Critical Review Form
Therapy

PGY-2

Lee YH, Lee KJ, Min YH, Ahn HC, Sohn YD, Lee WW, Oh YT, Cho GC, Seo JY, Shin DH, Park SO, Park SM. Refractory ventricular fibrillation treated with esmolol. Resuscitation. 2016 Oct;107:150-5.

Objectives: **"to compare the clinical outcomes in the RVF [refractory ventricular fibrillation] patients including ROSC [return of spontaneous circulation] and survival with good neurologic outcome between the esmolol used group and conventional group for RVF patients that suffered from out-of-hospital cardiac arrest (OHCA) using a pre-post study." (p. 151)**

Methods: **This retrospective, pre-post study was conducted from January 2012 to December 2015 using patients admitted to the Emergency Medical Centre at Hallym University Sacred Heart Hospital in South Korea. Patients aged 18 years or older with OHCA with an initial rhythm of ventricular fibrillation or ventricular tachycardia, with RVF were eligible for inclusion. RVF was defined as ventricular fibrillation that was resistant to ≥ 3 attempts at defibrillation, 3 mg of epinephrine, and 300 mg of amiodarone, with no ROSC after > 10 minutes of CPR. Exclusion criteria were severe head trauma, acute active bleeding, severe sepsis, terminal-stage malignancy, severe neurologic deficits, and beta-blocker therapy prior to cardiac arrest.**

During the "pre" phase of the study (January 2012 to December 2013), patients with RVF did not receive esmolol, while during the "post" phase of the study (January 2014 to December 2015), patients with RVF were given a loading dose of 500 µg/kg of esmolol, followed by an infusion of 0-100 µg/kg/min.

The primary outcome was sustained ROSC (> 20 minutes without recurrence of cardiac arrest). Secondary outcomes were survival to hospital admission, survival to hospital discharge, and survival with a cerebral performance category (CPC) score of 1-2 (i.e. a good neurologic outcome) at 30 days, 3 months, and 6 months.

A total of 383 patients with OHCA were identified, of whom 183 had ventricular fibrillation or ventricular tachycardia as their initial rhythm (93 in the "pre" phase and 90 in the "post" phase). After exclusions, there were 25 patients included in the "pre" phase and 16 patients in the "post" phase.

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. This was a before and after study, and group allocation was determined solely by which phase of the study they were recruited in.
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?	N/A. The study was not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	Again, patients were not randomized. The authors do mention whether any patients in the "pre" group received esmolol, or whether any patients in the "post" group failed to receive esmolol, and whether such patients were included or excluded from the analysis. Presumably, patients were analyzed according to which time-frame their cardiac arrest occurred in.
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, percent with witnessed arrest and bystander CPR, percent with an initial rhythm of ventricular fibrillation, time to EMS arrival, total prehospital time, total CPR time, and therapies received. Information on past medical history was not provided.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. Patients were in cardiac arrest at the time of enrollment, and hence would not be aware of group allocation and would not be at risk of performance bias.
2.	Were clinicians aware of group allocation?	Yes. Group allocation was based on which phase the study was in, and hence blinding was not possible. It is possible, though unlikely, that performance bias on the part of clinicians could have affected outcomes.
3.	Were outcome assessors aware of group allocation?	Uncertain. For short-term outcomes (ROSC, survival to admission, and survival to discharge) outcome assessors would not have been blinded

		to group allocation. The authors make no mention of blinding of long-term outcome assessors, i.e. those assessing CPC scores at 30 days, 3 months, and 6 months. Lack of blinded could potentially lead to observer bias.
4.	Was follow-up complete?	Presumably yes. The authors report that all patients were followed "until either discharge or death." The authors provide no information regarding how follow-up was provided for those patients who survived to hospital discharge, and do not mention any loss to follow-up among these patients.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• Sustained ROSC (and survival to hospital admission) was more common in the esmolol group compared to the control group: 56% vs. 16%; RR 3.5, 95% CI 1.3 to 9.5. • Survival at 30 days, 3 months, and 6 months, and survival at each timeframe with a CPC of 1 or 2 was slightly higher in the esmolol group compared to the control group: 18.8% vs. 8%; RR 2.3, 95% CI 0.4 to 12.5 for all outcomes.
2.	How precise was the estimate of the treatment effect?	See above. This was a relatively small study, and the resulting 95% CIs are quite wide.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Mostly yes. This study was conducted in Korea, and hence the patient comorbidities may be different from those in our patient population. However, these were adult patients with atraumatic cardiac arrest, and hence it is likely that treatment effects would be similar for patients in our practice environment.
2.	Were all clinically important outcomes considered?	Yes. The authors considered both short-term and long-term survival, and assessed neurologic outcomes. They did not assess cost, though in such a small study this would likely not be necessary.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a very small, retrospective study with several methodological limitations. The result was that while esmolol improved sustained ROSC in patients with RVF, it did not have much of an affect on long-term outcomes. Larger studies would be necessary to properly

		evaluate the effect on long-term survival and neurologic outcomes, given that so few patients survive beyond hospital admission.

Limitations:

1. **This was a very small study and clearly lacked the power to determine if a potentially clinically significant effect size was achieved with statistical significance.**

2. **This was a retrospective chart review conducted on a before and after sample of patients and hence is at risk of selection bias, observer bias, and ascertainment bias.**

3. **The authors do not specify how follow-up was conducted to determine long-term outcomes. They also do not mention whether or not there was any loss to follow-up.**

4. **There is no description of the chart review methods used (Gilbert 1996 and Worster 2004).**

Bottom Line:

This small, retrospective, before and after study conducted in Korea found that while patients with RVF treated with esmolol had an increased chance of ROSC RR 3.5, 95% CI 1.3 to 9.5), there was no statistically significant difference in long-term survival or neurologically intact survival (RR 2.3, 95% CI 0.4 to 12.5 for all outcomes). The small sample size resulted in a highly underpowered study that was incapable of detecting a clinically significant benefit with statistical significance, and the study was limited by flaws in both methodology and reporting.