Oxygen therapy for acute myocardial infarction –

a systematic review and meta-analysis

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Abstract

Background

Oxygen is widely recommended in international guidelines for treatment of acute myocardial infarction (AMI), but there is uncertainty about its safety and benefits.

Objectives

A systematic review and meta-analysis were performed to determine whether inhaled oxygen in AMI improves pain or the risk of death.

Methods

Cochrane CENTRAL Register of Controlled Trials, MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, LILACS and PASCAL were searched from start date through February 2010. Other sources included British Library ZETOC, Web of Science, ISI Proceedings, conferences of relevant societies, contact with experts. Randomised controlled trials of inhaled oxygen (at normal pressure) versus air in patients with suspected or proven AMI of less than 24 hours onset were included. Two authors independently reviewed studies to see if they met inclusion criteria and undertook data abstraction. Quality of studies and risk of bias was assessed according to Cochrane Collaboration guidance. The main outcomes were death, pain, and complications. The measure of effect used was the relative risk (RR).

Results

Three trials, involving 387 patients were included. The pooled RR of death on oxygen compared to air was 2.88 (95%CI 0.88 to 9.39) on an ITT analysis and 3.03 (95%CI 0.93 to 9.83) in confirmed AMI. While suggestive of harm, 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).

Conclusion

The evidence in this area is sparse, of poor quality and pre-dates advances in reperfusion techniques and trial methods. What evidence there is, is suggestive of harm but lacks power and excess deaths in the O₂ group could be due to chance. More research is urgently needed to clarify the role of oxygen in AMI.
Systematic review registration number

Original protocol registered with the Cochrane Collaboration.

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Abbreviations

$O_2$ Oxygen

AMI Acute myocardial infarction

ECG Electrocardiograph

PCI Primary coronary intervention

$SaO_2$ Oxygen saturation

STEMI ST segment elevation myocardial infarction

RCT Randomised controlled trial
Introduction

The cornerstone of contemporary management of AMI presenting with ST segment elevation is reperfusion therapy. Other recommended treatments include: aspirin; nitrates; morphine; and O₂. While O₂ administration is mentioned in most AMI guidelines, recommendations are inconsistent.¹⁻⁹

The rationale for providing O₂ in AMI is to improve oxygenation of ischaemic myocardial tissue. This has face validity but is there supporting evidence? A systematic review, including non-randomised studies, did not confirm that O₂ reduces acute myocardial ischaemia (some evidence suggested it may actually increase ischaemia).¹⁰ A systematic review of the effect on infarct size concluded ‘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’.¹¹

A recent narrative review¹² also suggested that oxygen may do more harm than good. The British Heart Foundation’s response to this was: ‘The current practice of giving high-flow O₂ 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 O₂ therapy in heart attacks.’¹³ This view is consistent with that held by many clinicians who treat AMI.¹⁴,¹⁵

Given the uncertainty surrounding this widely used treatment, we undertook a systematic review to look at the effect on patient-centred clinical outcomes of giving O₂ to people with suspected AMI.

Methods

Protocol and registration

The protocol was registered on the Cochrane Library.¹⁶

Eligibility criteria

**Study design:** randomised controlled trials, with any length of follow up.

**Participants:** patients treated in a pre-hospital or a hospital setting for suspected or proven uncomplicated AMI of less than 24 hours onset, regardless of co-therapies (e.g. reperfusion), provided these were the same in both arms.
**Intervention**: inhaled O\(_2\), at normal pressure, for one hour or more, at any stage within 24 hours after the onset of AMI. Hyperbaric and aqueous O\(_2\) therapy trials were excluded.

**Comparator**: air

**Publication status**: any

**Language**: any

**Years**: any

**Information sources**

We searched the Cochrane CENTRAL Register of Controlled Trials, MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, LILACS and PASCAL, UK National Research Register (NRR) to 2007, the NRR Archive and NIHR CRN portfolio, Current Controlled Trials metaRegister and ClinicalTrials.gov. Other sources included British Library ZETOC, Web of Science, ISI Proceedings, annual meetings and conferences of the American College of Cardiology, American Heart Association, British Cardiovascular Society and European Society of Cardiology.

**Search strategy**

Databases were searched from their start date through February 2010. The strategy specified in the protocol was amended to increase sensitivity by truncating the term “oxygen”. (See appendix 1 for full strategy).

**Study selection**

Two authors independently reviewed titles and abstracts of identified studies to see if they met the inclusion criteria. If this could not be decided from the title or abstract study reports were obtained in full. There were no discrepancies.

**Data collection process**

Data were abstracted using a piloted data extraction form independently by two reviewers and entered by one reviewer and checked by two others. Differences were resolved by discussion.

**Data items**
The primary outcome was pre-specified as mortality; secondary outcomes were pain (or opiate use as a proxy), quality of life and any other reported patient-centred outcomes. Surrogate outcomes such as arrhythmias, infarct size and SaO$_2$ were not collected.

**Risk of bias in individual studies**

We used the Cochrane Collaboration two-part tool.$^{17}$ We considered six domains: 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 the design characteristics relating to each domain we judged the risk of bias associated with the main outcome using a nominal scale: ‘Yes’ (low risk of bias) ‘No’ (high risk of bias) or ‘Unclear’ (uncertain risk of bias), for all the relevant outcomes in the relevant domains.

**Risk of bias across studies**

We assessed overall risk of bias for every outcome by each domain using the following scale: **low** (‘Yes’ in all domains), **unclear** (‘Unclear’ for one or more domains) and **high** (‘No’ for one or more domains).

Where meta-analysis was undertaken, we summarised risk of bias across studies. Disagreements were resolved by consensus.

**Summary measures**

We calculated risk difference and relative risk (RR) of death. As the trials were old, we anticipated that control event rates would be higher than those expected today and therefore pre-specified that we would preferentially report the RR. Intention-to-treat (ITT) analysis was performed whenever possible.

**Synthesis of results**

We used RevMan 5.0. Meta-analyses were performed when clinically sensible and data available using a fixed effects model. ITT analysis was the primary analysis but we also looked at results in patients with proven AMI. We assessed heterogeneity by visual inspection and the $I^2$ statistic ($I^2 < 60\%$ was considered moderate).

**Additional analyses**

We undertook a best-case worst-case sensitivity analysis for missing data on death for confirmed AMI and ITT populations.
Results

Study selection

We identified 2529 articles. Removal of duplicates left 2228. Based on title and abstract, 2094 were excluded, 134 full papers retrieved. A further 115 were excluded, leaving four papers reporting three trials\textsuperscript{17-20} that met the inclusion criteria. (Figure 1 gives reasons for exclusions.)

Study characteristics

All three studies were parallel design RCTs. One\textsuperscript{18} was double-blind, the others were open label. Table 1 shows the main characteristics of included studies.

Rawles\textsuperscript{18} 1976

This study was the largest (N=200) and had the best methodology. It was performed in the pre-reperfusion era. Patients with suspected AMI were randomised and followed to discharge.

Wilson\textsuperscript{19} 1997

This was a small RCT of 50 people with confirmed uncomplicated AMI, followed to discharge. Its primary purpose was to look at the effect of O\textsubscript{2} on hypoxaemia and did not record most of the outcomes of interest to this review. It was reported along with a postal survey on the use of O\textsubscript{2} and pulse oximetry in 252 cardiac care units in the UK.

Ukholkina\textsuperscript{20,21} 2005

This study was published in English\textsuperscript{20} and Russian.\textsuperscript{21} It is the only trial performed in the PCI era and included 137 patients with confirmed uncomplicated AMI. Its primary purpose was to look at infarct size. Patients were followed for 10 days.
<table>
<thead>
<tr>
<th>Trial &amp; year</th>
<th>Study design and sample size</th>
<th>Clinical setting</th>
<th>Participants</th>
<th>Exclusions</th>
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<th>Clinical Context and parallel care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rawles 1976</td>
<td>Double-blind, randomised controlled trial N=200</td>
<td>Single site coronary care unit in the UK</td>
<td>Suspected acute myocardial infarction (MI) presenting within 24 hours of onset of pain</td>
<td>Patients with heart failure, Bronchitis, emphysema, or other respiratory problems</td>
<td>Inhaled oxygen at normal pressure given at 6L/min by MC mask for 24 hours N: 105</td>
<td>Air at normal pressure given at 6L/min by MC mask. N: 95</td>
<td>Death, arrhythmias, use of analgesics, length of stay (LOS).</td>
<td>Discharge</td>
<td>Pre-thrombolysis period</td>
</tr>
<tr>
<td>Wilson 1997</td>
<td>Open label randomised controlled trial N=50</td>
<td>Single site coronary care unit in the UK</td>
<td>Confirmed uncomplicated acute MI</td>
<td>Patients with heart failure, cyanosis central or pulmonary disease requiring O₂</td>
<td>Oxygen for 24 hours administered via face mask at 4L/min. N:25</td>
<td>Air breathed normally N:25</td>
<td>Hypoxaemia, Arrhythmias, analgesics, and Cardiac enzymes</td>
<td>Discharge</td>
<td>Thrombolysis period</td>
</tr>
<tr>
<td>Ukholkina 2005</td>
<td>Open label randomised controlled trial N=137</td>
<td>Single site coronary care unit in Russia</td>
<td>Confirmed uncomplicated acute MI</td>
<td>Patients with complicated MI, congestive heart failure, pulmonary disease, or anaemia.</td>
<td>Oxygen for 3 hours administered via nasal cannulae 3-6 L/min (Fio2 30-40%) N:58</td>
<td>Air breathed normally N: 79</td>
<td>Death, recurrent AMI, post-infarction angina, heart failure, area of tissue damage measured by ECG mapping, cardiac enzymes.</td>
<td>10 days</td>
<td>PCI era</td>
</tr>
</tbody>
</table>
Risk of bias within studies

Risk of bias for each study is summarised in figure 2. Reasons underlying these classifications are given below.

**Rawles** 18 1976

There is no description of how the randomisation sequence was generated. Allocation was concealed using numbered sealed envelopes. The groups had similar baseline characteristics. Blinding of patients and staff was by shrouding gas cylinders. There is no information on how effective this was. If patients required O₂ due to severe hypoxaemia or cardiac arrest, blinding was not broken - the tube was attached to a wall supply of O₂. While the primary outcome of this review, death, is not subject to observer bias, the possibility of performance bias due to unblinding cannot be excluded. The patients withdrawn from the study are not reported, so we cannot estimate the possible impact of performance bias on outcomes. Nursing staff were not aware that routine recording of opiate administration would be used as a proxy measurement of pain.

There was no loss to follow-up, but randomisation was undertaken before the diagnosis was confirmed. Of the 105 people randomised to O₂ and the 95 to air, AMI was not confirmed in 25 and 18 patients, respectively. Characteristics of those in whom AMI was not confirmed were similar in both groups and there were no deaths in these individuals. No selective reporting bias was identified.

**Wilson** 19 1997

There is no description of how the randomisation was done. Allocation was concealed using sealed envelopes. The baseline characteristics showed the groups to be similar in mean age and smoking habits. The study was not blind. In total eight patients were excluded from the analysis: 1 death, 1 stroke, 4 withdrew consent and 2 because of incomplete data. Death was recorded, but the patient who died was excluded from the study and it was not reported whether they received O₂. No other selective reporting was identified.
There is no description of how randomisation sequence was generated or whether allocation was concealed. Baseline characteristics differ in the two groups for: time to revascularisation (41 minutes shorter in the air group \((P=0.052)\)) and Killip classification: (Killip class II was present in 10% \(O_2\) vs. 1% air group \((P=0.08)\) (class III and IV were excluded from the study)). Both are potential confounders which could have led to overestimation of comparative mortality in the \(O_2\) group.

Blinding was not undertaken. The primary outcome, death, and other outcomes such as recurrent MI and pericarditis are hard outcomes and unlikely to be subjected to significant observer bias. It may have led to performance bias. The study has possible bias in infarct size estimation: CPK-MB was not measured at the same time from onset in all patients and PCI can alter biomarker release; no information is provided about number or blinding of observers, reliability and repeatability of measurements for ECG mapping. Furthermore, ECG-mapping for assessing infarct size was used only in a subset of patients.

No patients were lost to follow up. There is no explicit data on patients excluded post-randomisation due to failed revascularisation, or the number of failed revascularisations per group. The mismatch between numbers reported in the tables and the text suggest two patients may have been excluded from the air group and four from the \(O_2\) group. Data in Table 3 of the study report did not make sense for “No complications” for the air group. We recalculated complication rates for this group for the outcome tables in our analysis.

**Results of individual studies**

**Rawles** \(^{18}\) 1976

8.6% of randomised patients (11.2% with confirmed AMI) in the \(O_2\) group died (one in the first 24 hours while still on therapy) and 3.2% of randomised patients (3.9% of those with confirmed MI) in the air group died (two of them in the first 24 hours). RR of death was 2.89 (95%CI 0.81 to 10.27) in confirmed AMI and 2.71 (95%CI 0.76 to 9.73) in ITT population.

Diamorphine use was reported as a proxy for pain. It was administered in 54.3% of the \(O_2\) group (71.3% of those with confirmed AMI). The average was 2.1 doses (SD 1.5), but it is unclear whether the denominator was those using diamorphine or all patients. In the air group, 54.7% received diamorphine (67.5% of those with confirmed AMI). The average was 2.0 doses (SD 1.4), but the denominator was unclear. The RR for the use of
analgesia was 1.06 (95%CI 0.86 to 1.30) in confirmed AMI and 0.99 (95%CI 0.77 to 1.28) in the ITT population.

Wilson 19 1997

There was one death, but we were unable to determine in which group this occurred. Both authors confirmed they no longer had the trial data and did not remember in which arm the death and the stroke occurred. 25 were randomised into each group.

Opiate use was recorded as a proxy for pain. Although 50 patients were randomised, results were only reported for 42. Sixteen out of 22 patients (72.7%) in the O₂ group used opiates and 18 out of 20 patients (90%) in the air group used opiates. The RR of need for analgesia was 0.81 (95%CI 0.60 to 1.08) in the reported groups and 0.89 (95%CI 0.61 to 1.30) on an ITT basis. There was no difference in ECG ST-segment changes between the groups

Ukholkina 20,21 2005

One patient out of 58 died in the O₂ group and none out of 79 in the air group. RR of death was 4.07 (95%CI 0.17 to 98.10).

Complications of AMI (excluding angina), were reported in 8 out of 58 (13.8%) in the oxygen group and 24 out of 79 (30.4%) in the air group. RR of complications was 0.45 (95%CI 0.22 to 0.94).

The authors used several techniques to estimate the infarct size. Although they conclude that oxygen “reduced the area of necrosis and peri-infarction area, improved central hemodynamic, and decreased the rate of postoperative rhythm disorders as compared to patients breathing ambient air”, we felt that this could not be concluded confidently because of the methodological weaknesses discussed above.

Synthesis of results

There were only sufficient data to perform meta-analyses for death and opiate use from two of the three trials (Rawles 18 and Ukholkina 20,21 for death, and Rawles 18 and Wilson 19 for pain). There was no heterogeneity in the ITT analyses.

The meta-analysis showed a RR of death for patients in the O₂ group of 3.03 (95%CI 0.93 to 9.83) in confirmed AMI and 2.88 (95%CI 0.88 to 9.38) in the ITT population (Figure 3).

The meta-analysis for analgesic use gives a RR of 0.99 (95%CI 0.83 to 1.18) in confirmed AMI and 0.97 (95%CI 0.78 to 1.20) (Figure 4) in the ITT population.
Risk of bias across studies

The risk of bias across studies is high. Risk of bias is “Unclear” for adequate sequence generation and allocation concealment and “High” for blinding, completeness of outcome data, selective outcome reporting and other biases.

Additional analysis

We did a sensitivity analysis for missing information on the arm in which the death occurred in the Wilson trial. The worst-case scenario assumes that the patient who died was in the O\textsubscript{2} arm and gives a RR of death of 2.88 (95%CI 0.88 to 9.38) using ITT analysis. The best-case scenario assumes that the patient who died received air, giving a RR of death of 2.06 (95%CI 0.67 to 6.37) using ITT analysis.

Discussion

Only three trials, involving a total of 387 patients, were found. None demonstrated that O\textsubscript{2} therapy in AMI does more good than harm. In both the ITT and the confirmed AMI meta-analyses, there were more deaths amongst those on O\textsubscript{2} than those 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. In the meta-analysis for analgesic use in confirmed AMI we found moderate heterogeneity ($I^2 = 54\%$) but it disappeared in the ITT analysis. While the two studies used in the meta-analysis had differences in design (blind vs. open label) and attrition rates (higher in the Wilson study), it is not possible to investigate 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 analyse if there was any publication bias using formal methods as only three studies were found. The possibility that there are unpublished studies and or other published studies, especially in foreign languages, that are not indexed in the electronic databases cannot be excluded.

Secondly, the quality of included studies was generally poor and risk of bias was high for both outcomes. Two studies (Rawles and Wilson) were old and prior to improvements in trial design, conduct and reporting that have taken place in the last decade. Therefore results must be interpreted with caution.

Thirdly, the Rawles study was undertaken in the pre-reperfusion era and thus may not be applicable today. Moreover, case fatality rates from AMI have fallen over the last 30
years due to improved management including reperfusion and the use of medical treatments such as beta-blockers, aspirin or angiotensin-converting enzyme inhibitors.\textsuperscript{22}

Finally, overall death rate among controls during hospital stay in the included studies was only 1.7%. This is lower than observed in contemporaneous routinely collected data.\textsuperscript{22} While this may be explained by the fact that low risk patients were recruited, it could also be due to a chance deficit of mortality in the control arm (which could have contributed to the apparent excess of deaths in the $O_2$ arm).

**Conclusion**

The evidence in this area is sparse, of poor quality and pre-dates advances in reperfusion techniques and trial methods. What evidence there is, is suggestive of harm but lacks power and excess deaths in the $O_2$ group could be due to chance. Current evidence neither supports nor refutes the routine use of $O_2$ in patients with uncomplicated AMI.

**Implications for research**

As long ago as 1950, it was demonstrated that the administration of pure $O_2$ via face mask not only failed to reduce duration of angina pain, but also prolonged ECG changes indicative of acute myocardial ischaemia.\textsuperscript{23} This topic was identified as requiring further research over three decades ago.\textsuperscript{24} It is surprising that a definitive study has not been undertaken.

We searched ClinicalTrials.gov and the World Health Organisation International Clinical Trials Registry Platform for ongoing trials of oxygen in AMI and identified two studies, from Australia and New Zealand, neither of which (one hospital based, the other pre-hospital, recruiting around 200 patients each) is powered for mortality. We have calculated that around 10 thousand patients would need to be randomised to receive oxygen, and another 10 thousand to air, to address the question of whether oxygen improves or increases mortality. We are working with colleagues from ambulance services, cardiology, emergency medicine and public health to plan such a trial. Given the widespread use of oxygen in AMI, the inconsistency in guideline 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.

A strong *a priori* belief,\textsuperscript{14,15,25} based on pathophysiological reasoning, that $O_2$ administration is beneficial, may have precluded funding of a definitive trial to date.

**Potential mechanisms causing harm**
It is biologically plausible that O$_2$ is doing harm. Potentially harmful mechanisms include the paradoxical effect of reducing coronary blood flow and increasing coronary vascular resistance$^{26,27}$; reduced stroke volume and cardiac output$^{28}$; other adverse haemodynamic consequences, such as increased vascular resistance from hyperoxia; and reperfusion injury from increased oxygen free radicals$^{29,30}$.

Potential mechanisms by which O$_2$ might harm cardiac patients have been explored in two recent reviews. In their systematic review, Farquhar et al$^{30}$ concluded that hyperoxia caused significant reduction in coronary blood flow due to a mean increase in coronary vascular resistance, suggesting that hyperoxia is a potent vasoconstrictor stimulus to the coronary circulation, functioning at level of microvascular resistance vessels. They also found that hyperoxia led to a reduction in myocardial O$_2$ consumption, due both to reduction in O$_2$ delivery and myocardial O$_2$ demand, shown to be associated with reduced myocardial contractility (although they identify conflicting study results). Moradkhan and Sinoway,$^{31}$ in a narrative review, suggest that, with widespread use of high concentration O$_2$ in cardiac patients to maintain oxygen saturations close to 100%, many patients are consequently exposed to significant periods of hyperoxia, resulting in coronary vasoconstriction as a result of generation of reactive oxygen species, a fall in intracellular ATP concentrations mediating opening of ATP-sensitive potassium channels, in turn causing hyperpolarisation of vascular smooth muscle cells and vasodilation. Hyperoxia may also induce vasoconstriction through acting directly on L-type calcium channels, and may affect release of angiotensin II, with subsequent changes in endothelin-1 levels, increasing vascular tone. Hyperoxia is also thought to increase production of the potent vasoconstrictor 20-HETE. Moreover, in critically ill patients, high flow O$_2$ causes misdistribution of microcirculatory blood flow, with increased O$_2$ shunting and reduction in O$_2$ consumption.$^{31}$

**A new consensus?**

Emerging guidelines are beginning to diverge from the previous consensus that O$_2$ should routinely be administered in AMI, but this ‘new consensus’ is largely based on expert opinion rather than robust evidence of what we should do.$^{8,9,32-35}$ A recent BMJ editorial argued that O$_2$ continue to be routinely used based on pathophysiological reasoning, as none of the studies in the Farquhar$^{30}$ review included patients with AMI$^{36}$. Clearly there is ongoing uncertainty about the role of O$_2$ in AMI.

Decades after the Rawles trial,$^{18}$ we still do not know whether routine O$_2$ administration is beneficial, harmful, or irrelevant in AMI. Nor do we have robust evidence that O$_2$ is
beneficial in ‘complicated’ patients such as those with shock or arrhythmia, and
care concern has been raised about hyperoxia in patients resuscitated from cardiac arrest.\(^{37}\)
We need to generate good evidence, from adequately powered randomised controlled
trials (RCTs) to guide decisions on which patients - if any - should receive \(O_2\), at what
dose, and for how long.

Given widespread use, the inconsistency in recommendations about when and to whom it
should be given, and the fact that the best current evidence is suggestive - but not
conclusive proof - of potential harm from \(O_2\), the need to clarify this uncertainty is urgent.

Author contributions.

ICMJE criteria for authorship read and met: AJB, JIE, SB designed the first protocol.
JBC, JIE participated in protocol amendments. AJB, JIE, JBC, SB participated in the
data acquisition. AJB, JIE, JBC, TQ participated in the analysis and interpretation of
data. JBC, AJB and JIE wrote the paper. TQ and SB revised critically the article. All
the authors approved the version to be published.

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issue 6. (see [www.thecochranelibrary.com](http://www.thecochranelibrary.com) for information) Cochrane reviews are regularly
updated as new evidence emerges and in response to feedback, and the Cochrane
Library should be consulted for the most recent version of the review.

Competing interest: AB and TQ are co-applicants on a grant application for a clinical
trial of oxygen in AMI.

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