Critical Review Form
Therapy

PGY-3

Ranchord AM, Argyle R, Beynon R, Perrin K, et al. High-concentration versus titrated oxygen therapy in ST-elevation myocardial infarction: A pilot randomized controlled trial. Am Heart J 2012; 163(2): 168---175.

Objectives: To compare high-concentration versus titrated oxygen therapy in uncomplicated ST-elevation MI (STEMI).

Methods: A prospective, randomized, unblended trial was performed at Wellington Hospital in New Zealand and South Manchester University Hospital NHS Trust in Manchester, United Kingdom. The study was funded by funded by the Cardiology Research Trust, Capital Cardiovascular Research Trust, Health Research Council of New Zealand, and J P Moulton Charitable Foundation. The study population consisted of patients aged 18 or older who presented within 12 hours of the onset of symptoms with STEMI between November 2007 and August 2009. STEMI was confirmed on ECG by the presence of either 1) > 0.1 mV of ST elevation in 2 contiguous limb leads, 2) > 0.2 mV of ST elevation in 2 or more precordial leads, or 3) new onset left bundle branch block (LBBB).

Exclusion criteria:

1) **Previous myocardial infarction (MI)**
2) **Severe COPD or type II respiratory failure**
3) **Cardiogenic shock**
4) **Oxygen saturation < 85% at the time of presentation**
5) **Pregnancy**
6) **Previous bleomycin treatment**
7) **Participation in another clinical trial.**

Patients who were later diagnosed with a condition other than STEMI, who had en exclusion criteria found after randomization, or in whom formal consent was not documented were withdrawn from the study and not included in the analysis.

Patients were randomized to receive either high-concentration oxygen (6 L/min oxygen delivered by medium concentration mask) or titrated oxygen (oxygen administered via nasal cannula to keep oxygen saturation between 93% and 96%). 209 subjects presented with MI during the study period; 61 were excluded (no reason listed for 22 subjects). 148 subjects were randomized, with 12 subsequently withdrawn, leaving 136 subjects. 68 were randomized to high concentration and oxygen and 68 were randomized to titrated oxygen.

The primary outcomes were 30-day mortality and troponin T level (as a marker of infarct size) 66-78 hours after randomization. Secondary outcome measures were infarct mass and left ventricular ejection fraction (LVEF) determined by cardiac MRI at 4-6 weeks, and N-terminal pro-brain natriuretic peptide (NT-proBNP) measured 24 hours after randomization. The cardiac MRI was analyzed by a cardiologist accredited in cardiac magnetic resonance imaging, blinded to the treatment arms and biomarker data.

Additionally, the authors conducted a systematic review and meta-analysis of the literature to determine the relative risk of mortality with oxygen use. However, the do not include a detailed search strategy.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, though they do not describe how the randomization sequence was generated.
2.	Was randomization concealed (blinded)?	No. Both patients and treating physicians were aware of allocation, which could potentially lead to performance bias. It is unclear if data collectors or outcome assessors were blinded. The cardiologist analyzing the MRI results was blinded to allocation.
3.	Were patients analyzed in the groups to which they were randomized?	Mostly. Of 136 patients included in the study, 68 were randomized to each arm and were analyzed in the groups to which they were randomized. However, 12 patients were withdrawn after randomization (4 in the high concentration group and 8 in the titrated group) and were not included in the analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Table I shows similarities between the 2 groups with respect to age, sex, BMI, medical history, and medications. As shown in Table II, There was a significant difference between the 2 groups with respect to infarct location: 26.5% and 72% with anterior and inferior/posterior MI, respectively, in the high concentration group compared to 45.6% and 54.1% in the titrated group. Anterior MI location has been shown to result in higher in-hospital mortality, larger infarct size, lower admission left-ventricular ejection fraction, and higher incidence of heart failure (Stone 1988). This discordance would tend to bias the results in favor of high-concentration oxygen.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes. There was no blinding.
2.	Were clinicians aware of group allocation?	Yes. There was no blinding.
3.	Were outcome assessors aware of group allocation?	Unclear. It is known that the cardiologist who analyzed the MRI results was blinded to group

		allocation, but it is unclear if those assessing other outcomes were blinded, although this is likely unimportant as all other outcomes (mortality and troponin T measurements) are objective and unlikely to be subject to bias.
4.	Was follow-up complete?	Yes and no. For 30-day mortality, follow-up appears to be complete, though the authors do not describe the follow-up process. Cardiac biomarker data was available for all patients included. MRI was only performed in 71 patients (43 in the high-concentration group, and 28 in the titrated group) due to patient refusal.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	30-day mortality: There was 1 death in the high-concentration group and 2 deaths in the titrated group, for a relative risk (RR) of 0.5 (95% CI 0.05-5.4, p = 0.56). Troponin T level: The ratio of means based on the logarithm-transformed data between the high-concentration and titrated groups was 0.74 (95% CI 0.50-1.1, p = 0.14). NT-proBNP level: The ratio of means based on the logarithm-transformed data between the high-concentration and titrated groups was 0.82 (95% CI 0.50-1.37, p = 0.45). MRI results: Difference in mean infarct mass between the high-concentration and titrated groups was -0.8 g (95% CI -7.6 g to 6.1 g, p = 0.82). Percent infarct mass between the high-concentration and titrated groups was -0.6% (95% CI -5.6% to 4.5%, p = 0.83). Mean difference in LVEF between high-concentration and titrated groups was -0.08% (95% CI -5.4% to 5.2%, p = 0.98). Meta-analysis results: Fixed effects and random effects odds ratio of death associated with high-concentration oxygen compared to room air was 2.2 (95% CI 0.8-6.0) and 2.1 (95% CI 0.7-6.5) respectively.

2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Uncertain. While age is similar, I would expect our patients with STEMI to have a higher incidence of associated medical condition (hypertension, diabetes, and hyperlipidemia).
2.	Were all clinically important outcomes considered?	No. While mortality was considered, the authors used surrogate outcomes (troponin T and cardiac MRI) rather than consider more clinically useful markers of functional status and quality of life, such as the Kansas City Cardiomyopathy Questionnaire and the Quality of Life after Myocardial Infarction (QLMI) instrument. Hospital length of stay and cost were also not considered.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While these data suggest similar outcomes in patients treated with high-concentration and titrated oxygen, the study was highly underpowered to detect a difference in mortality, and many patient-important outcomes were not considered.

Limitations:

1) **The study was underpowered to detect a difference in mortality between the oxygen and room air groups. The performance of an *a priori* power analysis and larger study may provide further insight into the effects of oxygen on mortality in AMI. Other outcome measures (troponin T levels and cardiac MRI) represent surrogate outcomes, which may not translate to changes in patient-important outcomes.**
2) **The authors do not describe how the randomization sequence was generated. More importantly, the lack of blinding results in a high risk of performance bias.**
3) **The difference in rates of anterior MI between the two groups, with a significantly high proportion in the titrated oxygen group, would tend to bias the results in favor of the high-concentration oxygen group (Stone 1988).**
4) **There is no search strategy included in the systematic review and meta-analysis.**

Bottom Line:

This small, non-blinded, randomized controlled trial comparing high-concentration vs. titrated oxygen in the management of AMI found no statistically significant difference in mortality, troponin T, NT-proBNP, or cardiac MRI results (assessing infarct mass and LVEF). The small study size, lack of blinding, and different prognosis between the two groups (due primarily to different proportions of anterior MI) make generalization of the results difficult.