Critical Review Form
Therapy

Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA. 2009 Nov 25;302(20):2222-9.

Objectives: **to compare "outcomes for patients receiving standard ACLS with intravenous [IV] drug administration (control) and patients receiving ACLS without intravenous drug administration (intervention)."**

Methods: **This open-label randomized controlled trial was conducted in Oslo, Norway, a city with a single-tiered emergency medical service system. Patients 18 years and older with nontraumatic, out-of-hospital cardiac arrest (OHCA) seen between May 1, 2003 and April 28, 2008 were eligible for enrollment. Patients with cardiac arrest witnessed by the ambulance crew, those with resuscitation care provided by or interrupted by physicians not part of the ambulance team, or this with cardiac arrest related to asthma or anaphylaxis were excluded.**

Patients were randomized by ambulance personnel once cardiac arrest was confirmed. Randomization occurred via the use of sealed envelopes provided by the investigators, with patients randomized to either ACLS with intravenous drug administration, or ACLS without access to intravenous drugs. Patients were analyzed according to randomization group (intention to treat analysis) rather than the actual treatment received.

The primary endpoint was survival to hospital discharge. Secondary endpoints included hospital admission with return of spontaneous circulation (ROSC), neurologic outcomes based on cerebral performance category (CPC), 1-year survival, and quality of CPR.

Out of 1183 patients with cardiac arrest who underwent resuscitation during the study period, 946 were eligible for enrollment and 851 were ultimately randomized. There were 433 eligible subjects randomized to the no IV group, of whom 45 had IV access established prior to ROSC; 418 eligible subjects were randomized to the IV group, of whom 74 did not have IV access established prior to ROSC.

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. "Simple randomization occurred directly after ambulance personnel confirmed the cardiac arrest and then opened the sealed envelopes provided by the investigators." (p. 2223)
2.	Was randomization concealed (blinded)?	Uncertain. The authors mention that randomized was performed via "sealed envelopes," but they do not note how the randomization sequence was selected, how the envelopes were prepared and ordered, and whether the envelopes were opaque. It is possible, though unlikely, that the randomization process could have been subverted (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. The intervention in this study was IV access and hence concomitant IV drug administration. There were 42 patients (10%) in the no IV group who received IV drugs, with 37 (9%) getting IV epinephrine, 20 (5%) getting IV atropine, and 17 (4%) getting IV amiodarone. In the IV group, only 343 patients (82%) received any IV drugs, presumably a result of cessation of resuscitative efforts prior to drug administration in the vast majority of cases. The patients were analyzed based on group allocation, not based on the administration of IV drugs (intention to treat analysis).
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, location of arrest, percent with bystander-witnessed arrest, initial rhythm, response interval, need for intubation, and CPR quality. Patients in the no IV group who were defibrillated received fewer shocks than those in the IV group (median 2 vs. 3, $p = 0.008$).
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?	No. Patients were in cardiac arrest at the time of randomization and treatment, and hence would not be aware of group allocation.
2.	Were clinicians aware of group allocation?	Yes. Patients either had an IV placed by EMS personnel or did not, and it would not be possible to blind either the EMS personnel or the clinicians in the hospital to group

<table>
<tr><td></td><td></td><td>allocation.</td></tr>
<tr><td>3.</td><td>Were outcome assessors aware of group allocation?</td><td>Uncertain. The authors do not specifically mention blinding of outcome assessors, and it is unclear how CPC scores were measured and by whom. The majority of the outcomes were objective, however observer bias could have influenced CPC score reporting.</td></tr>
<tr><td>4.</td><td>Was follow-up complete?</td><td>Almost. Follow-up data were available up to hospital discharge for all patients enrolled. 1-year follow-up data were not available for 2 patients in the no IV group and 1 patient in the IV group.</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>IV access resulted in increased rates of ROSC and ICU admission, but did not improve the chances of surviving to discharge or surviving with good neurologic function (see Table 1).

Table 1. Results
<table><tr><td></td><td>No IV (n = 433)</td><td>Yes IV (n = 418)</td><td>Odds ratio (95% CI)</td></tr><tr><td>ROSC</td><td>107 (25%)</td><td>165 (40%)</td><td>1.99 (1.48-2.67)</td></tr><tr><td>Admitted to ICU</td><td>88 (20%)</td><td>125 (30%)</td><td>1.67 (1.22-2.29)</td></tr><tr><td>Discharged Alive</td><td>40 (9.2%)</td><td>44 (10.5%)</td><td>1.16 (0.74-1.82)</td></tr><tr><td>Discharged with CPC 1-2</td><td>35 (8.1%)</td><td>41 (9.8%)</td><td>1.24 (0.77-1.98)</td></tr></table>
Sub group analysis of patients with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) revealed no statistically significant difference in outcomes between the groups.

Table 2. Results for patients with VF or VT
<table><tr><td></td><td>No IV (n = 142)</td><td>Yes IV (n = 144)</td><td>P value</td></tr><tr><td>ROSC</td><td>75 (53%)</td><td>85 (59%)</td><td>0.35</td></tr><tr><td>Admitted to ICU</td><td>60 (42%)</td><td>125 (30%)</td><td>0.15</td></tr><tr><td>Discharged Alive</td><td>32 (23%)</td><td>39 (27%)</td><td>0.45</td></tr><tr><td>Discharged with CPC 1-2</td><td>29 (20%)</td><td>37 (26%)</td><td>0.36</td></tr></table></td></tr>
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<tr><td></td><td></td><td>Sub group analysis of patients with asystole or PEA revealed an improvement in ROSC and survival to ICU admission with IV access, but no statistically significant difference in the rates of survival or survival with food neurologic outcomes.

Table 2. Results for patients with asystole or PEA
<table>
<tr><th></th><th>No IV (n = 291)</th><th>Yes IV (n = 274)</th><th>P value</th></tr>
<tr><td>ROSC</td><td>32 (11%)</td><td>80 (29%)</td><td>< 0.001</td></tr>
<tr><td>Admitted to ICU</td><td>28 (10%)</td><td>51 (19%)</td><td>< 0.001</td></tr>
<tr><td>Discharged Alive</td><td>8 (3%)</td><td>5 (2%)</td><td>0.45</td></tr>
<tr><td>Discharged with CPC 1-2</td><td>6 (2%)</td><td>4 (2%)</td><td>0.36</td></tr>
</table></td></tr>
<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above. The 95% confidence intervals remain wide, and a clinically important treatment effect is still possible.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>No. These were patients cared for in a Norwegian prehospital system. Ambulances in this system are staffed by 2 paramedics and a physician. In addition to having on-site medical control, this constitutes one additional provider to care for patients. This would allow CPR to continue uninterrupted while IV access is initiated; in the US system, only two providers are on most ambulances, necessitating interruptions to CPR in order to gain IV access. Additional differences include the increasing use of intraosseous (IO) access in most US ambulance systems, differences in medical comorbidities, use of angiography in the post-arrest period, and the use of therapeutic hypothermia.</td></tr>
<tr><td>2.</td><td>Were all clinically important outcomes considered?</td><td>Yes. The authors considered ROSC, ROSC on arrival to the hospital, ICU admission, survival to hospital discharge, and neurologically intact survival. The authors did not assess cost or patient/family satisfaction.</td></tr>
<tr><td>3.</td><td>Are the likely treatment benefits worth the potential harm and costs?</td><td>Uncertain. While this study demonstrated no clear benefit to intravenous access in out of hospital cardiac arrest, the study was underpowered to detect a potentially clinically significant difference of 1.7% for neurologically intact survival (translating to a NNT of 59). This was also an unblinded study with potential performance bias. The differences in ambulance services in Norway compared to the US also limit the external validity of the study results.</td></tr>
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Limitations:

1. **Of 946 eligible patients, 95 were not randomized (selection bias).**
2. **There were numerous protocol violations in both groups: 45 patients (10.4%) in the no IV group received IV drugs while 74 patients (17.7%) in the IV group did not receive IV drugs.**
3. **A type II error is possible: the study was underpowered to detect a potentially clinically significant difference of 1.7% for neurologically intact survival, translating to a NNT of 59 (power analysis).**
4. **This was an unblended study, and hence there is the potential for performance bias.**
5. **This study was conduced in Norway, where differences in ambulance personnel, the prevalence of medical comorbidities, and potential differences in post-cardiac arrest care may limit the applicability of the results to our patients (external validity).**

Bottom Line:

This very interesting study out of Norway demonstrated a significant increase in the rates of ROSC and ICU admission with the initiation of IV access in out-of-hospital cardiac arrest, with no statistically significant change in rates of survival to discharge (OR 1.16, 95% CI 0.74-1.82), or survival with a CPC score of 1 or 2 (OR 1.24, 95% CI 0.77-1.98). Unfortunately, a type II error is possible and the study was underpowered to detect a potentially clinically significant difference in outcomes. The study does, however, demonstrate that there is clinical equipoise, and points to the need for a larger randomized trial.