

Oxygen therapy for acute myocardial infarction: A systematic review and meta-analysis



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ABSTRACT

Background: Potential benefits or risks of oxygen inhalation for patients with acute myocardial infarction are not fully understood.

Objective: We performed this study to systematically assess the effectiveness and safety of oxygen therapy for patients with acute myocardial infarction.

Design: A systematic review and meta-analysis.

Data sources: We searched randomized controlled trials systematically in PubMed, EMBASE, Web of Science and Cochrane Library up to June 2016.

Review methods: Randomized controlled trials that estimated the effectiveness and safety of oxygen therapy for patients with acute myocardial infarction were identified by two independent reviewers. The primary outcomes were short-term mortality and recurrent rate of myocardial infarction, and the secondary outcomes were arrhythmia incidence and pain incidence. Relative risks (RRs) and 95% confidence intervals (CIs) were used to measure the pooled data.

Results: A total of five randomized controlled trials were in accordance with inclusion criteria and were included in this meta-analysis. Compared with no oxygen group, the oxygen group did not significantly reduce short-term death (RR: 1.08, 95%CI: 0.31–3.74), and there was moderate heterogeneity ($I^2 = 50.8\%$, $P < 0.107$) among studies. We found a significant increase in the rate of recurrent myocardial infarction (RR: 6.73, 95%CI: 1.80–25.17, $I^2 = 0.0\%$, $P = 0.598$) in the oxygen group. The oxygen group did not have a significant reduction in arrhythmia (RR: 1.12, 95%CI: 0.91–1.36; $I^2 = 46.2\%$, $P < 0.156$) or pain (RR: 0.97, 95%CI: 0.91–1.04; $I^2 = 7.2\%$, $P = 0.340$).

Conclusions: Oxygen inhalation did not benefit patients with acute myocardial infarction with normal oxygen saturation. It may increase the rate of recurrent myocardial infarction. High quality trials with larger sample sizes are required.

What is already known about the topic?

- Oxygen therapy has commonly been used in the initial treatment for patients with acute myocardial infarction, while potential benefits or risks of oxygen therapy for these patients remain inconclusive.
- Previous research has not shown consistent results, and some studies identified adverse outcomes such as increased myocardial injury for supplemental oxygen administration during acute myocardial infarction.

What this paper adds

- Oxygen therapy can neither significantly reduce in-hospital mortality, nor reduce the rate of arrhythmia and pain.
- Oxygen inhalation does benefit patients with acute myocardial infarction with normal oxygen saturation.

1. Introduction

Oxygen therapy has become a treatment for patients with acute myocardial infarction for more than 100 years (Steele, 1900). Some

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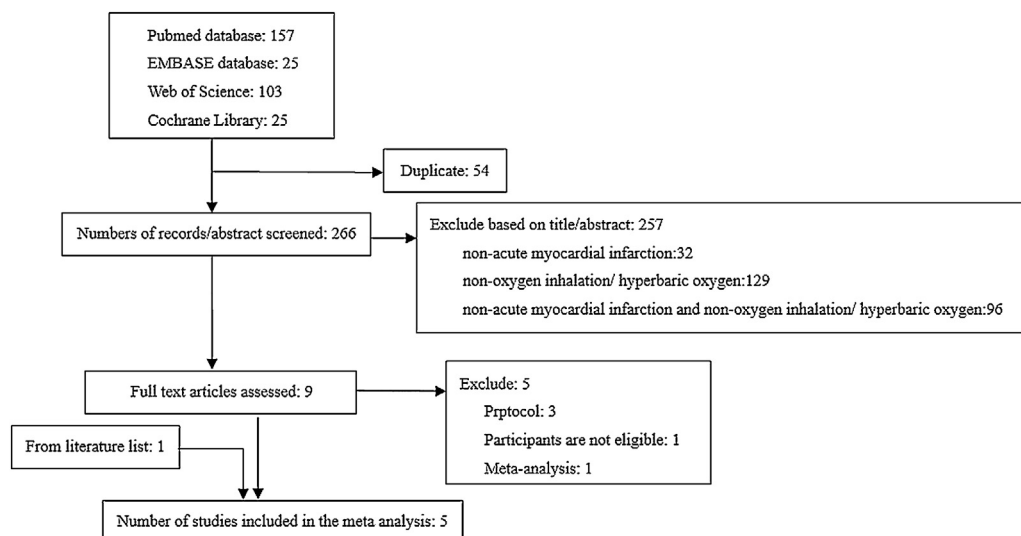


Fig. 1. The flow diagram of literature review process.

studies indicated that oxygen therapy may increase oxygen delivery to ischemic myocardium and hence reduce myocardial injury (Maroko et al., 1975; Kelly et al., 1995). In addition, more than 90% of patients with acute myocardial infarction received oxygen therapy in a clinical context (Beasley et al., 2007). However, potential benefits or risks of oxygen therapy for patients with acute myocardial infarction remain inconclusive. Some studies found no clear benefits or risks that oxygen therapy brings for patients with acute myocardial infarction (David et al., 2013; Rawles and Kenmure, 1976), other studies found that oxygen therapy may lead to harm (Kenmure et al., 1968; Dion et al., 2015). A systematic review and meta-analysis (Cabello et al., 2013) did not report a clear conclusion. Furthermore, one recent study (Dion et al., 2015) identified some new evidence that oxygen therapy could increase the rate of recurrent myocardial infarction and arrhythmia. Therefore, we performed this meta-analysis of the latest and most convincing evidence to systematically assess the effectiveness and safety of oxygen therapy for patients with acute myocardial infarction.

2. Methods

2.1. Literature search and study selection

This study was conducted following the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Moher et al., 2009; Higgins and Green, 2011). We searched relevant articles in PubMed, EMBASE, Cochrane Library and Web of Science for randomized controlled trials (RCTs) that estimated the effectiveness and safety of oxygen therapy for patients with acute myocardial infarction until June 2016. Search strategy included following terms “acute myocardial infarction”, “oxygen therapy” and “randomized controlled trial” (an example of specific strategy is shown in supplementary material: Table S1). Titles and abstracts of the retrieved records were read, and some clearly irrelevant studies were excluded. Full texts of all remaining articles were read to determine eligible studies. Reference lists of identified trials and review articles were also hand screened to identify any additional relevant studies.

Studies satisfying the following criteria were included: (1) design: randomized and quasi-randomized controlled clinical trials; (2) population: patients with acute myocardial infarction less than 24 h; (3) intervention: oxygen inhalation at normal pressure, regardless of the oxygen flow rate (patients receiving home oxygen were not included); (4) data: adequate information was provided to calculate the relative risk (RR) and the corresponding 95% confidence interval (CI). There is no any language limitation.

2.2. Data extraction and outcome

We extracted data from each included study and put them into a data-extraction sheet. The following data were collected: the first author, year of publication, country of origin, the number of patients, intervention, control, outcomes data (short-term death, recurrent myocardial infarction, arrhythmia and pain) and follow up. We contacted the corresponding authors to request the data that need to be clarified or not be presented in the publication. The primary outcomes were short-term mortality (in-hospital mortality) and the rate of recurrent myocardial infarction. The recurrent myocardial infarction was measured at hospital: patients with typical clinical symptoms and signs of acute myocardial infarction (chest pains, pathological Q wave and serum levels change of cardiac markers), and previous medical history of acute myocardial infarction. Secondary outcomes included arrhythmia and pain.

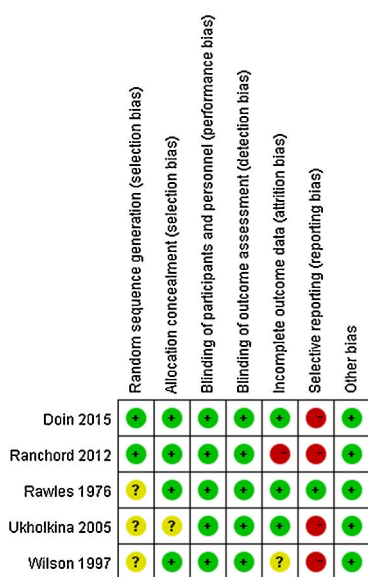


Fig. 2. The result of risk of bias assessment: each risk of bias item for included studies (green means low risk of bias, yellow means unclear risk of bias, red means high risk of bias). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Characteristics of studies (N = 5) included in current analysis.

Author/year	Country	No. of patients (I/C)	Intervention	Control	Short-term death (n)	Recurrent myocardial infarction (n)	Arrhythmia (n)	Pain (n)	Follow-up risk of bias
Dion et al. (2015)	Australia	441 (218/223)	Oxygen via face mask at 8 L/min for 1.32 h	Normal air	I: 4/218 C: 10/223	I: 15/218 C: 2/223	I: 88/218 C: 70/223	I: 192/218 C: 204/223	6 months high
Ranchord et al. (2012)	New Zealand	136 (68/68)	High-concentration oxygen of 6 L/min via medium concentration mask for 1.08 h	Titrate oxygen to achieve oxygen saturation 93–96%	I: 1/68 C: 2/68	I: 1/68 C: 0/68	NA	NA	1 month high
Ukholkina et al. (2005)	Russia	137 (58/79)	3–6 L/min of inhaled oxygen by nasal cannula for 3 h	Ambient room air	I: 1/58 C: 0/79	NA	I: 6/58 C: 13/79	NA	10 days high
Wilson and Channer (1997)	UK	50 (25/25)	Oxygen by face mask at 4 L/min for 24 h	Normal air	NA	NA	NA	I: 16/22 C: 18/20	NA high
Rawles and Kenmure (1976)	UK	157 (80/77)	Oxygen or compressed air administered by mask at 6 L/min for 24 h	Air at normal	I: 9/80 C: 3/77	NA	I: 34/80 C: 35/77	I: 57/80 C: 52/77	NA unclear

No.: number; I/C: intervention/control; N: number; NA: not available from publication.

2.3. Risk of bias assessment and quality of evidence assessment

Risk of bias of included studies was assessed by using the Cochrane Collaboration's tool (Higgins et al., 2011). Each study was assessed and scored as “high”, “low”, or “unclear” risk of bias to the following criteria: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Studies with high risk of bias for any one or more key domains were considered as at high risk of bias; while studies with low risk of bias for all key domains were considered as at low risk of bias; otherwise they were considered as at unclear risk of bias.

The quality of evidence for the outcomes was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias; classified as high, moderate, low or very low. Summary tables were constructed by the Grading of Recommendations Assessment, Development and Evaluation system (Guyatt et al., 2008a,b,c; Swiglo et al., 2008) (Grading of Recommendations Assessment, Development and Evaluation version 3.6).

The literature search, study selection, data extraction, risk of bias assessment and evidence grade assessment were done independently by two authors (SF and XL) using the same approach. Disagreements were resolved by discussion among all authors.

2.4. Statistical analysis

Since all the outcomes (in-hospital mortality, the rate of recurrent myocardial infarction, arrhythmia incidence and pain incidence) are dichotomous, we pooled the RR with corresponding 95%CI by using the random-effects model, when significant between-study heterogeneity existed. Alternatively, we used an inverse-variance fixed effect model, when there was no significant heterogeneity among studies (DerSimonian and Laird, 1986). Heterogeneity across studies was quantified by using the I^2 statistic (Higgins et al., 2003) (the $I^2 > 50\%$ indicated significant heterogeneity), and publication bias was assessed by using Begg's test and Egger's test ($P < 0.05$ was considered statistically significant for publication bias).

3. Results

3.1. Trial selection and risk of bias assessment

The initial search found 310 studies. After removing duplicates, 266 studies were retained. After screening the titles and abstracts, 257 studies were excluded (non-acute myocardial infarction: 32; non-oxygen inhalation/hyperbaric oxygen: 129; non-acute myocardial infarction and non-oxygen inhalation/hyperbaric oxygen: 96). 9 studies were selected for full-text review, and 4 studies (Rawles and Kenmure, 1976; Dion et al., 2015; Wilson and Channer, 1997; Ranchord et al., 2012) met inclusion criteria. One another study (Ukholkina et al., 2005) from reference lists of identified trials also met inclusion criteria. Therefore, 5 studies were finally included in the meta-analysis. The literature review process was shown in Fig. 1. According to the Cochrane Collaboration's tool, one trial (Rawles and Kenmure, 1976) was categorized as at unclear, four trails (Dion et al., 2015; Wilson and Channer, 1997; Ranchord et al., 2012; Ukholkina et al., 2005) as high risk of bias. All details of risk of bias were supplied in Fig. 2.

3.2. Characteristics of articles

These five studies involving 921 participants were published from 1976 to 2015. Among five included studies, four studies (Rawles and Kenmure, 1976; Dion et al., 2015; Ranchord et al., 2012; Ukholkina et al., 2005) reported short-term death, two studies (Dion et al., 2015; Ranchord et al., 2012) reported recurrent myocardial infarction, three

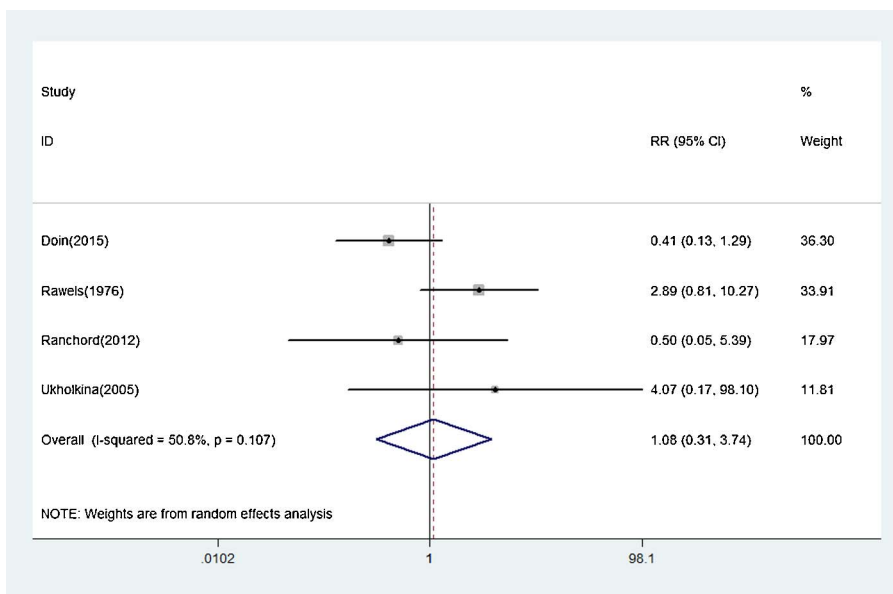


Fig. 3. Effect of oxygen inhalation versus normal air for reducing in-hospital mortality.

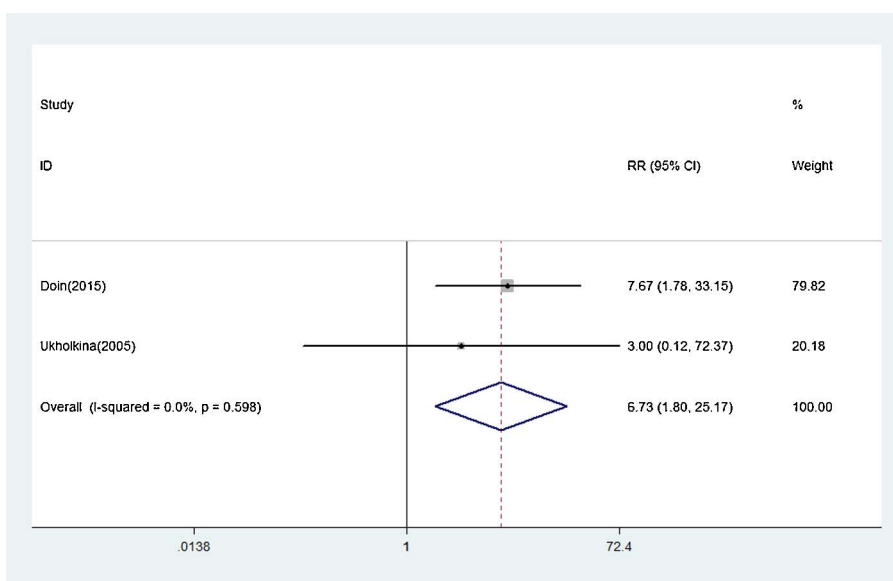


Fig. 4. Effect of oxygen inhalation versus normal air for reducing recurrent myocardial infarction.

studies (Rawles and Kenmure, 1976; Dion et al., 2015; Ukholkina et al., 2005) reported arrhythmia, and three studies (Rawles and Kenmure, 1976; Dion et al., 2015; Wilson and Channer, 1997) reported the number of patients used painkiller (equal to the number of patients occurred pain). Detailed characteristics of eligible studies were provided in Table 1.

3.3. Primary outcome

Primary outcomes are short-term death and the rate of recurrent myocardial infarction. Four studies totaling 871 participants provided data on short-term death. Compared with no oxygen group, oxygen inhalation did not significantly reduce short-term death (RR: 1.08, 95%CI: 0.31–3.74), and there was moderate heterogeneity ($I^2 = 50.8\%$, $P < 0.107$) among studies (Fig. 3). Two studies totaling 477 participants provided data on recurrent myocardial infarction. We found that oxygen inhalation significantly increased the rate of recurrent myocardial infarction (RR: 6.73, 95%CI: 1.80–25.17) compared with no oxygen group, and there was no significantly heterogeneity ($I^2 = 0.0\%$, $P = 0.598$) among studies (Fig. 4).

3.4. Secondary outcomes

Secondary outcomes included the arrhythmia incidence and pain incidence. Three studies (Rawles and Kenmure, 1976; Dion et al., 2015; Ukholkina et al., 2005) totaling 735 participants reported arrhythmia, and three studies (Rawles and Kenmure, 1976; Dion et al., 2015; Wilson and Channer, 1997) totaling 648 participants reported analgesic usage (pain). Compared with no oxygen group, oxygen inhalation did not significantly reduce the arrhythmia (RR: 1.12, 95%CI: 0.91–1.36; $I^2 = 46.2\%$, $P < 0.156$) or reduce the pain (RR: 0.97, 95%CI: 0.91–1.04; $I^2 = 7.2\%$, $P = 0.340$) (Figs. 5 and 6).

3.5. Strength of evidence and publication bias

The quality of evidence was evaluated by the Grading of Recommendations Assessment, Development and Evaluation system. Levels of evidences were at level B and moderate recommendation for short-term death and arrhythmia, while the level of evidence was at level C and low recommendation for pain. The level of evidence was at level C and very low recommendation for recurrent myocardial infarction. All evidence profiles for the primary and secondary outcomes

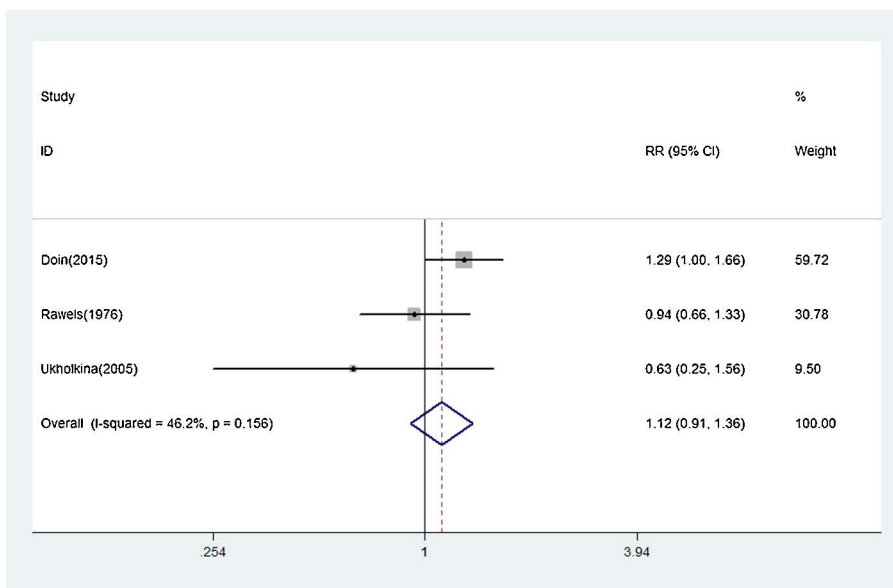


Fig. 5. Effect of oxygen inhalation versus normal air for reducing arrhythmia incidence.

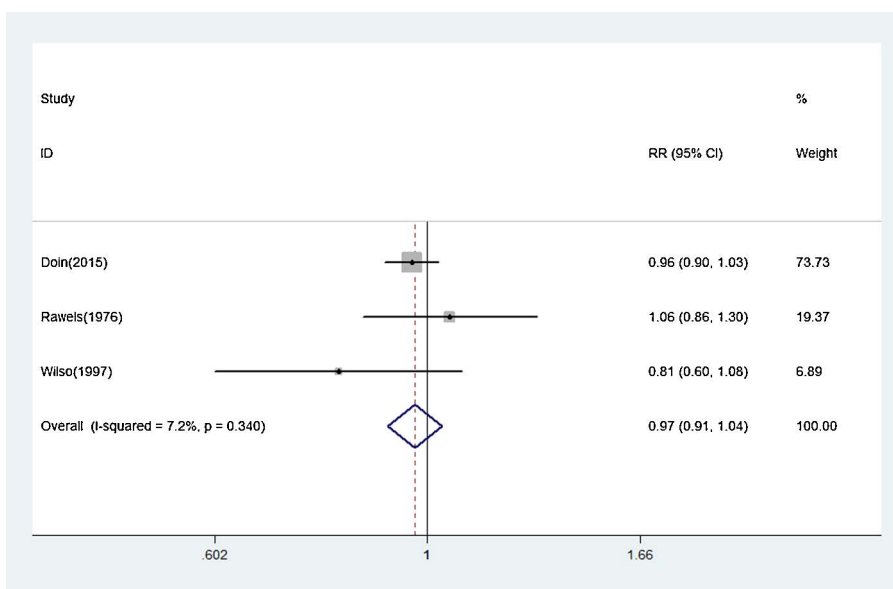


Fig. 6. Effect of oxygen inhalation versus normal air for reducing pain incidence.

were provided in Table 2. For the short-term death, no publication bias was observed by Begg's test and Egger's test (Begg's, $P = 0.497$; Egger's, $P = 0.786$). There are two studies provided data on recurrent myocardial infarction, thus Begg's test or Egger's test for visual assessment of publication bias for studies of recurrent myocardial infarction could not be done. Details of publication biases were provided in Fig. S1.

4. Discussion

4.1. Main findings

This systematic review and meta-analysis found that oxygen inhalation could not reduce in-hospital mortality, arrhythmia incidence or pain incidence in patients with acute myocardial infarction. Oxygen inhalation may increase the rate of recurrent myocardial infarction. This may be because that oxygen will promote leukocyte chemotaxis and inflammatory processes, which leads to myocardial cell death increase in the number (Zweier and Talukder, 2006). Previous study has found that oxygen could aggravate the oxidative stress and promote myocardial cell depolarization, which may cause lethal cardiac arrhythmias (Xie et al., 2009). While our study showed no evidence of

increased the arrhythmia incidence after oxygen inhalation. This could be because that the quality of most included studies was low and the sample size is small, and each outcome of our study involved a small number of studies. More high quality randomized controlled trials with larger samples are urgently required to get a firm conclusion.

4.2. Comparison with previous meta-analysis

In this meta-analysis, the conclusion that potential benefits or risks of oxygen therapy is consistent with previous meta-analysis (Cabello et al., 2013). While differences between our study and previous meta-analysis should be noted. Firstly, this study included 921 participants, while the previous analysis was fairly small, consisting of only 480 participants. Our study has a larger sample size, and the result would be more persuasive. Secondly, the previous study only found that oxygen therapy could not bring benefits. Furthermore, our study found that oxygen therapy may increase the rate of recurrent myocardial infarction. Finally, we evaluated the quality of evidence and the strength of recommendations. Therefore, this meta-analysis was the latest and the most comprehensive one.

Table 2
The Grading of Recommendations Assessment, Development and Evaluation evidence profile of oxygen therapy for acute myocardial infarction.

Quality assessment		No of patients			Effect		Quality		Importance			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxygen therapy	Control	Relative (95%CI)	Absolute		
Short-term death (follow-up 0–180 days; assessed with: table statistics)												
4	Randomized trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^a	Strong association ^a	15/424 (3.5%)	15/447 (3.4%)	RR 1.08 (0.31–3.74)	3 more per 1000 (from 23 fewer to 92 more) ^a	⊕⊕⊕O Moderate	Critical
Recurrent myocardial infarction (follow-up 0–180 days; assessed with: table statistics)												
2	Randomized trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^a	Reporting bias ^a	16/286 (5.6%)	2/291 (0.69%)	RR 6.73 (1.8–25.17)	591 more per 1000 (from 82 more to 1000 more) ^a	⊕○○○ Very low	Important
Arrhythmia (follow-up 0–180 days; assessed with: table statistics)												
3	Randomized trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^a	Strong association ^a	128/356 (36%)	118/379 (31.1%)	RR 1.12 (0.91–1.36)	38 more per 1000 (from 28 more to 114 more) ^a	⊕⊕⊕O Moderate	Important
Pain (follow-up 0–180 days; assessed with: table statistics)												
3	Randomized trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^a	None ^a	265/320 (82.8%)	274/320 (85.6%)	RR 0.97 (0.91–1.04)	26 fewer per 1000 (from 77 more to 34 more) ^a	⊕⊕○○ Low	Important

^a No explanation was provided.

4.3. Guidance for clinical practice

Our study found that the oxygen therapy tends to do more harm than good for patients with acute myocardial infarction, while this conclusion is only suitable for patients with normal oxygen saturation. According to guidelines from the European Society of Cardiology, it is recommended that patients with normal oxygen saturation (blood oxygen saturation $\geq 90\%$) not to receive oxygen therapy. Considering the serious consequences of hypoxia, acute myocardial infarction patients with hypoxemia are recommended to receive oxygen therapy (Marco et al., 2015).

4.4. Limitations

Our study also has limitations. (1) The quality of most studies was low and the sample size was small, and each outcome of our study involved a small number of studies. The reliability of the results can be affected. There is moderate heterogeneity among studies that reported short-term death and arrhythmia. It may also affect the reliability of the results. (2) Myocardial infarction size is one of the important indices for the safety and effectiveness evaluation of oxygen therapy, while most studies did not report it, and there was measurement inconsistency, thus we kept it out of the study. (3) Our study only compared the normal pressure oxygen inhalation with air group. Hyperbaric oxygen did not be taken into account. (4) In most studies, the choice of anticoagulation and percutaneous intervention strategy was at the discretion of the treating interventional cardiologist, according to hospital protocol. It could be a potential confounding factor which affects the results. It is not clear that whether patients with bronchial and pulmonary diseases or not in original studies. It may also affect the results of our study if patients had bronchial or pulmonary problem.

5. Conclusion

Our meta-analysis suggested that oxygen inhalation did not benefit patients with acute myocardial infarction. It may increase the rate of recurrent myocardial infarction. Given that the quality of most studies was low and the sample size was small, as well as each outcome of our study involved a small number of studies, high quality trials with larger sample sizes are required.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijnurstu.2017.04.005>.

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