Critical Review Form
Therapy

PGY-1

Driver BE, Debaty G, Plummer DW, Smith SW. Use of esmolol after failure of standard cardiopulmonary resuscitation to treat patients with refractory ventricular fibrillation. Resuscitation. 2014 Oct;85(10):1337-41.

Objectives: **"to compare the outcomes of patients who received esmolol to this who did not receive esmolol during RVF [refractory ventricular fibrillation] in the ED." (p. 1337)**

Methods: **This retrospective observational study was conducted at Hennepin County Medical Center in Minneapolis, MN from January 2011 to January 2014. The electronic medical record was searched for patients with a final ED diagnosis of cardiac arrest (CA), ventricular fibrillation (VF), or pulseless ventricular tachycardia (VT). Patients who either suffered CA in the ED with an initial rhythm of VF or VT or did so in the prehospital setting but remained in CA upon ED arrival, and who received at least 3 defibrillation attempts, 300 mg of amiodarone, and 3 mg of epinephrine were included. Patients who received esmolol before CA were excluded.**

Patients were analyzed according to whether or not they received esmolol during CA. Temporary return of spontaneous circulation (ROSC) was defined as ROSC lasting > 30 seconds by < 20 minutes, and sustained ROSC was defined as ROSC lasting > 20 minutes. Neurologic outcomes were measured using the Cerebral Performance Category (CPC) score.

Out of 90 patients with CA with an initial rhythm of VF or VT during the study period, 65 were excluded, leaving 25 in the final analysis. Of these, 6 patients received esmolol and 19 did not. Nearly all patients were male, and the median ages in the esmolol and no esmolol groups were 54.5 and 56 years, respectively.

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 retrospective study using data abstracted from an electronic medical record. The decision to give esmolol or not was made at the discretion of the paramedics and physicians, which could lead to selection bias.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the	N/A. The study was not randomized.

	randomization process to ensure that a patient would be "randomized" to a particular group?	
3.	Were patients analyzed in the groups to which they were randomized?	N/A. The study was not randomized and patients were analyzed according to whether or not they received esmolol.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Patients were similar with respect to age, gender (nearly all patients were male), initial rhythm, use of bystander CPR, and time from call to EMS arrival. **Median total pre-hospital time was much longer among patients not receiving esmolol (42 minutes) compared to those receiving esmolol (25 minutes).** This could serve to falsely inflate the treatment benefits of esmolol.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. While this was not a blinded study, patients were in cardiac arrest and hence would not have been aware of what treatments were being administered.
2.	Were clinicians aware of group allocation?	Yes. This was not a blinded study and hence paramedics and physicians would have been aware of what treatments were provided. Given that the study was conducted retrospectively, it seems unlikely that performance bias on the part of clinicians would have had any impact on outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. The authors note that a single reviewer abstracted all data from the medical record. Hence, this reviewer abstracted both treatment and outcome data and was not blinded. This poses a risk of observer bias.
4.	Was follow-up complete?	Purportedly yes. Since the outcomes of interest did not extend past hospital discharge, it seems likely that outcome data was available for all eligible patients. The authors do not specifically mention loss to follow-up.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• All 6 patients who received esmolol had at least temporary ROSC, compared to 8 of 19 in the no esmolol group (RR 2.4, 95% CI 1.4 to 4.0).

		• Four patients in the esmolol group achieved sustained ROSC compared to 6 in the no esmolol group (RR 2.1, 95% CI 0.9 to 5.0) • Three patients in the esmolol group survived to hospital discharge with good neurologic outcomes (CPC scores of 1, 2, and 2) compared to 2 patients in the no esmolol group (CPC score of 1 in both cases), for a RR of 4.8, 95% CI 1.0 to 22.
2.	How precise was the estimate of the treatment effect?	See above. This was a very small study with very wide confidence intervals.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. These were patients in an urban population suffering cardiac arrest with likely similar comorbidities (though these were not detailed) and similar EMS run times to those seen in our institution.
2.	Were all clinically important outcomes considered?	No. The study only addressed outcomes to hospital discharge. The Research Working Group of the American Heart Association Emergency Cardiovascular Care Committee has recommended that large trials designed to have a major impact should use longer-term endpoints at least 90 days out coupled with some neurological and quality-of-life assessment. They also did not address cost or quality of life.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This small, retrospective study demonstrated a statistically significant improvement in neurologically intact survival to hospital discharge with the use of esmolol on refractory v-fib. There were several methodological issues that bring these results into question, including the significant imbalance in pre-hospital time between the two groups, which be expected to inflate any potential benefits of giving esmolol. A prospective, randomized trial would be needed to validate these results.

Limitations:

1. **Data were abstracted from the charts by a single reviewer.**
2. **No primary outcome was defined *a priori*.**
3. **This was not a randomized trial. The decision to give esmolol or not was made at the discretion of the providers, which could lead to selection bias.**

4. **It is not clear who determined outcomes and whether or not they were blinded to group allocation (observer bias). In addition, 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.**

5. **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.**

6. **The two groups were not well balanced with regards to known predictive factors. Specifically, the median total prehospital time was significantly longer among patients not receiving esmolol compared to those who did receive esmolol (42 minutes vs. 25 minutes).**

7. **The 50% neurologically intact survival rate seen in patients with RVF receiving esmolol is highly inconsistent with prior rates of survival reported in large databases (McNally 2011).**

Bottom Line:

This small, retrospective study comparing the use of esmolol in RVF to standard ACLS demonstrated a statistically significant improvement in survival to hospital discharge with a good neurologic outcome with esmolol (RR 4.8, 95% CI 1.0 to 22). The retrospective nature of this study likely led to significant selection bias, with a large imbalance in median total pre-hospital time that would benefit patients receiving esmolol. In addition, the overall survival rate of 50% in this group is significantly higher than previously reported survival rates, which include all VF/VT cardiac arrests, and not just refractory VF cases. Future research will need to include randomized trials with balanced prognostic factors to minimize potential bias.