Commentary

Antiarrhythmic drugs in out-of-hospital cardiac arrest—what does the Amiodarone, Lidocaine, or Placebo Study tell us?

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Out-of-hospital cardiac arrest (OHCA) is a global health concern, accounting for over 350,000 unexpected deaths in North America (1). OHCA with shockable rhythms (ventricular fibrillation or pulseless ventricular tachycardia, VF/VT) is considered the most treatment-responsive, and the mainstay of treatment is early defibrillation. While antiarrhythmic drugs (particularly amiodarone and lidocaine) have been recommended for shock-refractory VF/VT in Advance Cardiac Life Support (ACLS) treatment guidelines (2), they are yet without proven survival benefits. Two smaller randomized controlled trials from over a decade ago addressed this question. A trial of 504 patients randomized to amiodarone or placebo found increased survival to hospital admission in the amiodarone group (3), while another trial of 347 patients randomized to either amiodarone or lidocaine found increased survival to hospital admission in the amiodarone group (4). These two trials were however not powered to demonstrate benefit in more meaningful outcomes such as good neurologic status on discharge or even survival to hospital discharge, both of which are more convincing outcomes in assessing interventions in cardiac arrest research.

In *the New England Journal of Medicine*, the Resuscitation Outcomes Consortium reported findings from the Amiodarone, Lidocaine, or Placebo Study (ALPS) (5). This was a multicenter randomized, double-blind, placebo-controlled, prehospital trial involving 55 Emergency Medical Service (EMS) systems from ten North American sites. Patients with non-traumatic shock-refractory ventricular fibrillation or pulseless ventricular tachycardia (defined as at least one shock) were randomized into three arms: a modified formulation of parenteral amiodarone that purported less hypotensive effects (Nexterone, Baxter Healthcare), lidocaine or placebo in a 1:1:1 ratio, along with standard care. Of 7,051 patients that were potentially eligible for the trial, the study was only able to enroll 3,026 patients after exclusions and drop-outs. The study was designed to detect a 6.3% difference in survival to hospital discharge between the amiodarone and placebo groups with 90% power. The groups were fairly well balanced for important prognostic and treatment features.

The per-protocol (primary analysis) population found 3.2% higher survival to hospital discharge (primary outcome) in the amiodarone group compared to placebo (P=0.08); while the lidocaine group had 2.6% higher survival to discharge compared to placebo (P=0.16). These differences did not amount to statistical significance. In addition, rates of favorable neurologic status at discharge were similar in all three groups (19% in the amiodarone group, 19% in the lidocaine group and 17% in the placebo group). In both outcomes there was no difference between amiodarone and lidocaine groups.

These results beg the question of whether the study was underpowered. An estimation of 6.3% survival difference used in the sample size calculation is perhaps an optimistic one. The treatment size of 3.2%, if not a product of chance, would require a study three times as large to demonstrate statistical significance.

Fortunately, a pre-planned subgroup analysis offers insight into this conundrum where the sample size is in doubt. In patients with witnessed OHCA, both drugs resulted in significantly increased survival over placebo, with no difference between amiodarone and lidocaine. Witnessed OHCA are a surrogate for early recognition, whereas the unwitnessed group have graver prognosis even before intervention, comprising patients with prolonged arrest with negligible survival regardless of subsequent treatment, owing to irreversible ischemic injury. It therefore makes sense to look only at witnessed OHCA, which removes the dilution effect on the treatment effect size. This is particularly important in a study that is probably underpowered and with fairly long delay to drug administrations (mean of 19.3 minutes).

The investigators of this study should be commended on the successful execution of the largest trial into the role of antiarrhythmics in OHCA to date. There are inherent complexities and difficulties surrounding large-scale resuscitation trials. First, very large sample sizes are needed to prove the incremental benefits of interventions where multiple factors can influence the final outcome. Second, exquisite attention needs to be paid to training and implementation to ensure that negative trials are not a result of quality of implementation rather than the therapy in question (6). While the data presented lacked granularity to suggest any problems with the implementation, it is easy to fathom how a new protocol (along with its inclusion, exclusion criteria, unlabeled packaging, et cetera) may throw off a paramedic already juggling several concurrent resuscitative tasks, and that a prehospital resuscitative intervention may achieve improved apparent efficacy over time.

Are these results practice changing? While tempting to conclude amiodarone and lidocaine to be ineffective, with the power of the study in question, and with a few finer details suggesting efficacy (active drug groups having survival benefit in witnessed OHCAs and requiring fewer shocks), the question merits further clarification. The takeaway messages for developed EMS systems and developing EMS systems are different. For developed EMS systems who have already included antiarrhythmics in their OHCA protocols, there is a suggestion of benefit without evidence of increased harm. This makes it difficult to deviate from current ACLS guidelines. For developing EMS systems (7), where cost effectiveness can be a consideration, it may be prudent to focus efforts on improving Basic Life Support rather than Advanced Life Support capabilities (like intravenous drugs) (8), as the interventions of early high quality chest compressions (9) and early defibrillation (10) have far larger effect sizes (11).

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Footnote

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