random$.tw. (362919)
19 randomized controlled trial/ (154703)
20 trial$.tw. (320034)
21 follow-up.tw. (327110)
22 double blind procedure/ (68338)
23 placebo$.tw. (103979)
24 placebo/ (110247)
25 factorial$.ti,ab. (7449)
26 (crossover$ or cross-over$).ti,ab. (37512)
27 (double$ adj blind$).ti,ab. (81051)
28 (singl$ adj blind$).ti,ab. (7041)
29 assign$.ti,ab. (101153)
30 allocat$.ti,ab. (31734)
31 volunteer$.ti,ab. (93982)
32 Crossover Procedure/ (19983)
33 Single Blind Procedure/ (7372)
34 or/17-33 (1287717)
35 16 and 34 (133)

ISI Web of Science

#3 (#1 or #2)
#2 ts=((counterpulsation or counterpressure or (counter same pressure) or (counter same pulsation) or eecp or ecp) and (angina* or (coronary same disease*) or (ischemic same heart) or (ischaemic same heart) or (myocardial same isch*)) and (random* or "clinical trial" or (clinical same trial*) or (clincal same study*)))
#1 ts=((counterpulsation or counterpressure or (counter same pressure) or (counter same pulsation) or eecp or ecp) and (angina* or (coronary same disease*) or (ischemic same heart) or (ischaemic same heart) or (myocardial same isch*))) AND Document Type=(Meeting Abstract OR Meeting-Abstract)

LILACS

counterpulsation or counterpressure or counter pressure or counter pulsation or eecp or ecp [Palavras] and angina$ or coronary or ischemic heart or ischaemic heart [Palavras]

WHAT'S NEW

Date	Event	Description
23 January 2013	Review declared as stable	Authors unable to update review.

CONTRIBUTIONS OF AUTHORS

Amani Al Hajeri (AAH) and Zbys Fedorowicz (ZF) were responsible for co-ordinating the review.
AAH, ZF and Bruce Manzer (BM) were responsible for screening the search results and the retrieved papers against the inclusion criteria.
AAH, ZF and BM were responsible for appraising the quality of papers.
BM was responsible for organising the retrieval of papers and ZF for writing to authors of papers for additional information.
ZF, BM and AAH were responsible for data management of the review, including extracting data from papers and entering data into RevMan.
ZF and BM were responsible for obtaining and screening data on unpublished studies.
ZF and BM were responsible for the interpretation and analysis of data.
AAH, BM and ZF were responsible for writing the review.
FA conceived the idea for the review and is the guarantor for the review.
ZF lead the review and ZF was the principal contact author.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

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External sources

- No sources of support supplied

NOTES

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INDEX TERMS

Medical Subject Headings (MeSH)

Angina Pectoris [*therapy]; Chronic Disease; Counterpulsation [*methods]

MeSH check words

Adult; Humans