

Amiodarone and lidocaine for shock refractory ventricular fibrillation or ventricular tachycardia in out-of-hospital cardiac arrest: are they really effective?

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In 2015, the American Heart Association and European Resuscitation Council updated the guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care according to the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (1-3). The guidelines recommend administration of amiodarone for sustained ventricular fibrillation (Vf) and ventricular tachycardia (VT) refractory to CPR, defibrillation, and vasopressor in out-of-hospital cardiac arrest. Lidocaine is recommended as an alternative to amiodarone. However, these recommendations remain weak and are based on the two previous randomized controlled trials (RCTs) performed more than 10 years ago. In these trials, compared with both placebo and lidocaine, amiodarone improved the rate of return of spontaneous circulation (ROSC) but not the survival to hospital discharge and neurological outcome (4). However, these studies were not statistically powered to investigate survival and neurological outcome, so the actual efficacy of amiodarone therapy remains undetermined.

To address this issue, the Resuscitation Outcomes Consortium performed the RCT called "ALPS", the results of which were published recently (5). In the trial, amiodarone, lidocaine, or placebo was administered by paramedics for sustained Vf/VT after at least one shock in patients with non-traumatic out-of-hospital cardiac arrest. As per-protocol population, 3,026 patients were evaluated, of whom 974 were assigned to the amiodarone group, 993 to the lidocaine group, and 1,059 to the placebo group. The proportion of survival to hospital discharge, which

was the primary outcome of this study, did not significantly differ between the three groups (24.4%, 23.7%, and 21.0% in the amiodarone, lidocaine, and placebo groups, respectively). The neurological function at discharge, which was the secondary outcome, also did not significantly differ. Regarding the ROSC at emergency department arrival, only lidocaine was significantly superior to placebo.

What do these results mean? Should we refrain from the use of amiodarone for shock-refractory Vf/VT in cardiac arrest?

This study gives us a different message when we focus on the time from collapse to the use of antiarrhythmic drugs. As the authors mentioned in the Discussion section, both amiodarone and lidocaine therapies resulted in significantly better rate of survival to hospital discharge than placebo in bystander-witnessed arrest (27.7%, 27.8%, and 22.7% with amiodarone, lidocaine, and placebo, respectively). Especially in emergency medical services-witnessed cardiac arrest, the rate of survival to discharge was twice higher with amiodarone than with placebo (38.6% *vs.* 16.7%). This study is the first RCT that showed the efficacy of amiodarone and lidocaine therapies in terms of survival to hospital discharge, although the result was obtained from the subanalysis. The immediate response to cardiac arrest and bystander CPR could be considered as the prerequisite to attaining the efficacy of antiarrhythmic drugs. It may be said that we should use amiodarone or lidocaine at least in witnessed arrest, instead of giving up the use of both drugs.

This study is a meaningful study also for lidocaine. Lidocaine has been widely used, but no RCT has shown its efficacy for ROSC in shock-refractory Vf/VT. Although the

rate of ROSC at ED arrival was the mechanistic outcome in this study, the rate of ROSC in the per-protocol population was significantly higher with lidocaine than with placebo. On the other hand, amiodarone failed to show this efficacy in the per-protocol population (35.9%, 39.9%, and 34.6% for amiodarone, lidocaine, and placebo, respectively).

Is lidocaine just an alternative to amiodarone? Piccini *et al.* reported that administration of amiodarone, but not lidocaine, was associated with increased mortality in patients with sustained Vf/VT (6). However, this was a retrospective study of GUST IIB and III, which enrolled patients with acute myocardial infarction, and not those who had an out-of-hospital cardiac arrest. From the ALPS trial, we cannot determine which between amiodarone and lidocaine is a more potent drug for shock refractory Vf/VT in cardiac arrest. As mentioned earlier, the rate of survival to discharge did not significantly differ between the two drugs both in the per-protocol population and in the witnessed-arrest patients. Considering the adverse events, the proportion of patients who needed temporary cardiac pacing was higher in the amiodarone group. Moreover, this study used the amiodarone formulation containing a solvent that does not cause hypotension. In countries where this formulation is unavailable, more attention might be paid to the adverse events, especially to hypotension. These results seem to be more advantageous for lidocaine rather than to amiodarone. However, about half of the patients assigned to lidocaine were given amiodarone within 24 h after hospital arrival. This shows that the physicians felt the necessity to use amiodarone, and we cannot simply prefer lidocaine to amiodarone.

The time from collapse is a key factor in the resuscitation of cardiac arrest patients. Joshua *et al.* reported that the probability of survival with good neurological outcome declined rapidly after about 16 min of CPR (7). The mean time from initial call to first drug administration in non-witnessed cardiac arrest patients was about 19 min in this trial. Within this time frame, the patients would have already fallen into the “metabolic phase” in the 3-phase model of cardiac arrest (8). Even CPR and defibrillation would become ineffective in this phase, so the antiarrhythmic drugs might play an insignificant role. For patients in the metabolic phase, we should seek the novel approach such as extracorporeal resuscitation, rather than expecting vasopressors or antiarrhythmic drugs to take effect.

In summary, ALPS showed that both amiodarone and lidocaine therapies would be effective for shock-refractory

Vf and pulseless VT in bystander-witnessed arrest but might be useless in the later phase of CPR. Immediate response to cardiac arrest and good-quality CPR are key to attaining the efficacy of antiarrhythmic drugs.

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Footnote

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