

Manuscript version: Author's Accepted Manuscript

The version presented in WRAP is the author's accepted manuscript and may differ from the published version or Version of Record.

Persistent WRAP URL:

<http://wrap.warwick.ac.uk/165951>

How to cite:

Please refer to published version for the most recent bibliographic citation information. If a published version is known of, the repository item page linked to above, will contain details on accessing it.

Copyright and reuse:

The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions.

Copyright © and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable the material made available in WRAP has been checked for eligibility before being made available.

Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Publisher's statement:

Please refer to the repository item page, publisher's statement section, for further information.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk.

What's New in Intensive Care: Drugs for Advanced Life Support

Authors

Lars W. Andersen^{1,2,3,4}, Jerry P. Nolan^{5,6}, and Claudio Sandroni^{7,8}

Affiliations

¹ Research Center for Emergency Medicine, Aarhus University Hospital, Aarhus, Denmark

² Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

³ Department of Anesthesiology and Intensive Care, Aarhus University hospital, Aarhus, Denmark

⁴ Prehospital Emergency Medical Services, Central Denmark Region, Denmark

⁵ University of Warwick, Warwick Medical School, Coventry, UK

⁶ Department of Anaesthesia and Intensive Care Medicine, Royal United Hospital, Bath, UK

⁷ Department of Emergency Medicine and Anaesthesiology, Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy

⁸ Institute of Anaesthesiology and Intensive Care Medicine, Università Cattolica del Sacro Cuore, Rome, Italy

Key words: Cardiac arrest; Adrenaline; Vasopressin; Calcium; Shen Fu; Sodium Nitrite.

Word count: 1058. References: 17

Corresponding author

Claudio Sandroni

Department of Intensive Care, Emergency Medicine and Anaesthesiology - Fondazione Policlinico Universitario A. Gemelli, IRCCS

Università Cattolica del Sacro Cuore – Rome, Italy

Largo Francesco Vito, 1, 00168 – Rome, Italy

email: claudio.sandroni@policlinicogemelli.it

Treatment of patients with cardiac arrest includes basic and advanced life support (ALS) as outlined by the European Resuscitation Council [1]. An integral part of ALS is the establishment of vascular access and administration of drugs including vasopressors and antiarrhythmics. Until recently, there has been limited evidence to show that administration of these drugs improved patient outcomes. However, several randomized clinical trials testing various drugs during cardiac arrest have been published within the last six years and we review these in this article (**Table 1**). Drugs that are given in special circumstances without new trial evidence are not covered [2].

Adrenaline(epinephrine)

Adrenaline is a potent vasoconstrictor with both α - and β -receptor affinity. During cardiac arrest, administration of adrenaline increases systemic vascular resistance and aortic diastolic pressure, which increases coronary and cerebral perfusion pressures. Before publication of the PARAMEDIC2 trial, evidence for a beneficial effect of adrenaline was based primarily on animal studies and a single small randomized trial [3]. The PARAMEDIC2 trial, which was published in 2018, included 8014 patients with out-of-hospital cardiac arrest (OHCA) in the United Kingdom (UK) [4]. Patients were randomized to adrenaline (1 mg per dose) or placebo. Survival at 30 days occurred in 130/4012 (3.2%) in the adrenaline group vs. 94/3995 (2.4%) in the placebo group corresponding to an odds ratio of 1.39 (95%CI: 1.06, 1.82). The implication of these results is controversial. Critics have argued that despite a very large increase in survival to hospital admission (24% vs. 8%), the increase in 30-day survival was negligible, i.e., a risk difference of only 0.8%. This has raised issues of cost-effectiveness as many patients are admitted to the hospital without ultimately surviving. In a life-time model incorporating indirect effects of increased organ donation, the incremental cost-effectiveness ratio was €18,499 per quality-adjusted life year gained. In a model not accounting for organ donation, the corresponding amount was €93,231 [5]. Whether this is considered cost-effective will depend on local and regional considerations, but both these costs will likely be acceptable in most high-income countries [6]. The overall survival was low in the PARAMEDIC2 trial compared with some other trials, and it remains unclear how the trial results generalize to other settings with a higher baseline survival. Specifically, if the relative increase in survival is constant, this will lead to a larger absolute increase in survival [7]. Another criticism has been that more patients in the adrenaline group survived to

hospital discharge with severe neurological impairment [4] probably because more patients with irreversible brain damage were resuscitated. However, at 3 months, more patients had a favourable neurological outcome in the adrenaline group (2.1% vs. 1.6%). With these considerations in mind, European guidelines continue to recommend adrenaline for both in- and out-of-hospital cardiac arrest [1].

There is ongoing debate about the optimal route for drug delivery during cardiac arrest (i.e., intravenous or intraosseous). In a follow-up study of PARAMEDIC2, the effect of adrenaline was not different when administered through an intravenous or an intraosseous access [8]. However, the trial was not powered for this outcome. The ongoing PARAMEDIC3 trial will directly compare intravenous to intraosseous access during OHCA in the UK (ISRCTN14223494). A similar smaller trial is being conducted in Denmark (IVIO trial, NCT05205031).

Antiarrhythmics

Antiarrhythmics have been used for cardiac arrest for decades, although the supporting evidence has been sparse. In 2016, the ALPS trial was published.[9] In this trial, 3026 patients with OHCA and a shockable rhythm in the United States were randomized to amiodarone, lidocaine, or placebo. In both the amiodarone and lidocaine groups, more patients were admitted to the hospital and there was a non-significant increase in survival to hospital discharge.[9] Despite these results and similar findings from a systematic review,[10] European guidelines continue to recommend the use of amiodarone or lidocaine for cardiac arrest with a shockable rhythm[1].

Shen Fu

In a trial published in 2020 from China involving 1201 OHCA patients, the traditional Chinese medicine Shen Fu was compared with placebo [11]. Although the results were promising, with some signal of improvement in the Shen Fu group, most differences were non-significant and further trials are needed to assess this medication.

Nitrite

Sodium nitrite has been postulated to limit ischaemia-reperfusion injury during cardiac arrest. In a trial published in 2021, 1502 OHCA patients with an initial shockable rhythm in the United States were randomized to two different doses of sodium nitrite (45 mg or 60 mg) or placebo [12]. There was no difference in the primary outcome of survival to hospital admission (41%, 43% and 44%) or in any of the secondary outcomes, including survival to hospital discharge.

Vasopressin and corticosteroids

In 2009 and 2013, two randomized trials from Greece were published that tested the combination of vasopressin and corticosteroids for patients with in-hospital cardiac arrest [13, 14]. Both trials, which included a combined 368 patients, found a large improvement in outcomes. The combination of vasopressin and corticosteroids was subsequently tested in a Danish trial published in 2021 [15]. In this trial, that included 501 patients, the combination of vasopressin and methylprednisolone resulted in an improvement in return of spontaneous circulation (ROSC) (42% vs. 33%), but no difference in survival at 30 days (10% vs. 12%). A subsequent patient-level meta-analysis found that the combination of drugs likely improves ROSC, but the effect on survival and neurological outcomes are more uncertain [16].

Calcium

Calcium is commonly used during cardiac arrest in some settings, although its effectiveness is unknown. A recent trial from Denmark, published in 2021, compared calcium with placebo in 391 OHCA patients [17]. The trial was stopped early because of a signal of harm in the calcium group. ROSC occurred in 19% of patients receiving calcium and 27% of patients receiving placebo (risk ratio: 0.72, 95%CI: 0.49, 1.03); survival was 5% and 9%, respectively. Although the interpretation of the trial results is limited by the early stopping, these findings suggest that calcium is not beneficial in undifferentiated cardiac arrest and might be harmful.

Conclusions

Despite an increase in clinical trials, there has been little change to the ALS algorithm over the last decades. The PARAMEDIC2 trial reinforced that adrenaline continues to have a role in the treatment of patients with cardiac arrest although the absolute effect on long-term outcomes is small [4]. There is a continuing need for high-quality clinical trials to test new drugs to improve outcomes for patients with cardiac arrest.

Conflict of interest statement

Lars W. Andersen was the principal investigator on the Danish vasopressin/steroid trial and the calcium trial and is the principal investigator on the ongoing “IVIO” trial in Denmark. Jerry Nolan was a co-investigator on the PARAMEDIC2 trial and is a co-investigator on the ongoing PARAMEDIC3 trial. Claudio Sandroni is Associate Editor of *Intensive Care Medicine*. There were no other conflicts of interest.

References

1. Soar J, Bottiger BW, Carli P, Couper K, Deakin CD, Djarv T, Lott C, Olasveengen T, Paal P, Pellis T, Perkins GD, Sandroni C, Nolan JP (2021) European Resuscitation Council Guidelines 2021: Adult advanced life support. *Resuscitation* 161: 115-151
2. Vallentin MF, Granfeldt A, Holmberg MJ, Andersen LW (2020) Drugs during cardiopulmonary resuscitation. *Curr Opin Crit Care* 26: 242-250
3. Jacobs IG, Finn JC, Jelinek GA, Oker HF, Thompson PL (2011) Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation* 82: 1138-1143
4. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scamperin C, Regan S, Long J, Slowther A, Pocock H, Black JJM, Moore F, Fothergill RT, Rees N, O'Shea L, Docherty M, Gunson I, Han K, Charlton K, Finn J, Petrou S, Stallard N, Gates S, Lall R, Collaborators P (2018) A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. *N Engl J Med*
5. Achana F, Petrou S, Madan J, Khan K, Ji C, Hossain A, Lall R, Slowther AM, Deakin CD, Quinn T, Nolan JP, Pocock H, Rees N, Smyth M, Gates S, Gardiner D, Perkins GD, Collaborators P (2020) Cost-effectiveness of adrenaline for out-of-hospital cardiac arrest. *Crit Care* 24: 579
6. World Health Organization (2003) Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization,
7. Andersen LW (2021) Absolute vs. relative effects-implications for subgroup analyses. *Trials* 22: 50
8. Nolan JP, Deakin CD, Ji C, Gates S, Rosser A, Lall R, Perkins GD (2020) Intraosseous versus intravenous administration of adrenaline in patients with out-of-hospital cardiac arrest: a secondary analysis of the PARAMEDIC2 placebo-controlled trial. *Intensive Care Med* 46: 954-962
9. Kudenchuk PJ, Brown SP, Daya M, Rea T, Nichol G, Morrison LJ, Leroux B, Vaillancourt C, Wittwer L, Callaway CW, Christenson J, Egan D, Ornato JP, Weisfeldt ML, Stiell IG, Idris AH, Aufderheide TP, Dunford JV, Colella MR, Vilke GM, Brienza AM, Desvigne-Nickens P, Gray PC, Gray R, Seals N, Straight R, Dorian P, Resuscitation Outcomes Consortium I (2016) Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 374: 1711-1722
10. Ali MU, Fitzpatrick-Lewis D, Kenny M, Raina P, Atkins DL, Soar J, Nolan J, Ristagno G, Sherifali D (2018) Effectiveness of antiarrhythmic drugs for shockable cardiac arrest: A systematic review. *Resuscitation* 132: 63-72

11. Shao F, Li H, Li D, Li C (2020) Effects of Shenfu injection on survival and neurological outcome after out-of-hospital cardiac arrest: A randomised controlled trial. *Resuscitation* 150: 139-144
12. Kim F, Maynard C, Dezfoulian C, Sayre M, Kudenchuk P, Rea T, Sampson D, Olsufka M, May S, Nichol G (2021) Effect of Out-of-Hospital Sodium Nitrite on Survival to Hospital Admission After Cardiac Arrest: A Randomized Clinical Trial. *JAMA* 325: 138-145
13. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, Katsios N, Papastylianou A, Gkisioti S, Stathopoulos A, Kollintza A, Stamataki E, Roussos C (2009) Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 169: 15-24
14. Mentzelopoulos SD, Malachias S, Chamos C, Konstantopoulos D, Ntaidou T, Papastylianou A, Kolliantzaki I, Theodoridi M, Ischaki H, Makris D, Zakynthinos E, Zintzaras E, Sourlas S, Aloizos S, Zakynthinos SG (2013) Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA* 310: 270-279
15. Andersen LW, Isbye D, Kjaergaard J, Kristensen CM, Darling S, Zwisler ST, Fisker S, Schmidt JC, Kirkegaard H, Grejs AM, Rossau JRG, Larsen JM, Rasmussen BS, Riddersholm S, Iversen K, Schultz M, Nielsen JL, Lofgren B, Lauridsen KG, Solling C, Paelestik K, Kjaergaard AG, Due-Rasmussen D, Folke F, Charlot MG, Jepsen R, Wiberg S, Donnino M, Kurth T, Hoybye M, Sindberg B, Holmberg MJ, Granfeldt A (2021) Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest: A Randomized Clinical Trial. *JAMA* 326: 1586-1594
16. Holmberg MJ, Granfeldt A, Mentzelopoulos SD, Andersen LW (2022) Vasopressin and glucocorticoids for in-hospital cardiac arrest: A systematic review and meta-analysis of individual participant data. *Resuscitation* 171: 48-56
17. Vallentin MF, Granfeldt A, Meilandt C, Povlsen AL, Sindberg B, Holmberg MJ, Iversen BN, Maerkedahl R, Mortensen LR, Nyboe R, Vandborg MP, Tarpgaard M, Runge C, Christiansen CF, Dissing TH, Terkelsen CJ, Christensen S, Kirkegaard H, Andersen LW (2021) Effect of Intravenous or Intraosseous Calcium vs Saline on Return of Spontaneous Circulation in Adults With Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. *JAMA* 326: 2268-2276