CRITICAL REVIEW FORM:
THERAPY ARTICLES

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Citation:
Kelly GS, Branstetter LA, Moran TP, Hanzelka N, Cooper CD. Low- versus high-dose nitroglycerin infusion in the management of acute pulmonary edema. Am J Emerg Med. 2023 Mar;65:71-75. doi: 10.1016/j.ajem.2022.12.022. Epub 2022 Dec 25. PMID: 36587564.

Study Objective: To characterize clinical outcomes including time to resolution of severe hypertension when using initial low dose (<10 micrograms/min) vs. high dose (>100 micrograms/min) in treatment of acute pulmonary edema

Study Methodology: Retrospective observational study performed at a single, urban, tertiary academic emergency department in Atlanta, GA. (Emory). Data was acquired from EMR and EMS databases using a standardized data collection entry form. Charts were identified primarily by charge capture when NTG infusions were ordered or

GUIDE	COMMENTS
I. Are the results valid?	
A. Did experimental and control groups begin the study with a similar prognosis	
1. Were patients randomized?	No, since this was a retrospective observational study the patient's were not randomized. There were certain inclusion criteria (>18 years old, clinical dx of acute pulmonary edema, at least one severely elevated BP >180 systolic or >120 diastolic and initiation of NTG infusion while in ED)
2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	No, since there was no randomization.
3. Were patients analyzed in the groups to which they were randomized?	The patient's were analyzed in the groups that they were deemed to fit in (low dose vs. high dose) and then analyzed further based on individual factors such as age, comorbidities, medications, initial blood

	pressure
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Not really. The authors do not provide CI's or p values regarding lack of differences in demographics however there were a few standouts: (Table 1): • No men in high dose (HD) group • ESRD in 57% of HD vs. 40% low dose (LD) • DM in 21.4% HD vs.62.9% of LD • Initial BP levels and Hx of HTN were same
5. Were patients aware of group allocation?	Since the study is restrospective chart review there was no official "groups" for the patient to be aware of. Patient's may have known at the time if they received high dose nitroglycerin vs. low dose but this is unknown.
6. Were clinicians aware of group allocation?	The decision to use high dose vs. low dose was completely physician dependent and since this was a retrospective study the study itself did not play a role in treatment decisions for the patients. This obviously may predispose to a host of confounders that predispose to selection bias.
7. Were outcome assessors aware of group allocation?	Yes, the people assessing the outcomes were aware of whether the patient received high dose or low dose nitroglycerin for initial management. This is something that is easy to blind even in retrospective studies but was not.
8. Was follow-up complete?	Yes. The study outcome was based on decrease in blood pressure by 25% in 1 hours time so this was observed for all patients in the study. Secondary outcomes were also assessed including intubation, ICU admission, hypotension.
What are the results ?	
1. How large was the treatment effect?	Primary Outcome: 25% reduction in bp Group with high-dose reached BP faster on average with **hazard ratio=3.5 (95% CI 1.2-10.1).** This finding remained significant in the adjusted model for age, gender, initial SBP, initial DBP, comorbid conditions, medications, and prior NTG administration **(hazard ratio=7.7, 95% CI: 1.7–34.4).** Study was underpowered to provide any substantative data regarding secondary safety outcome measures.
2. How precise was the estimate of the treatment effect? (CI's?)	See above
III **How can I apply the results to patient care?**	

1. Were the study patients similar to my patient?	Maybe. Suprisingly, no racial demographics were reported. Emory however has a similar Southern, inner-city population. We often see patient's at Norfolk general presenting in acute pulmonary edema with severely elevated blood pressure and multiple co-morbidities such as the ones included in this trial
2. Were all clinically important outcomes considered?	No. There were no truly patient-centered outcomes included. They elected to use BP reduction. Patient-centered outcomes such as symptom relief, Level of dyspnea, need for supplemental O2 were omitted.
3. Are the likely treatment benefits worth the potential harm and costs?	There was insufficient data to identify and harms such as hypotension, mental status changes seen with precipitous changes in lowering bp or tachycardia as previously described potential harms of NTG. There was no cost analysis.

Limitations:

Restrospective design
Chart review that is vulnerable to bias from omissions and missed data
No sample size calculation to inform the number of patients needed to be enrolled to identify a significant difference between groups.
Demographics were disparate i.e. no men in HD group, Higher # of ESRD patients in HD group
CI's in adjusted models was very wide (1.7-34.4)
The use of high-dose vs. low-dose nitroglycerin was completety at the discretion of the physician at the time of patient presenation and we do not know what factors influenced this decision. This means cofounding variables and bias can not be accounted for.

Clinical Bottom Line:
This observational study that was likely underpowered suggested that there may be a benefit in treating acute pulmonary edema with high-dose nitroglycerin vs. low-dose nitroglycerin with titration. Additional randomized-controlled studies are likely to better inform this question.