Critical Review Form
Therapy

PGY-4

HYPERLINK "http://pmid.us/7864705"Skorodin MS, Tenholder MF, Yetter B, Owen KA, Waller RF, Khandelwahl S, Maki K, Rohail T, D'Alfonso N. Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. Arch Intern Med. 1995 Mar 13;155(5):496-500.

Objectives: **"to determine whether intravenous magnesium sulfate would be of benefit in the treatment of acute exacerbations of COPD in a well-defined group of patients whose conditions were refractory to standard treatment regimens." (p. 496)**

Methods: **This randomized controlled trial was conducted at two Veterans Affairs hospital in Hines, IL and Augusta, GA. Patients aged 35 years or older presenting to the EDs of these hospitals with acute exacerbations of COPD were eligible for inclusion. Exclusion criteria were temperature > 37.9 ℃, systolic blood pressure < 100 mmHg, history of kidney disease, evidence of pneumonia, baseline peak expiratory flow (PEF) > 250 L/min, and a repeat PEF 20 minutes after nebulized albuterol administration ≥ twice the baseline PEF.**

All subjects received nebulized albuterol, 2.5 mg, after initial PEF measurement, and then received either 1.2 mg of magnesium sulfate in 150 mL of saline or placebo (2.4 mL of saline in 150 mL of saline), given over 20 minutes. Dyspnea was gauged by patients on an ordinal scale from 1 to 7 (1 = extremely short of breath, 7 = not at all short of breath) at the beginning of infusion and at 5, 10, 15, 20, 30, and 45 minutes. Respiratory rate (RR), PEF, SPO2, heart rate, and blood pressure were also measured at these time periods. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were assessed at the start of the infusion and 20 and 45 minutes later. No other medications were administered until 45 minutes from the start of the infusion. Patients were contacted 2 weeks following the index ED visit to assess for repeat ED visits during that time period.

There were 72 patients enrolled in the study, of whom 36 received placebo and 36 received magnesium sulfate. All but 2 subjects (1 in each treatment group) were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. The authors do not mention stratification or block permutation.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be	Uncertain. The authors provide no information about how randomization occurred, including sequence generation or methods aimed at allocation concealment.

	"randomized" to a particular group?	
3.	Were patients analyzed in the groups to which they were randomized?	Uncertain. The authors do not specify that an intention to treat analysis was performed. They also not mention whether there was any crossover or if all patients received the treatment to which they were assigned.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, smoking history, duration of COPD, baseline serum magnesium level, and baseline vital signs and PEF. The authors do not provide information on medical comorbidities, symptoms of respiratory infection, home medication use, or need for home oxygen therapy.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "The placebo and magnesium sulfate solutions were prepackaged in identical vials in the pharmacy, coded from a randomized list, and added to the normal saline in the pharmacy before delivery to the emergency department." (p. 497)\
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	Presumably no. While not specifically mentioned, it seems likely that outcome assessors were not aware of group allocation.
4.	Was follow-up complete?	Yes. There were no patients lost to follow-up.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• The mean difference in PEF from initiation of the infusion to 30 and 45 minutes later was significantly larger in the magnesium group (25.1±35.7 L/min) than in the placebo group (7.4±33.3 L/min); p = 0.03. • There was no significant difference in changes in dyspnea scores, MIP, or MEP. • There was a trend toward decreased hospital admission in the magnesium group (28.1% vs. 41.9%), though this did not achieve statistical significance (p = 0.25). • There was no difference in repeat ED visits in the subsequent 2 weeks.

2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	No, This study was conducted in two VA hospitals where a more homogenous population of older males would be expected than that seen in non-VA and non-military settings (**external validity**). Additionally, this study was conducted before the use of nebulized ipratropium and the authors do not mention the administration of steroids. Patients received a single 2.5 mg dose of nebulized albuterol, while our patients typically receive larger doses that are repeated if there is not significant improvement.
2.	Were all clinically important outcomes considered?	No. The authors considered several surrogate outcomes as primary outcomes, but did also assess rates of discharge from the ED and repeat ED utilization within 2 weeks. They did not assess hospital length of stay, ED length of stay, need for intubation, or need for ICU admission.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This small study conducted in the EDs of 2 VA hospitals found that use of IV magnesium resulted in significantly greater improvements in PEF compared to placebo, with no significant difference in dyspnea scores, MIP, or MEP. These are surrogate outcomes and do not necessarily correlate with patient-centered outcomes. The authors did note a trend toward increased rates of ED discharge with use of IV magnesium, but this difference did not achieve statistical significance due to lack of sufficient study power.

Limitations:

1. **Authors do not report the dates over which the study was conducted, do not provide information on patients screened but not eligible, and do not mention whether this was a consecutive or convenience sample.**

2. **Following a single 2.5 mg nebulized albuterol treatment, no other medications (including steroids and additional nebulized treatments) were administered until 45 minutes following the initiation of the infusion.**

3. **No primary outcome was specified. The outcomes measured were primarily surrogate outcomes rather than patient-centered outcomes.**

4. **This study was conducted in two VA hospitals where a more homogenous population of older males would be expected than that seen in non-VA and non-military settings (external validity).**

5. **This was a small study that was underpowered to detect potentially clinically meaningful differences in ED discharge rates (a practice some have called unethical).**

Bottom Line:

This randomized controlled trial conducted in the EDs of 2 VA hospitals found that the administration of IV magnesium sulfate in acute exacerbations of COPD resulted in a statistically significant improvement in PEF 45 minutes following administration when compared to placebo. While there was a trend toward decreased hospital admission rates (28.1% vs. 41.9%), this difference did not achieve statistical significance.