Refractory angina is a growing challenge for palliative medicine: a systematic review of non-invasive interventions

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**ABSTRACT**

**Background**

Refractory angina can have a significant effect on quality of life. Non-invasive interventions have been suggested but there are few guidelines on management. Our aim was to systematically review all studies that reported non-invasive interventions for refractory angina and report on their effectiveness and safety.

**Methods**

We performed a literature search of six databases and a grey literature search. Treatments considered first- or second-line according to the European Society of Cardiology were excluded, as were interventions that had undergone review within the last three years. Design, setting and outcomes were extracted and quality was assessed. A narrative synthesis was undertaken, including an analysis of adverse effects.

**Results**

4476 studies were screened, 14 studies were included in our analysis. Interventions were specialist multi-disciplinary programmes, transcutaneous electrical nerve stimulation (TENS), perhexiline, medical optimisation, morphine and intranasal alfentanil. The effects of specialist programmes and perhexiline treatment were mixed. Positive effects were reported with TENS, opioids and medical optimisation, with improvements in symptoms, exercise capacity and quality of life. No major adverse effects were noted in any of the treatments.

**Conclusion**

There are non-invasive treatments for refractory angina that are over-looked by current guidelines. While the quality of these studies varies, positive changes have been reported in symptoms, exercise tolerance and quality of life with few adverse effects. There is a need for further research into these treatments which could be useful within the contexts of cardiology and palliative care.

**BACKGROUND**

Angina is common condition across the world, affecting up to 2 million people in the UK and approximately 9 million in the US.[1-3] Improved technology and novel treatments mean the global prevalence of angina has decreased over the last 30 years, however a large number of patients suffer with symptoms that are resistant to treatment and according to the European Society of Cardiology (ESC) the incidence of refractory angina is a growing with the ageing of the population.[4] Refractory angina, as described by the ESC, refers to symptoms caused by reversible ischaemia from obstructive coronary artery disease (i.e. stable angina) which cannot be adequately controlled by conventional pharmacological therapies or revascularisation. Refractory angina is estimated to affect 5-10% of all people with angina and has a significant negative effect of quality of life.[5, 6]

The 2019 ESC Guidelines recommend a stepwise treatment regime to control stable angina, starting with the combination of a beta-blocker and a calcium channel blocker and introducing in turn long-acting nitrates, nicorandil, ranolazine, ivabradine and trimetazidine if symptoms remain uncontrolled. Short-acting GTN is recommended for the immediate relief of symptoms. Alongside this, the importance of lifestyle changes and risk factor control are emphasised, and surgical and endovascular revascularisation has a role as an ‘adjunct to medical therapy’.[4]

ESC Guidelines advise that patients with refractory angina are best treated in specialist ‘angina clinics’ where multidisciplinary teams can advise on novel treatments for each individual. However, the benefits of these treatments are yet to be confirmed. Some have already undergone systematic review: enhanced external counterpulsation,[7-9] extracorporeal shockwave therapy,[10] coronary sinus reducer implantation,[11] spinal cord stimulation and sympathectomy.[12-14] These may improve symptoms but further research with larger randomised-controlled trials (RCTs) is required. Gene and cell therapy for the treatment of refractory angina are the subject of ongoing research.[15] Transmyocardial and percutaneous laser revascularisation have been shown to pose unacceptable risks outweighing any potential clinical benefit.[16]

Many of these interventions are invasive, involving surgery or the injection of medication. Some these procedures also require the use of local or general anaesthetic. There is a known association between symptomatic coronary artery disease and frailty and patients with these conditions are less likely to tolerate invasive procedures.[17] The benefit of non-invasive interventions is that they can often be performed in multiple settings, including hospice and community. The aim of this review is to identify non-invasive interventions that may improve symptoms and quality of life in patients with refractory angina. The objectives are to 1) inform on beneficial interventions in refractory angina, 2) report on the safety of these interventions, and 3) ensure all relevant literature on refractory angina is collated.

**METHOD**

**Protocol**

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display\_record.php?RecordID=122936

**Research questions:**

1. What non-invasive interventions exist that may improve symptoms and quality of life in patients with refractory angina?
2. What are the effects of these interventions?

**Search strategy**

We undertook an electronic search of the following databases: AMED, BNI, CINAHL, EMBASE, PsycINFO, MEDLINE.Databases were searched from inception to 13th February 2019. A search for grey literature was undertaken through databases OpenGrey and EThOS. Reference lists of review articles identified during searching were also included.

Search terms were developed with input from a librarian experienced in systematic searching. A search strategy was developed for each database. An example of search terms used is seen in Table 1.

|  |
| --- |
| 1. Angina |
| Angina OR Coronary Artery Disease OR Myocardial ischaemia OR Atherosclerosis OR Chest pain OR Stenocardia |
| 1. Intervention |
| Pain management OR Analgesia OR Intervention or Therapy |
| 1. Refractory |
| Resistant OR Refractory OR Intractable OR Recalcitrant |

Table 1: Terms used in search strategy

**Definitions**

Refractory angina is defined by the European Society of Cardiology as ‘long-lasting symptoms (for ≥3 months) due to established reversible ischaemia in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, bypass grafting, or stenting including PCI of chronic total coronary occlusion’.[4]

**Inclusion and exclusion criteria**

Studies were considered eligible if they included patients with chronic stable angina and described an intervention for the management of refractory angina (pharmacological and non-pharmacological). Interventions for stable angina listed in the 2019 ESC Guidelines on Chronic Coronary Syndromes, including revascularisation procedures, were excluded as patients receiving these would not be considered to have refractory symptoms according to the definition above. Invasive procedures including coronary sinus reducer implantation, spinal cord stimulation, sympathectomy, gene/stem cell therapy and laser revascularisation were not included as our aim was to identify non-invasive interventions.

Studies on enhanced external counterpulsation and extracorporeal shockwave therapy were not included as these have already undergone systematic review within the last three years.

Studies that concerned children (aged below 18 years), studies concerning only patients with unstable or vasospastic (variant/’Prinzmetal’) angina, studies that reported only physiological outcomes and studies not published in English were excluded.

All empirical research meeting inclusion criteria was considered, including RCTs, cohort studies, case-control studies, case series and case reports. Reviews, guidelines, opinion pieces and commentaries were excluded. Studies published only as conference abstracts were excluded if an associated full text paper could not be identified.

**Abstract screening and full text review**

Two authors (IM and AS) independently reviewed the abstracts of all identified studies for inclusion in full text screening. Due to time-constraints, one author (IM) reviewed all included full text articles and a second author (AS) reviewed 10% of these. We recognise this as a limitation of our review and future updates should aim for authors to review all full-text articles. A third author (AG) was available where conflicts could not be resolved, but this consultation was not required as all conflicts were discussed and resolved verbally.

**Data extraction and quality assessment**

Data extraction was performed using a data extraction template. The form was piloted to ensure suitability. One author (IM) performed extraction on all included studies and a second author (AS) extracted data from 10% of these. Where data values were unavailable, data was extracted from graphs using Web Plot Digitizer. Results were compared and conflicts were again discussed. Consultation with a third author (AG) was available but not required.

All outcome measures relating to symptom control and quality of life were extracted, including angina history, Canadian Cardiovascular Society (CCS) functional class, anti-anginal drug use, quality of life, exercise tolerance and hospitalisation rate. Data on safety and adverse effects was also extracted. Studies in all settings were included, including hospital, hospice and community.

Quality assessment was performed using the Quality Assessment Tool by Hawker et al.[18] Studies were graded from 1 (very poor) to 4 (good) in nine criteria and given an overall grade of ‘high’ (30-36), ‘medium’ (24-29) or ‘low’ (9-23) according to total score. One author (IM) assessed all included studies. Studies were not excluded based on this appraisal, but it was incorporated into subsequent narrative synthesis.

**Data synthesis**

Data was combined using narrative synthesis. Meta-analysis could not be performed due methodological heterogeneity and because even when studies reported on similar interventions, similar outcomes were not reported.

**RESULTS**

Our search strategy identified 6547 records from six databases. 21 records were included from grey literature and reference list searching. After removing duplicates, 4778 records underwent title and abstract screening. 4133 records were excluded based on their abstract and subsequently 645 records underwent full text review.14 full text articles were selected for inclusion in this review. The number of articles excluded at each stage and reasons for exclusion can be found in Figure 1.

14 studies were included in our review. This included two RCTs: one parallel conventional therapy-controlled trial and one double-blind placebo-controlled crossover trial. There were four prospective and six retrospective case series. There were also two case reports.

Interventions used in the included studies were specialist multi-disciplinary programmes (five), transcutaneous electrical nerve stimulation (TENS) (three), perhexiline (two), optimal medical therapy (two), prolonged-release oral morphine (one) and intranasal alfentanil (one).

Sample sizes ranged from one to 433 participants. 1,049 participants were included across all 14 included studies. All participants had severe angina, CCS class III-IV, which had not been adequately controlled by escalating conventional medical therapy.

Included studies were conducted in Australia, Brazil, Germany, Israel, UK and US. All studies included outpatients, although participants who were not local to the study centre stayed as inpatients for five days in one study.

The characteristics of each included study can be found in Table 2.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author + Year | Country | Design | Setting | Participants | Intervention | Follow up details | Primary outcome and measures | Relevant secondary outcome measures |
| Asbury et al. 2012[19] | UK | RCT | Cardiology (including specialist angina clinic) and pain clinic outpatients | 40  1 admitted to hospital so final analysis: 19 intervention, 20 control | 8-week cardiac rehabilitation and symptom monitoring programme.  *Control: 8-week symptom monitoring only.* | Assessed at baseline, after final session and 8 weeks after intervention | Anxiety and depression (HAQ, HADS) | SF-36, York Angina Belief Scale, self-reported angina frequency, PSW |
| Moore et al. 2005[22] | UK | Prospective case series | Specialist refractory angina clinic at a tertiary cardiac referral centre | 69  2 died, 1 did not complete follow up questionnaire | Refractory angina programme consisting of education, drug optimisation, cardiac rehabilitation and cognitive behaviour therapy. | Assessed at baseline and one year after intervention | Health-related quality of life (SAQ, SF-12) | HADS |
| Moore et al. 2007[23] | UK | Retrospective case series | Specialist refractory angina clinic at a tertiary cardiac referral centre | 433 | Two-hour interview, stress management advice, relaxation training and a graduated exercise program. | Data was collected for one year pre- and post-intervention | Hospitalisation rate, morbidity and mortality | None |
| Patel et al. 2016[21] | UK | Prospective case series | Specialised refractory angina clinic | 33  3 underwent revascularisation and were excluded | Four-week 'pragmatic rehabilitation course’ combining cognitive behavioural therapy and an education programme. | Assessed at baseline, one-month and two years | Quality of life (SF-36), mood (HADS), self-reported angina and weekly GTN usage (estimated via SAQ) | None |
| Tinson et al. 2016[20] | UK | Retrospective case series | Outpatients, referred by cardiologists and GPs | 135  Missing data for 66 participants but still included in some analyses | 9-week angina management programme run by a cognitive-behavioural therapist and physiotherapist. | Assessed at baseline, after final session and two months after intervention | Self-reported angina frequency (per week), duration (min) and severity (0-100); weekly GTN usage | HADS, Roland Morris Disability Questionnaire, Pain Self-Efficacy Questionnaire, York Angina Misconceptions Questionnaire, use of cardiology resources |
| Meyler et al. 1994[24] | Germany | Retrospective case series | Outpatient pain clinic at a University Hospital | 193, 16 of whom had refractory angina | TENS – applied by participants at home, one hour three times per day | Assessed at 2-4 weeks and after six months of treatment | Patient-reported efficacy | None |
| Nitz and Cheras 1993[25] | Australia | Prospective case series | Cardiology outpatients (those who did not live locally stayed as inpatients) | 11 | TENS – performed by a physiotherapist, once daily or twice daily (for inpatients) for 10 90-minute sessions. | Assessed at baseline and after final session | Visual analogue pain scale, self-reported angina frequency (per week) | None |
| West and Colquhoun 1993[26] | Australia | Retrospective case series | Not described (outpatients) | 3 | TENS – applied by participants at home, one hour twice or three times per day | Regular follow up over three months to three years | None stated | Self-reported angina history |
| Cole et al. 1990[27] | US | Double-blind randomised, placebo-controlled crossover trial | Medical and cardiology (including coronary care) outpatients | 17 (crossover trial)  1 did not complete baseline exercise testing | Perhexiline – mean dose 135 ± 79mg/day  *Control: Placebo dose with similar titration* | Assessed at baseline, 3 months (after initial treatment) and 6 months (after crossover phase) | Exercise tolerance - duration (s), capacity (W), self-reported angina history | None |
| Phan et al. 2009[28] | UK | Retrospective case series | Cardiology (including coronary care) outpatients at two tertiary hospitals | 151 | Perhexiline – mean dose (at 3 months) 189 ± 84mg/day | Regular follow up for an average of 20 ± 14 months. Perhexiline levels were assessed at 1, 4 and 12 weeks. | Therapeutic drug level monitoring, self-reported angina history, mortality | None |
| Dourado et al. 2015[29] | Brazil | Prospective case series | Specialised angina clinic at a tertiary university hospital | 136 | Optimisation of medications according to stable angina guidelines | Assessed every 4 weeks for 3 months | CCS class, self-reported angina frequency (per week), weekly GTN usage | None |
| Gowdak 2017[30] | Brazil | Case report | Outpatient clinic at a University hospital | 1 | Optimisation of medical therapy at consecutive medical reviews | Not stated | None stated | Self-reported angina history |
| Mouallem et al. 2000[31] | Israel | Retrospective case series | Not described (outpatients) | 4 | Prolonged-release oral morphine – doses between 20-100mg/day | Retrospective data collected on admissions for up to three years | None stated | Hospitalisation rate |
| Osborn and Jefferson 2010[32] | UK | Case report | Not described (outpatients) | 1 | Intranasal alfentanil – one spray to each nostril (280 micrograms) as required | Not stated | None stated | Effects of alfentanil treatment |

Table 2: Summary of included studies

**Effects of interventions**

Results of included studies can be seen in Table 3.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Intervention** | **Design** | **Primary outcome** | **Secondary outcomes** | **Quality assessment** |
| **Asbury et al. 2012[19]** | Cardiac rehabilitation | RCT | Intervention vs. control:  Reduced HAQ reassurance scores (1.71 ± 1.72 vs. 1.14 ± 1.23, p=0.026).  Control vs. intervention:  Reduced HADS anxiety (7.25 ± 4.25 vs 6.18 ± 3.52, p=0.04), reduced total HADS (13.12 ± 7.09 vs 11.75 ± 6.49, p=0.05) and HAQ health worry (6.94 ± 4.53 vs 5.00 ± 2.95, p=0.013). | Intervention showed reduced angina severity (p=0.07), improved York Angina Belief threat perception (p=0.05), greater improvements in PSW level (p=0.002) and distance covered (p=0.015).  Controls showed increased SF-36 pain perception (p=0.025) and improved SF-36 physical health (0.05). | 33 (high) |
| **Moore et al. 2005[22]** | Multidisciplinary refractory angina programme | Prospective case series | Improvements in all SAQ and SF-12 subscales, with significant improvements in SAQ angina stability (p=0.028), angina frequency (p=0.02), treatment satisfaction (p=0.001) and quality of life (p<0.001), and SF-12 mental (p=0.028) subscales. | Significant improvements in HADS anxiety (p=0.015) and depression (p=0.018). | 29 (medium) |
| **Moore et al. 2007[23]** | Two-hour interview | Retrospective case series | Significant improvements in admissions (p<0.001) and hospital days (p<0.001).  Significant reductions in admissions and hospital days for chest pain (p<0.001), cardiac problems (p<0.001) and MI (p=0.02).  No significant reduction in number of non-cardiac admissions or non-cardiac hospital days. | None | 26 (medium)  Objectives not adequately described. Outcome data collected retrospectively. |
| **Patel et al. 2016[21]** | ‘Pragmatic rehabilitation course’ | Prospective case series | Despite no change in angina frequency or weekly GTN usage, there were significant improvements in SF-36 (p=0.0001) and HADS depression scores (p=0.015) which were maintained at two-year follow up.  No improvement in HADS anxiety. | None | 31 (high) |
| **Tinson et al. 2016[20]** | Angina management programme | Retrospective case series | Significant improvements in angina frequency (p<0.001) and duration (p=0.02), and weekly GTN usage (p<0.001) which were maintained at two-month follow up.  No significant improvement in angina severity. | Significant improvements in total HADS (16 to 9, p<0.001) and clinically significant depression (p=0.003) and anxiety (p=0.002).  Significant improvements in Roland Morris Disability, Pain Self-Efficacy and York Angina Beliefs Questionnaires (p<0.001). Reduced use of cardiology resources. | 27 (medium)  Outcome data collected retrospectively. |
| **Meyler et al. 1994[24]** | TENS – one hour, three times per day | Retrospective case series | TENS was reported to have a long-standing and beneficial effect in 75% (12/16) of participants with refractory angina. | None | 22 (low)  No baseline measures. No formal observation of intervention. No outcome measures defined. |
| **Nitz and Cheras 1993[25]** | TENS – 90-minutes, 10 sessions | Prospective case series | Improvements in pain score (p<0.005) and angina frequency (p<0.01) were seen following treatment. | None | 27 (medium)  No data tables, results extracted from graphs. No long-term follow up. |
| **West and Colquhoun 1993[26]** | TENS – one hour, twice or three times per day | Retrospective case series | No primary outcome stated | All three patients had reduction or complete resolution of pain which lasted from 3 months to over a year. | 21 (low)  Anecdotal - no pre-defined method or outcome measures. |
| **Cole et al. 1990[27]** | Perhexiline – mean dose 135 ± 79mg/day | Double-blind randomised and placebo-controlled crossover trial | No significant difference between peak exercise load or duration as compared with baseline in either intervention or placebo groups.  Significantly greater proportion of ‘positive responders’ with perhexiline treatment according to pre-defined criteria (63% vs. 18%, p<0.05) and subjective symptom review (p<0.005). | None | 30 (high)  No comparison of outcome data between intervention and control groups. |
| **Phan et al. 2009[28]** | Perhexiline – mean dose (at 3 months) 189 ± 84mg/day | Retrospective case series | 58.9% of participants reported feeling better on perhexiline. 64.6% reported a reduction in angina frequency and/or severity and a reduction in GTN use. | None | 23 (low)  Anecdotal - no pre-defined methods, outcomes collected retrospectively. No objective outcome measures. |
| **Dourado et al. 2015[29]** | Optimisation of medications | Prospective case series | 50.7% of participants showed improvement of at least one CCS functional class (p<0.001). Significant improvements in angina frequency (p<0.001) and weekly GTN usage (p=0.001). | None | 22 (low)  Study presented as a ‘letter to the editor’ – no abstract, minimal details on objectives, methods, results. |
| **Gowdak 2017[30]** | Optimisation of medications | Case report | No primary outcome stated. | Following two clinic reviews and medication optimisation, the patient was generally pain free with occasional use of GTN and could resume most daily activities. | 15 (low)  Anecdotal - no pre-defined objectives, methods or outcome measures. |
| **Mouallem et al. 2000[31]** | Prolonged-release oral morphine | Retrospective case series | No primary outcome stated. | Mean number of hospitalisations per year decreased from 6 to 1.5 after one year of treatment. Mean hospital days decreased from 42 to 6 (p<0.05). | 22 (low)  Anecdotal – no pre-defined objectives or methods. Outcome data collected retrospectively. |
| **Osborn and Jefferson 2010[32]** | Intranasal alfentanil (as required) | Case report | No primary outcome stated. | Effective at relieving angina in less than five minutes and prevented hospitalisation for six months. | 18 (low)  Anecdotal – no pre-defined objectives, methods or outcome measures. No comment data analysis or bias. |

Table 3: Results of included studies

Specialist multi-disciplinary programmes, cardiac rehabilitation and cognitive behavioural therapy (CBT)

Five studies were included which described the effects of a specialist, multi-disciplinary refractory angina programme, involving CBT, education and/or rehabilitation.

Mixed effects were reported across three studies regarding self-reported angina. Asbury et al. reported a non-significant trend towards reduced angina severity among rehabilitation participants (p=0.07), but no difference in angina frequency was found at any time point.[19] Tinson et al. found significant improvements in self-reported angina frequency (p<0.001), duration (p=0.02) and GTN use (p<0.001) following CBT, which were maintained at two months (p<0.001, p=0.039, p=0.005 respectively).[20] However, no significant improvement in angina severity was reported. Patel et al. found no significant improvement in angina frequency or GTN use at one month or at two years in patients who underwent CBT.[21]

Rehabilitation and CBT appear to have positive effects on health-related quality of life. At one year follow up, Moore et al. found improvements in Short Form 12 (SF-12) and Seattle Angina Questionnaire (SAQ) scores with rehabilitation and Patel et al. reported significant improvements in quality of life at one month following CBT (p=0.0001) which was sustained at long-term follow up.[22] Asbury et al. found a significant deterioration in SF-36 pain perception subscale scores among control participants, from 63.43 to 55.46 (p=0.025), which was not seen among participants who took part in rehabilitation. However, control participants showed greater improvements compared to rehabilitation participants in SF-36 physical health subscale scores (p=0.05).

Mixed effects were reported across four studies which used the Hospital Anxiety and Depression Scale (HADS) and Health Anxiety Questionnaire (HAQ) to measure the effects of the programmes on patient mental health. Tinson et al. found that total HADS scores were significantly reduced post-intervention (p<0.001) and again at two months (p=<0.001), with significant reductions in clinically significant depression (p=0.003) and anxiety (p=0.002), but Asbury et al. conversely reported improved HADS scores in control group participants (p=0.05). Moore et al. found significant improvements in HADS depression scores at one year (p=0.018), which were also seen by Patel et al. at one month (p=0.015) and two years (p=0.004). Moore et al. also reported significant improvements in HADS anxiety scores (p=0.015) and a significant decrease in the percentage of ‘definite cases’ of anxiety (p=0.008). Asbury et al. reported significant improvements in HAQ reassurance subscale scores (p=0.026) with rehabilitation but also found improved HADS anxiety (p=0.04) and HAQ health worry subscale (p=0.013) scores in control group participants.

Improvements were also seen in Progressive Shuffle Walk (PSW) exercise tolerance testing (Asbury et al, p<0.001), York Angina Beliefs Questionnaire scores (Tinson et al, p=0.05; Asbury et al, p<0.01), Roland Morris Disability Questionnaire scores (Tinson et al, p<0.001) and Pain Self-Efficacy Questionnaire scores (Tinson et al, p<0.001). Moore et al. reported significant reductions in the number of admissions and hospital days per year, specifically for chest pain (p<0.001), cardiac problems (p<0.001) and myocardial infarction (p=0.02),[23] and Tinson et al. reported a reduction in the use of cardiology resources for inpatient and outpatient visits at two year follow up (p<0.001).

Transcutaneous electrical nerve stimulation (TENS)

Three studies were included which looked at the effects of TENS in patients with refractory angina. In a study on 193 patients with different pain syndromes, Meyler et al. reported that TENS was beneficial in reducing pain at six months follow up in 12/16 patients (75%) who had refractory angina.[24] Adverse effects occurred in 35% (67/193) of all participants, including skin irritation (43 participants) and increased pain (16 participants), but the incidence of adverse effects among patients with refractory angina was not specifically reported. Nitz and Cheras reported significant improvements in angina severity (p<0.005) and frequency (p<0.01) after 10 90-minute treatments although no long-term follow up data was available.[25] West and Colquhoun described the use of TENS as an adjunct in three patients; all three of whom noted either a marked reduction or the total resolution of self-reported angina for a period of three to 12 months.[26]Kathryn

Perhexiline

Two studies assessed the effects of perhexiline in patients with refractory angina. Cole et al. found no significant increase in exercise tolerance with perhexiline treatment, although seven of 16 patients achieved at least a 20% increase in peak exercise duration with perhexiline.[27] Significant differences were seen in number of ‘responders’ according to pre-defined criteria (p<0.05) and double-blind review of angina diaries suggested that 11 of 17 patients subjectively felt a significant improvement in symptoms with perhexiline treatment compared with placebo (p<0.05). Five patients (29.4%) developed side effects with perhexiline, including transient ataxia, nausea, dizziness and nail changes although no derangement in blood tests or cardiovascular side effects were noted.

Phan et al. found that 64.6% of refractory angina patients and 61.1% of patients with both refractory angina and chronic heart failure had a symptomatic response to perhexiline.[28] A symptomatic response was considered as a reduction in self-reported angina frequency or severity with a lower requirement for GTN use. Side effects included deranged liver function tests and 23.8% of all participants had transient side effects including anorexia, weight loss and lethargy.

Optimal medical therapy

Dourado et al. looked at the optimisation of medical therapy in a case series of 136 patients with symptoms thought to be refractory to conventional anti-anginal medication.[29] Through regular medical review over three months, 69 patients (50.7%) showed improvement of at least one CCS functional class (p<0.001). There were also significant improvements in angina frequency (p<0.001) and weekly GTN use (p=0.001).

Gowdak also described the role of optimal medical therapy in a case report from outpatient clinic.[30] Regular review and clinical assessment, with the addition and titration of new antianginal medications (trimetazidine, ivabradine) controlled one patient’s previously refractory symptoms and allowed them to resume most daily activities without pain.

Opioids

Mouallem et al. looked at the effects of prolonged-release oral morphine in a case series of four patients with refractory angina.[31] Annual hospital admissions decreased from a mean average of 6 to 1.5 after a year of treatment, with hospitalisation days decreasing from 42 to 6. There was also a general decline in number and intensity of self-reported anginal episodes. Two patients suffered constipation which was relieved by simple laxatives. One patient had an episode of confusion and one patient was admitted to hospital due to biliary colic, both possibly related to opioid use.

Osborn and Jefferson published a case report on the use of intranasal alfentanil in one patient with refractory angina, where prolonged-release morphine had been insufficient in reducing symptoms and alfentanil was found to provide rapid relief of chest pain within 5 minutes.[32] Over a follow up period of six months, no hospital admissions and no adverse effects were reported.

**Quality** **assessment**

Quality assessment was performed according to Hawker et al’s Quality Assessment Tool and results can be seen in Table 3.[18]

The quality of included studies was mixed with 7/14 (50%) being assigned a ‘low’ grade. Meyler et al. and Phan et al. were retrospective case series which lacked pre-defined methods. Gowdak, Mouallem et al, Osborn and Jefferson, and West and Colquhoun were anecdotal reports and did not have pre-defined objectives and methods. Dourado et al. gave some detail on objectives, methods, results and analysis but was written in the form of a letter and lacked both an abstract and sufficient background information to give context to the intervention. Three studies were assigned a ‘medium’ grade: Moore et al. (2007) and Tinson et al. collected data retrospectively, although descriptions of objectives, methods and analysis were good; Nitz and Cheras only provided a brief abstract and provided no long-term follow up data. Four studies attained a ‘high’ quality assessment result, all of which provided good background, method, results and analysis. None of the studies included in our review provided evidence of sample justification (most were case series of consecutive patients) which affected scores for sampling and transferability. 10 studies made no suggestions for future research and three studies provided no implications for policy or practice.

**DISCUSSION**

This systematic review has identified several non-invasive interventions for patients with refractory angina which may be useful in both cardiology and palliative medicine. Current guidelines do not sufficiently cover the management of refractory angina and patients may suffer with debilitating symptoms despite the availability of potential treatments.

Five studies involving specialist multi-disciplinary programmes showed improvements in health-related quality of life, but effects on self-reported angina and mental health were mixed. Cardiac rehabilitation is understood to produce some improvements in physical fitness for patients with stable angina, but recent Cochrane review concluded that more high-quality studies should be undertaken to better understand its effects on mortality, morbidity and quality of life.[33] One high-quality RCT included in our review failed to show convincing improvements in angina severity or frequency, quality of life or mental health following cardiac rehabilitation. To our knowledge, this is the first published RCT in cardiac rehabilitation for refractory angina and does not provide sufficient evidence for its use.

TENS appears to have a positive effect in patients with refractory angina. Improvements in symptom control and exercise capacity were reported across three studies included in our review, however none of these studies were randomised or controlled and none were considered high-quality. Recent Cochrane reviews have been unable to conclude whether TENS is effective or safe for relieving neuropathic, chronic or cancer-related pain and the results of our review correlate with these.[34-36] Adverse effects (skin irritation and increased pain) may be common following TENS treatment but the frequency and severity of these effects were inadequately reported. There is also concern that TENS use may interfere with the function of pacemakers or implanted cardiac defibrillators (ICD) although no included studies commented on this risk.[37-39] TENS is an easily accessible treatment, available over the counter in most UK pharmacies, but the total number of patients across all included studies was small and further high-quality research is required before recommendations can be made.

It should be noted that our review did not identify any studies on the use of neuromodulatory drugs for the management of refractory angina although there is evidence for their usefulness in cardiac pain. Rosen writes about the complex nature of cardiac pain and the potential for modulation of pain pathways at multiple levels of the neuraxis (tissue, spinal cord and brain).[REF] Low dose tricyclic antidepressants, gabapentinoids, α-agonists and selective serotonin reuptake inhibitors may be of use and Wallin et at. discuss the use of gabapentin in combination with spinal cord stimulation,[REF] however studies in relevant patient populations are required before full analysis of these interventions can be performed.

Perhexiline is an anti-anginal medication that was first introduced in the 1970s.[40] It was effective in relieving angina, but its mechanism was poorly understood. It was found to cause hepatic and neurological toxicity and although these effects were rare, its use quickly diminished. It is currently only available off-licence in the UK, on a named patient and named cardiologist basis.[28] One high-quality RCT included in our reviewed failed to show significant improvements in exercise capacity, although symptom control was subjectively better. Some adverse effects were noted, but none of these were considered serious. The importance of regular monitoring of serum perhexiline levels was stressed, which minimises the chance of serious adverse effects, but could cause patients to consider treatment unfavourable.[27]

As stated in the current ESC guidelines, optimisation of medical therapy should remain a key principle of refractory angina management.[4] One non-controlled study with a total of 137 patients showed that titration of anti-anginal medications can reduce angina frequency and increase functional capacity in patients previously considered to have symptoms resistant to pharmacological treatment. However, the studies included in our review were among the lowest in quality, lacking clear descriptions of their setting, objective, methods and results. High-quality research could expand the current guidelines for the medical management of refractory angina but performing controlled trials could be of ethical concern if patients were denied access to the best standard of care.

Opioid treatment appears to have a positive effect in patients with refractory angina, reducing symptoms and annual hospital admissions. However, the total number of participants (five) was the smallest of all included interventions. Both studies were of low quality, lacking details on how data was collected and analysed and there was heterogeneity between studies, with one looking at acute pain relief and the other at prolonged-release opioids. The short- and long-term adverse effects of opioids are well documented,[41, 42] although Mouallem et al. found that low doses were generally well tolerated without need for dose escalation. There is also fear amongst clinicians that opioid use could mask ischaemic episodes although this was not the case in this study.[31] Patients have been described as willing to try morphine in the context of heart disease, but guidance on safe and appropriate prescribing is needed for clinicians.[43]

The ORBITA trial was a randomised-controlled trial that compared percutaneous coronary intervention (PCI) with placebo procedure in participants with stable angina.[REF] The trial showed no significant improvement in exercise time with PCI suggesting the presence of a significant placebo component. The trial was included in the 2019 ESC Guidelines, however due to small sample size and insufficient statistical power it was not used in the development of the guidance.[4] It is important to consider this trial when discussing the management of refractory angina as it highlights the potential placebo component of all interventions, yet to be accurately assessed.

**Strengths and limitations**

Several steps were taken to enhance the methodological rigour of our review. We developed a systematic search strategy, with the involvement of an experienced librarian, with the aim of collating all relevant literature. Search terms and outcomes were intentionally broad to ensure the widest ‘catch’ of available research, with the largest percentage of studies excluded at abstract screening. Six electronic databases, as well as grey literature were searched, with no restriction on age of publication and up to date cardiology guidance and recent publications were studied to minimise repetition in the recommendations of our review.

According to our quality assessment, the quality of the included studies was mixed with half being assigned a ‘low’ grade. The reasons for this varied between studies but no studies included a justification of sample size which limited scores for sampling and transferability. Only two controlled studies were identified with most studies being case series, limiting recommendations for clinical practice. The need for further high-quality research has already been stated, particularly in TENS and specialised angina programmes.

Due to limitations in resources, full text screening, data extraction and quality assessment could not be completed by two independent researchers for all included studies. Studies only published as conference abstracts, where full text publications could not be identified, were excluded from this review, although the description of methods and results in these conference abstracts is often of poorer quality. Studies not written in English were also excluded due to resource issues. Our search was restricted to ‘refractory’ angina but treatments for stable angina could also be relevant given the positive effect medical optimisation has in patients previously thought to be resistant to medical therapy.

Our review was designed to assess effects on symptom control and quality of life. The subjective nature of these outcomes can lead to heterogeneity between studies in both the measures used and also between participants in how those measures are interpreted. The use of validated instruments such as SAQ, SF-12/36, HADS and HAQ can mitigate some of this variability but many of our included studies used pain scales and self-reported angina histories which may limit their reproducibility. Some included studies did not specify whether patients suffered with stable or unstable angina but there is an understanding that these conditions can be difficult to differentiate with worse angina classes. Some studies did not state how patients were diagnosed which could allow scrutiny of which participants were included, and some studies lacked baseline or follow up data, with researchers having to extract some data from graphs which can lead to inaccuracies. Data synthesis was completed by one researcher which could lead to researcher bias. Finally, invasive treatments were excluded from this review, although there could be a role for these interventions within the context of palliative care.

**CONCLUSION**

The palliative management of patients with refractory angina is not sufficiently covered by current guidance, despite the known effect refractory angina can have on quality of life. This review has identified several non-invasive interventions which could be useful in inpatient or outpatient settings for both cardiology and palliative specialties. TENS appears useful but high-quality RCTs are required before recommendations can be made. Specialist angina programmes appear to have mixed effects and further research would help elucidate the true benefits. Medical optimisation should remain a key principle, but further research could clarify titration regimes for patients with refractory angina. Despite years of experience, perhexiline lacks high-quality evidence to support its use in refractory angina. Opioids may be useful, but no recommendations could be made from this review.

**Implications for research**

High-quality RCTs should be undertaken in TENS to clarify its effectiveness and rate of adverse effects. This would allow the formation of recommendations for patients with refractory angina. Large scale RCTs on the use of specialised angina programmes would clarify their positive and negative effects on symptoms, quality of life and mental health. Further research into medical optimisation in patients with suspected refractory angina could lead to the development of titration guidelines. Further research into the use of opioids in refractory angina could clarify their effectiveness in reducing cardiac pain.

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