Oxygen therapy for acute myocardial infarction (Review)

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TABLE OF CONTENTS

[Intervention Review]

Oxygen therapy for acute myocardial infarction

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ABSTRACT

Background

Oxygen (O_2) is widely recommended for patients with myocardial infarction yet a narrative review has suggested it may do more harm than good. Systematic reviews have concluded that there was insufficient evidence to know whether oxygen reduced, increased or had no effect on the heart ischaemia or infarct size.

Objectives

To review the evidence from randomised controlled trials to establish whether routine use of inhaled oxygen in acute myocardial infarction (AMI) improves patient-centred outcomes, in particular pain and death.

Search methods

The following bibliographic databases were searched (to the end of February 2010): Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, LILACS and PASCAL, British Library ZETOC, Web of Science ISI Proceedings. Experts were also contacted to identify any studies. No language restrictions were applied.

Selection criteria

Randomised controlled trials of people with suspected or proven AMI, less than 24 hours after onset, in which the intervention was inhaled oxygen (at normal pressure) compared to air and regardless of co-therapies provided these were the same in both arms of the trial.

Data collection and analysis

Two review authors independently reviewed the titles and abstracts of identified studies to see if they met the inclusion criteria and independently undertook the data extraction. The quality of studies and the risk of bias were assessed according to guidance in the Cochrane Handbook. The primary outcomes were death, pain and complications. The measure of effect used was the relative risk (RR).

Main results

Three trials involving 387 patients were included and 14 deaths occurred. The pooled RR of death was 2.88 (95% CI 0.88 to 9.39) in an intention-to-treat analysis and 3.03 (95% CI 0.93 to 9.83) in patients with confirmed AMI. While suggestive of harm, the small number of deaths recorded meant that this could be a chance occurrence. Pain was measured by analgesic use. The pooled RR for the use of analgesics was 0.97 (95% CI 0.78 to 1.20).

Authors' conclusions

There is no conclusive evidence from randomised controlled trials to support the routine use of inhaled oxygen in patients with acute AMI. A definitive randomised controlled trial is urgently required given the mismatch between trial evidence suggestive of possible harm from routine oxygen use and recommendations for its use in clinical practice guidelines.

PLAIN LANGUAGE SUMMARY

Routine use of oxygen in people who have had a heart attack

Most guidelines for the treatment of people who are having a heart attack recommend that the patient should be given oxygen to breathe. We looked for the evidence to support this practice by searching for randomised controlled trials that compared the outcomes in patients given oxygen to the outcomes for patients given normal air to breathe. We were primarily interested in seeing whether there was a difference in the number of people who died but we also looked at whether administering oxygen reduced pain.

We found three randomised controlled trials that compared one group given oxygen to another group given air. These trials involved a total of 387 patients of whom 14 died. Of those who died, nearly three times as many people known to have been given oxygen died compared to those known to have been given air. However, because the trials had few participants and few deaths this result does not necessarily mean that giving oxygen increases the risk of death. The difference in numbers may have occurred simply by chance. Nonetheless, since the evidence suggests that oxygen may in fact be harmful, we think it is important to evaluate this widely used treatment in a large trial, as soon as possible, to make sure that current practice is not causing harm to people who have had a heart attack.

BACKGROUND

Description of the condition

Coronary heart disease (CHD) is an important cause of death worldwide. In the United Kingdom (UK) and the United States (US) it is the leading cause of death, accounting for about one-third of all deaths in people aged 35 years or over (BHF 2007; Thom 1998). Mortality rates for cardiovascular disease and CHD in men and women have fallen in most developed countries. For example, comparing the 1982 to 1992 cohort to the 1971 to 1982 cohort in the US the rate was 31% lower for mortality from cardiovascular disease, 21% lower for incidence of CHD and 28% lower for 28-day case fatality (after adjustment for age, sex and race) (Ergin 2004). The report commissioned by the UK Department of Health estimated a reduction in the case fatality rate for acute myocardial infarction (AMI) at 29 days, from 19.1% to 16.4% (Mason 2005). This reduction was associated with both a decline in the incidence of CHD and a reduction in the case fatality rate. Approximately 45% of the reduction in CHD mortality is attributable to improvement in medical therapies for coronary disease (Capewell 2000).

The most serious complications of AMI are cardiogenic shock, heart failure, ventricular fibrillation and recurrent Ischaemia. Around 8% of patients with AMI develop cardiogenic shock (Babaev 2005) however this was still present in only 29% of those patients on admission to hospital. The Global Registry of Acute Coronary Events (GRACE) reported that heart failure occurred in 15.6% or 15.7% of patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI, respectively; but heart failure was only present in 13% of these patients on admission to hospital (Steg 2004). Ventricular fibrillation occured in 1.9% of AMI patients (Goldberg 2008) and recurrent Ischaemia in 21% of patients with acute coronary syndromes (Yan 2009), of which about half presented in the first 24 hours. Other possible compli-

cations of AMI include pericarditis, mitral insufficiency, arrhythmias and conduction disturbances.

The cornerstone of contemporary management of patients with AMI presenting with ST-segment elevation is reperfusion therapy, with either primary percutaneous coronary intervention (PCI) or thrombolytic treatment, if less than 12 hours has elapsed from the onset of symptoms (Anderson 2007; O'Driscoll 2008; SIGN 2007; Van de Werf 2008). Other recommended treatments in international guidelines include oxygen, aspirin, nitrates and morphine (Anderson 2007; O'Driscoll 2008; SIGN 2007; Van de Werf 2008). Some of these treatments have a well established research base, others do not (O'Driscoll 2008; SIGN 2007).

Description of the intervention

Inhaled oxygen at normal pressure delivered by face mask or nasal cannula, at any concentration.

How the intervention might work

Myocardial infarction occurs when the flow of oxygenated blood in the heart is interrupted for a sustained period of time. The rationale for providing supplemental oxygen to a patient with AMI is that it may improve the oxygenation of the ischaemic myocardial tissue and reduce ischaemic symptoms (pain), infarct size and consequent morbidity and mortality. This pathophysiological reasoning has face validity.

Why it is important to do this review

Although it is biologically plausible that oxygen is helpful, it is also biologically plausible that it may be harmful. Potentially harmful mechanisms include the paradoxical effect of oxygen in reducing coronary artery blood flow and increasing coronary vascular resistance, measured by intracoronary Doppler ultrasonography (McNulty 2005; McNulty 2007); reduced stroke volume and cardiac output (Milone 1999); other adverse haemodynamic consequences, such as increased vascular resistance from hyperoxia; and reperfusion injury from increased oxygen free radicals (Rousseau 2005).

A systematic review of human studies that included non-randomised studies did not confirm that oxygen administration diminishes acute myocardial ischaemia (Nicholson 2004). Indeed, some evidence suggested that oxygen may increase myocardial ischaemia (Nicholson 2004). Another recent narrative review on oxygen therapy (Beasley 2007) also sounded a cautionary note. It referenced a randomised controlled trial (RCT) conducted in 1976 (Rawles 1976) showing that the relative risk of death was 2.89 (95% CI 0.81 to 10.27) in patients receiving oxygen compared to those breathing air. While this suggested that oxygen may be harmful, the increased risk of death could easily have been a chance finding. A recent review (Wijesinghe 2009) looked at the effect of oxygen on infarct size in patients with AMI and concluded that, "There is little evidence by which to determine the efficacy and safety of high flow oxygen therapy in MI. The evidence that does exist suggests that the routine use of high flow oxygen in uncomplicated MI may result in a greater infarct size and possibly increase the risk of mortality".

Despite this, oxygen administration is commonly mentioned in international guidelines for AMI (AHA 2005; Anderson 2007; Antman 2002; Bassand 2007; ILCOR 2005; SIGN 2007; Van de Werf 2008). For example, 'generic' guidelines on the acute care of patients with AMI recommend oxygen use (AARC 2002). The American College of Cardiology (Antman 2002) identified oxygen as a 'routine measure', with a recommendation that it should be administered to patients with arterial oxygen desaturation (SaO_2) less than 90% and that it was 'reasonable' to administer it to all patients with STEMI during the first six hours. This is also the updated guidance from the American College of Cardiology and the American Heart Association for STEMI and non-STEMI, which recommends oxygen use where oxygen saturation is < 90% and for all other patients during the first six hours (Anderson 2007).

The International Liaison Committee on Resuscitation suggests that, "Given the safety profile of oxygen in this population and the potential benefit in the patient with unrecognized hypoxia, it is reasonable to give supplementary oxygen to all patients with STEMI during the first six hours of emergency management" (ILCOR 2005). On the other hand, the recent European guideline (Bassand 2007) does not recommend routine oxygen use in acute coronary syndrome (ACS) and the most recent Scottish Intercollegiate Guidelines Network (SIGN) guidance only recommends oxygen use in hypoxaemia (< 90% saturation) and points out that there is no clinical evidence for its effectiveness but refers to animal models that show a reduction in infarct size (SIGN 2007).

The British Heart Foundation, in response to the doubts about oxygen use raised by Beasley 2007, stated in an article in The Guardian that "The current practice of giving high-flow oxygen is an important part of heart attack treatment. Best practice methods have been developed and refined over the years to ensure the best possible outcome for patients. There is not enough evidence to change the current use of oxygen therapy in heart attacks". We think that given the evidence cited it would have been more appropriate to conclude that despite decades of use there is inadequate clinical trial evidence to unequivocally support routine administration of oxygen.

With the lack of collective certainty about the use of oxygen, perhaps it is time that this treatment is reassessed. In general, practice should not be based on tradition but on proven benefit and safety. Given that the 1976 trial (Rawles 1976) was suggestive of potential harm from oxygen in suspected AMI, it is important that the evidence base for the current guidance recommending the use of oxygen be systematically reviewed and, if necessary, further

research undertaken to clarify whether this intervention does do more harm than good. If the only robust evidence is suggestive of potentially serious harm, even if the result is not statistically significant, it reinforces our opinion that this intervention should not be routinely used however sound the underpinning pathophysiological reasoning.

OBJECTIVES

To determine if routinely giving oxygen to people with suspected and proven AMI does more good than harm by reviewing the evidence from randomised controlled trials using patient-centred outcomes, in particular death and pain.

METHODS

Criteria for considering studies for this review

Types of studies

We decided we would include randomised controlled trials in any language, with any length of follow up and any publication status (full publication, abstract only or unpublished).

Types of participants

Adult patients of any age treated in a pre-hospital or a hospital setting for suspected or proven AMI less than 24 hours after onset and regardless of any co-therapy (for example a reperfusion technique) provided this was the same in both arms of the trial.

Types of interventions

The intervention was inhaled oxygen given by any device at normal pressure for one hour or more and at any stage within the first 24 hours after the onset of AMI symptoms. The comparator was air. Excluded interventions were hyperbaric oxygen or aqueous oxygen therapy (unless the studies included arms with air or oxygen at normal pressure).

Types of outcome measures

Only clinically relevant outcomes were sought. The primary outcome for the systematic review was pre-specified as mortality; the secondary outcomes were pain and any other complications (such as heart failure, pericarditis and rhythm disorders).
Surrogate outcomes, such as reperfusion arrhythmias and arterial oxygen saturation, were not included as these can be misleading.

Search methods for identification of studies

Electronic searches

The following bibliographic databases were searched (from start of database to end of February 2010):

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*);
- MEDLINE (Ovid);
- MEDLINE In-Process (Ovid);
- EMBASE (Ovid);
- CINAHL (EBSCO);
- LILACS (Latin American and Caribbean Health Sciences Literature database);
- PASCAL database (available to October 2008 at time of searching);
- British Library ZETOC;
- Web of Science ISI Proceedings.

The following databases were searched for ongoing trials:

- National Research Register (now archived);
- Current Controlled Trials metaRegister http://www.controlled-trials.com/mrct/;
- www.clinicaltrials.gov.

Details of the database search strategies are in Appendix 1.

Searching other resources

Annual meetings and conferences of professional bodies (American Heart Association, British Cardiovascular Society, European Society of Cardiology and American College of Cardiology) were searched for relevant abstracts.
Experts in the field were contacted to locate any unpublished studies and citations from key references were checked. No date or language restrictions were applied to the searches.

Data collection and analysis

We used the standard methods of The Cochrane Collaboration as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). This Handbook post-dates the publication of our protocol and we made minor amendments to the protocol (outlined below) so that the review methods are consistent with current recommendations. We used Revman 5.0 for the analysis.

Selection of studies

Two authors independently reviewed the titles and abstracts of studies identified in the searches to see if they met the above inclusion criteria. Study reports were obtained in full when inclusion could not be decided from the title or abstract.

Data extraction and management

Two authors independently evaluated the methodological quality and undertook independent data extraction using an agreed data extraction form. Differences were resolved by discussion. Data were analysed using RevMan 5. The data were entered by one review author and checked by two others.

Assessment of risk of bias in included studies

Risk of bias in individual studies

We used the two-part tool described in Section 8.5 of the Cochrane Handbook (Higgins 2008). We explored the six specific domains of: sequence generation; allocation concealment; blinding (participants, personnel and outcome assessors); incomplete outcome data; selective outcome reporting; and other potential threats to validity.

For each trial, two review authors first independently described the design characteristics relating to each domain and then judged the risk of bias when associated with the main outcome. A nominal scale was used for the judgement: 'Yes' (low risk of bias), 'No' (high risk of bias) or 'Unclear' (uncertain risk of bias). As the risk of bias is not the same with different outcomes, we repeated the process for all relevant outcomes in the relevant domains.

Risk of bias across studies

We did an overall assessment of risk of bias for every outcome within the review for each domain and using a similar scale: low risk of bias ('Yes' in all domains), unclear risk of bias ('Unclear' for one or more domains) and high risk of bias ('No' for one or more domains).

When meta-analysis was undertaken we summarised the risk of bias for the main outcomes, across studies. Disagreements between review authors in the description or in the judgement were resolved by consensus without the need for recourse to a third review author.

Measures of treatment effect

We looked at the relative risk (RR) of death and report this in preference to risk difference. This was because the trials were old (the main trial was undertaken in the era before thrombolysis was routine) and we anticipated that there would be higher control event rates than would be expected today. We also looked for differences in mean pain scores. These were not given, therefore we used the relative risk of opiate use as a proxy for pain.

Unit of analysis issues

In the main trial (Rawles 1976), 200 patients with AMI were randomised but the results were only analysed for the 157 who were later confirmed to have had an AMI. It is legitimately open to debate as to whether people who did not have an AMI should be included in a study of the benefits of oxygen in AMI. Theoretically diagnosis may be more certain today. On the other hand, we treat suspected MIs and these represent some of the patients to whom a treatment would be given. We have therefore performed two analyses: one in patients who had confirmed MI in Rawles 1976 plus all patients from the other two trials and a strict intention-to-treat (ITT) analysis that included the 43 patients from Rawles 1976 who did not have an AMI. This was to preserve the strict randomisation process and to minimise selection bias.

Dealing with missing data

An ITT analysis was conducted whenever possible. Authors were contacted for missing data (all the authors contacted did respond but not all original data were available).

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the outcomes tables and using the I^2 statistic (where an $I^2 < 60\%$ was considered to demonstrate moderate heterogeneity).

Assessment of reporting biases

There were only three studies that met the inclusion criteria, therefore it was not possible to explore reporting bias using funnel plots or the Begg and Egger tests.

Data synthesis

Meta-analyses were undertaken where data were available and it was clinically sensible to do so, using both the fixed-effect and random-effects models. We reported the results using both models because we recognise that readers may have different perspectives (for example priors, values or contexts) and different people may wish to see the results uwith the different mathematical assumptions.

Subgroup analysis and investigation of heterogeneity

The data were too sparse to permit adequate exploration of the subgroups that had been pre-specified for analysis (based on the effect of using primary PCI or thrombolysis; timing and duration of oxygen therapy; pre-existing levels of hypoxaemia; other measures of severity of infarction).

Sensitivity analysis

Similarly, our intention to explore the effect of trial quality in a sensitivity analysis was limited by the number of trials and the quality of reporting. We undertook separate analyses using the

confirmed AMI population and the ITT population and undertook a best case, worst case sensitivity analysis for the missing data on deaths (Wilson 1997).

RESULTS

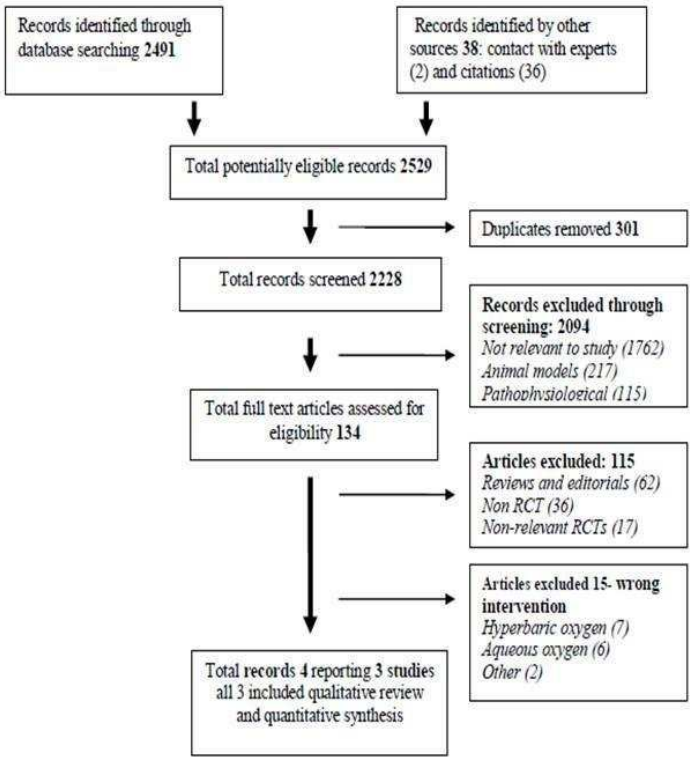
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 2529 articles. Removal of duplicates left 2228 articles for screening. Based on title and abstract, 2094 were excluded and 134 full papers retrieved. A further 115 were not RCTs or were RCTs not related to our review. Of the remaining 19 papers, 15 (reporting 9 RCTs) were excluded for various reasons leaving four papers reporting three trials that met the inclusion criteria (Rawles 1976; Wilson 1997; Ukholkina 2005). The process with reasons for exclusions are described in Figure 1 and the list of the 9 excluded trials given in the table 'Characteristics of excluded studies'.

Figure 1. Study selection flow diagram



Included studies

The three included trials were conducted between 1976 and 2005 (Rawles 1976; Wilson 1997; Ukholkina 2005). Two were conducted in the UK (Rawles 1976; Wilson 1997) and one in Russia (Ukholkina 2005). All three studies were parallel-design, ran-

domised controlled trials. One was double blind (Rawles 1976) and the other two (Wilson 1997; Ukholkina 2005) were open label.

Population: in total 387 participants were recruited, 74% were male. Patients with suspected AMI were also recruited in one study (Rawles 1976) and only patients with confirmed AMI in the other two. The mean ages in years (and standard errors where given) of the included patients in each group were as follow. Rawles 1976: air 50.8 (2.4), O_2 51.3 (1.7); Wilson 1997: air 64, O_2 65; Ukholkina 2005: air 53.5 (1.06), O_2 55.6 (1.33).

Intervention: in all three included trials the intervention was inhaled oxygen at 4 to 6 L/min. This was given by mask in two studies and by a nasal cannula in the other study. The comparator was air in all three studies, breathed normally in the two open-label studies and given at 4 to 6 L/min by facial mask in the double-blind study.

Outcomes: deaths were reported in all three studies. Pain or analgesic use (as a proxy for pain) was reported in two studies. One study included as surrogate outcomes the infarct size estimated by electrocardiogram (ECG) or biochemical markers.

The main characteristics of the included studies are in the table Characteristics of included studies.

Excluded studies

Of the 115 excluded articles, 62 did not report original data; 36 were not RCTs; 17 were RCTs of interventions which were not relevant to study; and 15 papers reporting on nine studies had a different oxygen intervention (six used hyperbaric oxygen, one aqueous oxygen, one oxygen associated with haemoglobin, one oxygen combined with nitric oxide versus placebo for pain control). The main characteristics of the included studies are in the table Characteristics of excluded studies

Risk of bias in included studies

Randomisation

There was no description of how the sequence for allocation was generated in any of the studies.

Allocation concealment

In two studies allocation was concealed using numbered sealed envelopes (Rawles 1976; Wilson 1997). The method of allocation concealment was not reported in the other study (Ukholkina 2005).

Blinding

Only Rawles 1976 was blinded. This was done by using shrouded cylinders but there is no information about how effective this was. Nursing staff were not aware that the record of opiate administration would be used as a proxy measure of pain. We think that the use of shrouded cylinders left blinding potentially compromised and therefore the possibility of performance and observer bias cannot be excluded. However, while this could affect the assessment of the surrogate outcomes for pain, it is much less likely to have affected the primary outcome of this review, which was death (Wood 2008).

Performance and observer bias were possible in the two unblinded studies. This may have affected the evaluation of the surrogate outcome for pain in the Wilson study (this outcome was not reported in the Ukholkina trial). The assessment of the primary outcome (death) and the other secondary outcome of complications such as recurrent ischaemia or AMI, heart failure, arrhythmias and pericarditis were less likely to be subject to significant observer bias.

Incomplete outcome data addressed

All patients were followed to discharge in Rawles 1976 but randomisation was undertaken before the diagnosis was confirmed. AMI was not confirmed in 21.5% of those with suspected AMI. Although this may appear high, it is not inconsistent with diagnostic techniques in the 1970s. Of the 105 people randomised to oxygen and the 95 to air, AMI was not confirmed in 25 and 18 participants respectively. The characteristics of those in whom AMI was not confirmed were similar in both groups and there were no deaths among the excluded individuals.

In Wilson, it was unclear how long patients were followed up for. Eight patients were excluded from the analysis: one death, one stroke, four who withdrew consent and two because data were incomplete. This is 16% of the participants and the expected effect on the results for the primary event was very low; therefore the risk of bias was high but its direction is unknown.

In Ukholkina 2005 the outcomes were measured for 10 days and no patients were lost to follow up. However, no explicit data were provided about the patients who were excluded post-randomisation because of failed revascularisation or the relative number of failed revascularisations in each group. The mismatch between the numbers reported in the tables and the text suggest that two patients may have been excluded from the air group and four from the oxygen group, but we cannot be certain. Consequently we could not include these patients in the intention-to-treat analysis. We therefore think there is a high risk of bias for the outcomes we measured.

Selective outcome reporting

No study protocols were available. Rawles 1976 was the best quality study and we believe that the report probably included all the pre-specified variables. In Wilson 1997 the primary purpose was to look at the incidence and degree of hypoxaemia and the effect of oxygen on hypoxaemia, rather than this review's primary out-

come of death; the patient who died was excluded from the analysis. Despite contacting the authors, we were unable to establish in which group the death occurred and this study could not be included in the meta-analysis. We carried out a sensitivity analysis to assess the potential risk of bias.
In Ukholkina 2005, ECGs were mapped to estimate the surrogate outcome of infarct size but only in a subset of 31 patients in the oxygen group; there was no information for the air group. We therefore believe that meaningful conclusions cannot be drawn about infarct size. We do not think the pain and death outcomes were subject to selective reporting.

Baseline characteristics

Overall, the two groups appeared similar after randomisation in Rawles 1976 and Wilson 1997. In Ukholkina 2005 the two groups appeared similar in age, smoking, hypertension, unstable angina and cholesterol. There was a difference (not statistically significant) in the Killip stage, with more Killip II in the oxygen group than the air group; time to revascularization was 41 minutes shorter in the air group (P = 0.052), which even if due to chance may have important clinical implications for our outcomes of interest.

Other biases

No other biases were identified in the Rawles 1976 and Wilson 1997 studies.
Ukholkina 2005 reported differences in infarct size between the two interventions but the authors did not specify the time after symptom onset when creatine phosphokinase M and B isoenzymes (MB-CPK) were measured; they were not measured at the same time in all patients. In addition, no information was provided about the consistency and validity of the method used to map myocardial damage (number and blinding of observers, reliability and repeatability of their measurements; whether there were disagreements and, if so, how these were resolved). While these methodological weaknesses call into question the reliability of the estimation of myocardial damage they do not affect the main outcomes of this review. Only Ukholkina 2005 reported complications but there was an inconsistency between the data in the table and the text. We re-calculated complication rates and used these data in our analysis.

Summary of risk of bias

Death as an outcome had a low risk of bias in Rawles 1976, was not reported adequately in Wilson 1997 and had a high risk of bias in Ukholkina 2005. We therefore consider the overall risk of bias in the meta-analyses to be high. For pain we considered the risk of bias in Rawles 1976 to be unclear and there to be a high risk of bias in Wilson 1997. Consequently we consider the risk of bias in the meta-analysis for pain to be high.

Effects of interventions

Mortality

All three papers reported the observed mortality. Rawles 1976 found more deaths in the group randomised to oxygen than in the air group, both for all randomised patients (suspected AMI) and for those with confirmed AMI. Wilson 1997 described one death but did not report in which group this occurred. We contacted both of the authors of the original paper. They confirmed that they no longer had the trial data and did not remember in which arm the death and the stroke had occurred; however they stated that 25 patients had been randomised into each group. In Ukholkina 2005, only one patient out of 58 died in the oxygen group and none out of 79 participants in the air group.
Only the results from two (Rawles 1976; Ukholkina 2005) of the three studies could be combined. When combined, three times as many patients on oxygen died than in the group given air. This suggests that oxygen may be harmful but, because of the small numbers of people in the trials, this result may simply have been due to chance. The complete results are given numerically below and a sensitivity analysis for the missing data from Wilson 1997 is also presented.
Meta-analysis for mortality in participants with confirmed AMI: RR 3.03 (95% CI 0.93 to 9.83; I^2 = 0%, fixed-effect model) (Analysis 1.1). This remained unchanged when applying a random-effects model (Analysis 1.2).
Meta-analysis for mortality in an ITT population (including those who did not have AMI): RR 2.88 (95% CI 0.88 to 9.38; I^2 = 0%, fixed-effect model) (Analysis 1.3).This remained unchanged when applying a random-effects model (Analysis 1.4).
Sensitivity analysis for missing information about the arm in which the death occurred in the Wilson trial (ITT analysis): a worst case scenario assuming that the patient who died was in the oxygen arm gave a RR of death of 2.88 (95% CI 0.88 to 9.38). A best case scenario assuming that the patient who died was in the air arm gave a RR of death of 2.06 (95% CI 0.67 to 6.37). In both cases we used a fixed-effect model.

Pain

Pain was not explicitly measured but the authors reported diamorphine use as a proxy for pain. In the Rawles 1976 study, a similar proportion of patients from both groups received analgesia. The total dosage was similar: 54.3% of randomised patients (71.3% of those with confirmed AMI) in the oxygen group received analgesia, average of 2.1 doses (standard deviation (SD) 1.5) but it was not clear whether the denominator was patients who used diamorphine or all patients; 54.7% of randomised patients (67.5% of those with confirmed AMI) in the air group received analgesia, average of 2.0 doses (SD 1.4) but again it was not clear what the denominator population was. In Wilson 1997 the authors re-

ported opiate use as a proxy for pain. Although 50 patients were randomised, results were only reported for 42, as follows: 16 of 22 patients (72.7%) in the oxygen group used opiates; 18 of 20 patients (90%) in the air group used opiates. Ukholkina 2005 did not measure pain or analgesic use.

Thus we could only combine results from two studies. There was no difference in analgesic use between the oxygen and the air groups. The complete results are given numerically below.

Meta-analysis for analgesic use in confirmed AMI: RR 0.99 (95% CI 0.83 to 1.18; I^2 = 54%, fixed-effect model) (Analysis 1.5). This was slightly altered when a random-effects model was applied: RR 0.94 (95% CI 0.72 to 1.23; I^2 = 54%) (Analysis 1.6).

Meta-analysis for analgesic use in the ITT population (including those who did not have an AMI): RR 0.97 (95% CI 0.78 to 1.20; I^2 = 0%, fixed-effect model) (Analysis 1.7). This remained unchanged using a random-effects model: RR 1.01 (95% CI 0.75 to 1.34; I^2 = 0%) (Analysis 1.8).

Complications

Ukholkina 2005 explored complications such as heart failure, pericarditis and rhythm disorders. The RR of complications (excluding recurrent ischaemia) was 0.45 (95% CI 0.22 to 0.94) (Analysis 1.9).

DISCUSSION

Three trials were found. None demonstrated that oxygen therapy in patients with acute myocardial infarction (AMI) does more good than harm on clinical outcomes. In both the intention-to-treat meta-analysis and the confirmed AMI meta-analysis, there were more deaths amongst those patients on oxygen than for patients on air although this did not reach statistical significance and could simply be a chance occurrence. There was no clinically or statistically significant difference in analgesia use between the two treatments. Nevertheless, in the meta-analysis for analgesic use in confirmed AMI we found moderate heterogeneity (I^2 = 54%), which disappeared in the intention-to-treat analysis. While the two studies used in the meta-analysis had differences in their design (for example blinded versus open label) and attrition rates (much higher in Wilson 1997), it was not possible to investigate the heterogeneity further with only two trials.

This review has a number of limitations. Firstly, the evidence in support of such a widespread practice is surprisingly sparse and scattered. We were unable to determine if there was any publication bias using formal methods as only three studies were found. The possibility that there are unpublished studies or other published studies, especially in foreign languages, that were not indexed in the electronic databases we searched cannot be excluded.

Secondly, the quality of the included studies was generally poor and the risk of bias was high for both of out main outcomes. Two of the studies (Rawles 1976; Wilson 1997) were not recent and were carried out prior to the improvements in trial design, conduct and reporting that have taken place in the last decade. Therefore results must be interpreted with caution.

Thirdly, Rawles 1976 was undertaken in the era before reperfusion (thrombolysis or percutaneous coronary intervention (PCI)) and thus may not be applicable in today's context. Moreover, case fatality rates from AMI have fallen over the last 30 years due to improved management (Babaev 2005; Movahed 2009; Steg 2004), including reperfusion and the use of medical treatments such as beta-blockers, aspirin or angiotensin-converting enzyme inhibitors.

Finally, the overall death rate among control participants during their hospital stay in the included studies was only 1.7%. This rate is lower than that observed in contemporary routinely collected data (Babaev 2005; Movahed 2009). While this may be explained by the fact that the lowest risk patients were recruited, it could also be due to a chance deficit of deaths in the control arm (which would have contributed to the apparent difference between the oxygen and control groups).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence in this area is sparse, of poor quality and pre-dates the advances in reperfusion techniques and trial methods. The evidence available is suggestive of harm but lacks power so this could be due to chance. Current evidence neither supports nor clearly refutes the routine use of oxygen in patients with AMI.

Implications for research

As long ago as 1950, it was demonstrated that the administration of pure oxygen via a facial mask not only failed to reduce the duration of angina pain but also prolonged the electrocardiographic changes indicative of an AMI (Russek 1950). This finding was explicitly identified as requiring further research, over three decades ago (Salzman 1975). Given that Rawles 1976 subsequently suggested possible harm, it is surprising that a definitive study to rule out the possibility that oxygen may do more harm than good has not been done.

Part of the reason for the failure to fund such a fundamental study may be the strong a priori belief (Cabello 2009; Danchin 2009), based on pathophysiological reasoning, that oxygen administration must reduce both the oxygen deficit in ischaemic myocardial tissue and consequent tissue death. Indeed, both the medical profession and the public are so familiar with the use of oxygen that

the general attitude may be that even if it is not doing any good it is not going to be of any harm.

We believe there is a need for a randomised controlled trial to establish the effectiveness of, or harm from, the administration of oxygen to patients with AMI. While there are pathophysiological reasons to believe that it may have the potential to reduce tissue damage, it is also biologically plausible that oxygen is doing harm (see above under 'Why it is important to do this review').

We know of no ongoing research or trials seeking to address the question of whether routine use of oxygen in AMI reduces pain or death. Given the widespread use of oxygen in AMI, the inconsistency in recommendations about when and to whom it should be given and the fact that the best current evidence is suggestive of potential clinically significant harm, the need to clarify this uncertainty is urgent.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Rawles 1976

Methods	Double-blind, randomised controlled trial
Participants	Patients with suspected AMI presenting within 24 hours after onset of symptoms. Sample size 200
Interventions	Oxygen or compressed air administered by MC mask at 6L/min over 24 hours Comparator: air at normal pressure given at 6L/min by MC mask
Outcomes	Death, arrhythmias, use of analgesics, maximum serum aspartate aminotransferase levels, length of stay, systolic ejection time, hypoxaemia
Notes	Clinical setting: single site coronary care unit in the UK

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	There was no description of how the sequence was generated
Allocation concealment?	Yes	Numbered sealed envelopes
Blinding? Death	Yes	Double-blinded using shrouded cylinders (but likely that the blinding could have been compromised)
Blinding? Pain (or surrogate)	Unclear	Double-blinded using shrouded cylinders (but likely that the blinding could have been compromised)
Blinding? infarct size ECG	No	Not applicable in this trial
Incomplete outcome data addressed? Death	Yes	There were post-randomisation exclusions due to unconfirmed AMI (19% air group and 24% O_2 group)
Incomplete outcome data addressed? infarct size ECG mapping	No	Not applicable in this trial
Free of selective reporting?	Yes	There was no protocol published but we judged that there was no bias in reporting the primary outcome

Rawles 1976 (*Continued*)

Free of other bias?	Yes	Other bias have been not identified
Baseline characteristics?	Yes	Consecutive patients, similar age, sex

Ukholkina 2005

Methods	Randomised, open-label, controlled trial
Participants	Confirmed AMI within 12 hours of onset of symptoms. Sample size 137
Interventions	Oxygen for 3 hours administered via nasal cannulae 3-6 L/min (FiO_2 30-40%)
Outcomes	Death, arrhythmias within 1 hour after reperfusion, surgery during hospital stay, recurrent AMI, post-infarction angina, hypoxaemia, heart failure, pericarditis, area of tissue damage measured by ECG mapping and cardiac enzymes
Notes	Single-site coronary care unit in Russia

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? Death	Yes	This was an open-label trial (but absence of blinding unlikely to introduces bias in this outcome)
Blinding? Pain (or surrogate)	No	Not applicable in this trial (pain was not a variable evaluated in the study)
Blinding? infarct size ECG	Unclear	This was an open-label trial (but the absence of blinding unlikely to introduce bias in this outcome)
Incomplete outcome data addressed? Death	No	While mortality was adequately reported for included patients, there was inadequate description of exclusion post randomisation in each group (e.g. failed revascularisation)
Incomplete outcome data addressed? infarct size ECG mapping	Unclear	Inadequate description of exclusion post randomisation in each group (e.g. failed revascularisation) consequently, these patients are not included in the infarct size comparison. There were problems of consis-

Ukholkina 2005 (*Continued*)

		tency in the measurement process of ECG mapping done to estimate infarct size
Free of selective reporting?	No	We have no information about the protocol, but the infarct size estimation was only reported in 31 patients in the oxygen group and no information in the air group
Free of other bias?	No	See baseline imbalances
Baseline characteristics?	No	The groups were different at baseline in two important variables: 1-clinical class Killip and Kimball (Killip II 10% O_2 versus 1% air group, P=0.08) and 2-time to revascularisation 41 min shorter in the air group

Wilson 1997

Methods	Randomised, open-label, controlled trial
Participants	Patients with confirmed AMI presenting within 24 hours of onset of symptoms. Sample size 50
Interventions	Oxygen by face mask at 4L/min or normal air over 24 hours
Outcomes	Hypoxaemia, arrhythmias, cardiac enzymes
Notes	Single-site coronary care unit in the UK. The primary purpose of this trial was to look at the effect of oxygen on hypoxaemia

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Yes	Sealed envelopes for randomisation
Blinding? Death	Yes	This was an open-label trial (but the absence of blinding is unlikely introduces bias in this outcome)
Blinding? Pain (or surrogate)	No	This was an open-label trial, therefore the risk of bias in this outcome cannot be ruled out

Wilson 1997 (*Continued*)

Blinding? infarct size ECG	No	Not relevant in this study
Incomplete outcome data addressed? Death	No	8 out of 50 missing data (group not specified); 1 death, 1 stroke, 4 withdrew consent, 2 with incomplete data
Incomplete outcome data addressed? infarct size ECG mapping	No	Not relevant in this study
Free of selective reporting?	No	The main variables of the study were incidence and degree of hypoxaemia and the effect of oxygen administration. The main outcome of this review (death) was not reported, in fact the only patient who died was not included in the analysis
Free of other bias?	Yes	Other biases were not identified
Baseline characteristics?	Yes	Consecutive patients, similar age, smoking and diabetes

ABBREVIATIONS
STEMI = ST-segment elevation myocardial infarction
CHD = coronary heart disease
AMI = myocardial infarction
ACS = acute coronary syndrome
SIGN = Scottish Intercollegiate Guidelines Network
RCT = randomised controlled trial
RR = relative risk
ECG = electrocardiogram
SD = standard deviation
SE = standard error
ITT = intention-to-treat analysis

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

Study	Reason for exclusion
AMIHOT 2003	Wrong intervention: aqueous oxygen therapy in STEMI
Dekleva 2004	Wrong intervention: hyperbaric oxygen versus air in patients after thrombolysis in AMI
Dotsenko 2007	Wrong intervention: hyperbaric oxygen versus air in conventionally treated patients with AMI

(*Continued*)

Haude 2007	Wrong intervention: supersaturated oxygen therapy after percutaneous coronary intervention in AMI
Kerr 1975	Different intervention: nitrous oxide 50% with ot without oxygen 50% versus air in-patients with AMI
Laden 1998	Wrong intervention: hyperbaric oxygen.
Shandling 1997	Wrong intervention: hyperbaric oxygen
Slagboom 2005	Wrong intervention: haemoglobin-based oxygen therapeutics in elective PCI
Stavitsky 1998	Wrong intervention: hyperbaric oxygen

DATA AND ANALYSES

Comparison 1. Oxygen versus air

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death in hospital for patients with acute MI	2	294	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.93, 9.83]
2 Death in hospital for patients with acute MI (random effects)	2	294	Risk Ratio (M-H, Random, 95% CI)	3.03 [0.93, 9.83]
3 Death in hospital for all patients (including those who did not have an AMI)	2	337	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.88, 9.38]
4 Death in hospital for all patients (including those who did not have an AMI) Random effects	2	337	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.88, 9.39]
5 Opiate use (as a proxy measure for pain) for patients with an AMI	2	199	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]
6 Opiate use (as a proxy measure for pain) for patients with an AMI (random effects)	2	199	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.72, 1.23]
7 Opiate use (as a proxy measure for pain) for all patients on ITT (including those who did not have an AMI)	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.20]
8 Opiate use (as a proxy measure for pain) for all patients on ITT (including those who did not have an AMI) Random effects	2	250	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.78, 1.38]
9 Complications of AMI	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.45, 1.03]

Analysis 1.1. Comparison 1 Oxygen versus air, Outcome 1 Death in hospital for patients with acute MI.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 1 Death in hospital for patients with acute MI

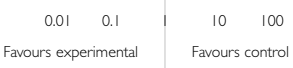
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rawles 1976	9/80	3/77		87.8 %	2.89 [0.81, 10.27]
Ukholkina 2005	1/58	0/79		12.2 %	4.07 [0.17, 98.10]
Total (95% CI)	**138**	**156**		**100.0 %**	**3.03 [0.93, 9.83]**

Total events: 10 (Experimental), 3 (Control)

Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%

Test for overall effect: Z = 1.85 (P = 0.065)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Oxygen versus air, Outcome 2 Death in hospital for patients with acute MI (random effects).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 2 Death in hospital for patients with acute MI (random effects)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rawles 1976	9/80	3/77		86.3 %	2.89 [0.81, 10.27]
Ukholkina 2005	1/58	0/79		13.7 %	4.07 [0.17, 98.10]
Total (95% CI)	**138**	**156**		**100.0 %**	**3.03 [0.93, 9.83]**

Total events: 10 (Experimental), 3 (Control)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%

Test for overall effect: Z = 1.84 (P = 0.066)

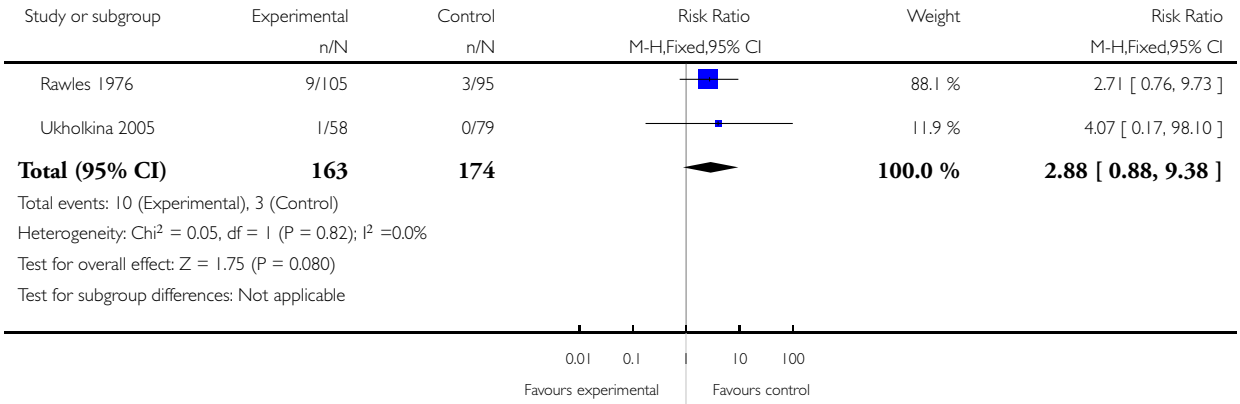
Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Oxygen versus air, Outcome 3 Death in hospital for all patients (including those who did not have an AMI).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 3 Death in hospital for all patients (including those who did not have an AMI)

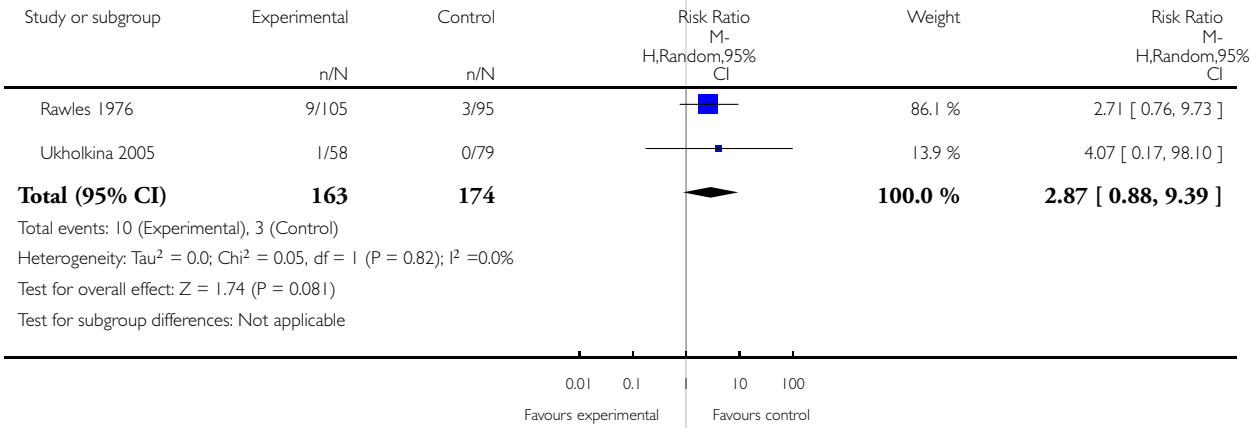


Analysis 1.4. Comparison 1 Oxygen versus air, Outcome 4 Death in hospital for all patients (including those who did not have an AMI) Random effects.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 4 Death in hospital for all patients (including those who did not have an AMI) Random effects



Analysis 1.5. Comparison 1 Oxygen versus air, Outcome 5 Opiate use (as a proxy measure for pain) for patients with an AMI.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

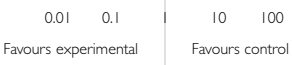
Outcome: 5 Opiate use (as a proxy measure for pain) for patients with an AMI

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wilson 1997	16/22	18/20		26.2 %	0.81 [0.60, 1.08]
Rawles 1976	57/80	52/77		73.8 %	1.06 [0.86, 1.30]
Total (95% CI)	**102**	**97**		**100.0 %**	**0.99 [0.83, 1.18]**

Total events: 73 (Experimental), 70 (Control)

Heterogeneity: Chi^2 = 2.18, df = 1 (P = 0.14); I^2 =54%

Test for overall effect: Z = 0.11 (P = 0.91)



Analysis 1.6. Comparison 1 Oxygen versus air, Outcome 6 Opiate use (as a proxy measure for pain) for patients with an AMI (random effects).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 6 Opiate use (as a proxy measure for pain) for patients with an AMI (random effects)

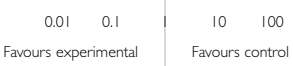
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rawles 1976	57/80	52/77		57.6 %	1.06 [0.86, 1.30]
Wilson 1997	16/22	18/20		42.4 %	0.81 [0.60, 1.08]
Total (95% CI)	**102**	**97**		**100.0 %**	**0.94 [0.72, 1.23]**

Total events: 73 (Experimental), 70 (Control)

Heterogeneity: Tau^2 = 0.02; Chi^2 = 2.18, df = 1 (P = 0.14); I^2 =54%

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Oxygen versus air, Outcome 7 Opiate use (as a proxy measure for pain) for all patients on ITT (including those who did not have an AMI).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 7 Opiate use (as a proxy measure for pain) for all patients on ITT (including those who did not have an AMI)

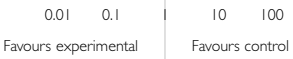
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rawles 1976	57/105	52/95		75.2 %	0.99 [0.77, 1.28]
Wilson 1997	16/25	18/25		24.8 %	0.89 [0.61, 1.30]
Total (95% CI)	**130**	**120**		**100.0 %**	**0.97 [0.78, 1.20]**

Total events: 73 (Experimental), 70 (Control)

Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.32 (P = 0.75)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Oxygen versus air, Outcome 8 Opiate use (as a proxy measure for pain) for all patients on ITT (including those who did not have an AMI) Random effects.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 8 Opiate use (as a proxy measure for pain) for all patients on ITT (including those who did not have an AMI) Random effects

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio(Non-event) M-H,Random,95% CI	Weight	Risk Ratio(Non-event) M-H,Random,95% CI
Rawles 1976	57/105	52/95		87.9 %	1.01 [0.75, 1.37]
Wilson 1997	16/25	18/25		12.1 %	1.29 [0.57, 2.91]
Total (95% CI)	**130**	**120**		**100.0 %**	**1.04 [0.78, 1.38]**

Total events: 73 (Experimental), 70 (Control)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.30, df = 1 (P = 0.59); I^2 =0.0%

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable

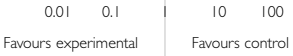
Analysis 1.9. Comparison 1 Oxygen versus air, Outcome 9 Complications of AMI.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 9 Complications of AMI

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ukholkina 2005	20/58	40/79		100.0 %	0.68 [0.45, 1.03]
Total (95% CI)	**58**	**79**		**100.0 %**	**0.68 [0.45, 1.03]**
Total events: 20 (Experimental), 40 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.070)					
Test for subgroup differences: Not applicable					



APPENDICES

Appendix 1. Search strategies

CENTRAL on The Cochrane Library

#1 MeSH descriptor Myocardial Infarction explode all trees
#2 myocardial next infarct*
#3 heart next infarct*
#4 (acute near/3 coronary)
#5 (coronary near/3 syndrome*)
#6 heart next attack*
#7 MeSH descriptor Coronary Thrombosis this term only
#8 coronary near/3 thrombosis
#9 ami
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 MeSH descriptor Oxygen Inhalation Therapy explode all trees
#12 oxygen
#13 (#10 and #12)

MEDLINE on Ovid

1 exp Myocardial Infarction/
2 myocardial infarct$.tw.
3 heart attack$.tw.
4 heart infarct$.tw.
5 (coronary adj3 syndrome$).tw.

6 acute coronary.tw.
7 Coronary Thrombosis/
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 Oxygen Inhalation Therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.13 oxygen.ti. or Oxygenotherapy/
14 or/11-13
15 10 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized controlled trials.sh.
19 random allocation.sh.
20 double blind method.sh.
21 single-blind method.sh.
22 or/16-21
23 (animals not humans).sh.
24 22 not 23
25 clinical trial.pt.
26 exp clinical trials/
27 (clin$ adj25 trial$).ti,ab.
28 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
29 placebos.sh.
30 placebo$.ti,ab.
31 random$.ti,ab.
32 research design.sh.
33 or/25-32
34 33 not 23
35 34 not 24
36 comparative study.sh.
37 exp evaluation studies/
38 follow up studies.sh.
39 prospective studies.sh.
40 (control$ or prospectiv$ or volunteer$).ti,ab.
41 or/36-40
42 41 not 23
43 42 not (24 or 35)
44 24 or 35 or 43
45 15 and 44

EMBASE on Ovid

1 exp Heart Infarction/
2 Coronary Artery Thrombosis/
3 myocardial infarct$.tw.
4 heart attack$.tw.
5 heart infarct$.tw.
6 (coronary adj3 syndrome$).tw.
7 acute coronary.tw.
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 oxygen therapy/

12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.
13 oxygen.ti.
14 or/11-13
15 10 and 14

Pascal

1 oxygen.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
2 myocardial infarction.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
3 acute coronary syndrome.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
4 2 or 3
5 1 and 4
6 random$.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
7 5 and 6

CINAHL (EBSCO)

(heart attack* or MI or AMI or heart infarct* or myocardial infarct* or coronary syndrome or coronary thrombosis) AND ((oxygen) AND (random* or control* or trial*)

LILACS (BIREME)

(heart or MI or AMI or myocardial or coronary) AND (oxygen) AND (random* or control* or trial*)

ISI Proceedings (Web of Knowledge)

(heart or MI or AMI or myocardial or coronary) AND (oxygen) AND (random* or control* or trial*)

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 6, 2010

CONTRIBUTIONS OF AUTHORS

Juan Cabello provided expert advice, co-wrote the protocol and helped with quality assessment, data extraction, writing the discussion and entering data into RevMan.

Amanda Burls co-wrote the protocol, contacted authors for further information and contributed to quality assessment, data extraction, analysis, writing the discussion, and entering data into RevMan.

Sue Bayliss undertook the electronic searches, helped obtain papers and proof read the review.

Jose Emparanza Knorr co-wrote the protocol and contributed to quality assessment, data extraction, analysis and writing the discussion.

Tom Quinn provided expert advice, contacted experts to find unpublished studies and contributed to quality assessment, data extraction and writing the discussion.

DECLARATIONS OF INTEREST

None on starting this review. After starting this systematic review some of the authors have put together, with other clinical colleagues, a proposal for a randomised controlled trial in the UK of oxygen in AMI in the pre-hospital setting.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- None, Not specified.

No financial support was received for this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Data were too sparse to permit adequate analysis of the subgroups that had been pre-specified for exploration.

We made two changes:

1. one minor change in the search strategy to improve the sensitivity, the inclusion of the text word 'oxygenotherapy' in the title (the original search failed to pick up the Russian article and we looked to see if it was in MEDLINE and, if so, why the search strategy had missed it);

2. after the protocol was published, a new version of the Cochrane Handbook recommended a new approach to assessment of risk of bias, we changed our method of assessment to be consistent with the recommendations.

INDEX TERMS

Medical Subject Headings (MeSH)

*Oxygen Inhalation Therapy [adverse effects; mortality]; Myocardial Infarction [mortality; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans