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Editorial

Interpreting observational data on adrenaline in cardiac arrest is complicated

The International Liaison Committee on Resuscitation (ILCOR) currently suggests routine administration of 1 mg of adrenaline every 3–5 min (undefined maximum) during cardiac arrest resuscitation until return of spontaneous circulation (ROSC) or termination of resuscitation; however, the available science supporting this recommendation is limited.[1] The effects of adrenaline are complex. In animal studies, adrenaline administration during cardiopulmonary resuscitation (CPR) is effective at improving coronary perfusion[2]; however, adrenaline also leads to cerebral vasoconstriction and decreased oxygenation, potentially leading to secondary neurological damage and brain death.[3,4] Randomized controlled trials (RCTs) and large observational studies suggest that higher cumulative doses of adrenaline improve short-term outcomes but not long-term outcomes.[5–7]

In this issue of *Resuscitation*, Fothergill et al. report the association of repeated doses of adrenaline with decreased survival in out-of-hospital (OHCA) patients resuscitated by the London Ambulance Service in the United Kingdom.[8] This study does not resolve the controversy but rather adds to previous observational studies suggesting potential harm of adrenaline. Prior observational studies reported decreasing survival with higher total doses of adrenaline.[9,10] There are several issues to consider in interpreting the current study.[8]

The study population in the current study included patients with initial ventricular fibrillation or pulseless ventricular tachycardia (VF/pVT), pulseless electrical activity (PEA) and asystole. This population is highly heterogeneous with different etiologies of cardiac arrest, different survival rates and different potential effects of epinephrine. Patients with VF/pVT are more likely to have a cardiac etiology and better survival outcomes whereas patients with PEA and asystole have heterogeneous etiologies and very poor outcomes. In the recent PARAMEDIC2 RCT comparing adrenaline to placebo, adrenaline improved overall survival up to 3 months; however, these positive results were mainly driven by patients with non-shockable rhythms, not with VF/pVT.[11] Although the current study was likely limited in sample size to perform subgroup analyses, its results may conflate the effects of adrenaline in different patient populations and conditions.[8]

The study also included patients who received adrenaline either by intravenous (IV) or intraosseous (IO) routes. The clinical effects and implications of receiving adrenaline by IO compared to IV are not the same. Although the practice of IO access in OHCA, particularly in the tibia, for administering fluids and medications has increased over time due to perceived rapidity, ease and effectiveness,[12,13] previous studies have shown that patients treated using IO had worse outcomes compared to IV.[14,15] This may be to due confounders related to establishing IO over IV access; IO is often an alternate approach when unable to establish IV in patients who are difficult to resuscitate. In swine studies, tibial IO administration of adrenaline showed a significantly longer time to reach peak blood concentrations.[16] The effect of the various routes of adrenaline administration on patient outcomes was not clear in the current study.

The timing of adrenaline administration is also a major confounder in all observational studies. The resuscitation protocol used by the London Ambulance Service in the current study was to administer adrenaline only after three unsuccessful defibrillation attempts for VF/pVT. This may not be generalizable to other emergency medical systems (EMS) where adrenaline is administered earlier in resuscitation. Delayed adrenaline administration also complicates the interpretation of the results, as the time from EMS call to first adrenaline dose will be longer compared to other EMS agencies. Studies have found an association between delays to adrenaline administration and decreased survival.[17,18] There are no RCTs on the timing of adrenaline in cardiac arrest. Similar to the current study, the mean time to adrenaline administration in the PARAMEDIC2 RCT was 21 min after call to 911,[11] suggesting that the drug was provided too late to have a positive effect on neurological outcomes.

ILCOR recently published a consensus statement on core outcomes for effectiveness trials, which include survival, neurological outcomes and quality of life measures.[19] Although the consensus statement was not primarily intended for observational studies, there is a need to better understand the effects of repeated doses of adrenaline on outcomes beyond survival. In the largest cohort study to date, there was an increased odds of mortality and poor neurologic function one month post-arrest with prehospital administration of adrenaline in a propensity matched analysis.[6] Nevertheless, all observational studies are unable to account for unmeasured or unmeasurable confounders, making interpretation of these studies difficult. Furthermore, observational studies on the cumulative dose of adrenaline are plagued by confounding and "resuscitation time bias" making it necessary to perform RCTs to answer this specific research question and knowledge gap.[20] To address this, the Canadian Resuscitation Outcomes Consortium (CanROC) will be leading an RCT to evaluate a low cumulative dose of adrenaline in OHCA resuscitation. The **Epi**nephrine **D**ose: **O**ptimal versus **S**tandard **E**valuation (EpiDOSE) trial is a multicentre, double-blinded RCT across sites in Canada evaluating a low cumulative dose (2 mg maximum) compared to the current standard (undefined maximum) dose of adrenaline (NCT03826524).

The study by Fothergill et al. adds important data to the controversial literature of adrenaline in cardiac arrest.[8] Due to the inherent limitations of interpreting data in observational cardiac arrest studies, there is a need for clinical trials to evaluate the cumulative dose of adrenaline during OHCA resuscitation.

Disclosures

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