Pak Heart J

ADRENALINE - FRIEND OR FOE?

Mohammad Hafizullah

Department of Cardiology, Lady Reading Hospital & Khyber Medical University, Peshawar, Pakistan

Address for Correspondence:

Dr. Mohammad Hafizullah,

Professor,
Department of Cardiology, Lady Reading Hospital &
Vice Chancellor,
Khyber Medical University, Peshawar, Pakistan

E-mail: mhu5555@gmail.com

This article may be cited as: Hafizullah M. Adrenaline - friend or foe? Pak Heart J 2014;47(3): 114-6.

Adrenaline has been ubiquitously recommended as a drug of choice in sudden cardiac death in the setting of asystolic, pulseless or fine ventricular fibrillation rhythm. In spite of being in vogue for more than half a century, there are only a few properly conducted randomized clinical studies to support its use.[1] Adrenaline is used during resuscitation primarily for its alpha-adrenergic effects i.e. vasoconstriction. Vasoconstriction increases cerebral and coronary blood flow during CPR by increasing mean arterial pressure and aortic diastolic pressure.[2] The current AHA ACLS guideline for Ventricular fibrillation/Pulseless VT recommends intravenous adrenaline every 3-5 minutes. Adrenaline administration does appear to improve return of spontaneous circulation.[3]

Its potent positive chronotropic and inotropic effect may behave like a double edge sword causing severe vasoconstriction resulting in ischeamia on one hand and proarrhythmia leading to further serious arrhythmias on the other hand. This raises some doubts about the efficacy and deleterious effects of adrenaline in the scenario of sudden death.[4,5] Animal models employing young dogs do not offer a good model to simulate chronically diseased ischaemic human hearts. However studies conducted in animal models produce conflicting results. In porcine hearts coronary perfusion below coronary lesions reduces and administration of adrenaline does not correlate with enhancement of coronary perfusion pressure during CPR.[6]

In a study, conducted in Los Angeles County from 2008 to 2013 enrolled 184 patients resuscitated from Out-of-Hospital Cardiac Arrest (OHCA). It recruited OHCA patients surviving to hospital admission and documented predictors of neurologic outcomes. Forty-three patients (23%) had a favorable outcome, median age was 65 years (interquartile range [IQR] 54 to 76), and 98 (53%) were men. They found that for patients surviving to hospital admission, a good neurologic outcome was associated with having received <1.5 mg of epinephrine and a lactate level <5 mmol/L.[7]

A trial compared blinded 10 mg aliquots of adrenaline with placebo in 194 cardiac arrest patients treated in hospital using American Heart Association guidelines. In-hospital and out-of-hospital arrests were included. Of the 339 eligible patients a large proportion (145 (45%)) were not randomised and received open 1 mg aliquots of adrenaline. Patients in asystole at the time of consideration for entry were preferentially placed in the trial group (114 (69%) vs. 170 (88%)) and patients in ventricular fibrillation were preferentially given open 1 mg adrenaline

(31 (21%) vs. 24 (12%) p< 0.03). The most beneficial rhythm changes which led to survival were sinus rhythm and ventricular tachycardia. Analysis of rhythm changes resulting from the dosing showed a significant (p = 0.01) change to a beneficial rhythm with 10 mg adrenaline but not for 1 mg adrenaline or placebo. This was not reflected by an improvement in immediate survival. No significant differences in immediate survival (IS) or hospital discharge (HD) exists between open 1 mg adrenaline (IS 14 (9.7%), HD 3 (2%)) or the 10 mg adrenaline (IS 9 (9.6%), HD 0) vs. placebo (IS 7 (7%), HD 0) trial arms. Patients reaching the point of use of adrenaline have a uniformly poor immediate survival (8.8%) and hospital discharge rate (0.9%). Dosing with 10 mg or 1 mg adrenaline does not influence outcome compared with placebo.[8]

Meta-analyses were performed using random effects modeling on randomized controlled trials (RCTs) evaluating standard dose adrenaline (SDA) to placebo, high dose adrenaline (HDA), or vasopressin (alone or combination) in adult OHCA patients. Subgroup analyses were performed stratified by cardiac rhythm and by number of drug doses. The primary outcome was survival to discharge and the secondary outcomes were return of spontaneous circulation (ROSC), survival to admission, and neurological outcome. Fourteen RCTs (n = 12,246) met inclusion criteria: one compared SDA to placebo (n = 534), six compared SDA to HDA (n = 6174), six compared SDA to an adrenaline/vasopressin combination (n = 5202), and one compared SDA to vasopressin alone (n = 336). There was no survival to discharge or neurological outcome differences in any comparison group, including subgroup analyses. SDA showed improved ROSC (RR 2.80, 95%CI 1.78-4.41, p < 0.001) and survival to admission (RR 1.95, 95%CI 1.34-2.84, p < 0.001) compared to placebo. SDA showed decreased ROSC (RR 0.85, 95%CI 0.75-0.97, p = 0.02; I2 = 48%) and survival to admission (RR 0.87, 95%CI 0.76-1.00, p = 0.049; I2 = 34%) compared to HDA. There were no differences in outcomes between SDA and vasopressin alone or in combination with adrenaline. There was no benefit of adrenaline in survival to discharge or neurological outcomes. There were improved rates of survival to admission and ROSC with SDA over placebo and HDA over SDA.[4]

The largest trial to date comparing vasopressin and epinephrine studied patients who had pulseless electrical activity or asystole. The study included 1186 patients, 589 assigned to receive vasopressin and 597 assigned to epinephrine. The initial rhythm for those treated with vasopressin and those treated with epinephrine was typically asystole (44.5% vs 44.6%, respectively) or ventricular fibrillation or tachycardia (37.9% vs. 41.7%), whereas pulseless electrical activity was more common in those receiving vasopressin (17.7% vs. 13.7%, p=0.06). The average time to CPR for both groups was 7.9 ± 6.4 minutes with similar times between initiation of basic life support to defibrillation, first injection of study drug, and hospital admission. The rates of hospital admission between the vasopressin and epinephrine groups, respectively, did not differ significantly among patients with ventricular fibrillation (46.2% vs. 43.0%, p=0.48) or pulseless electrical activity (33.7% vs. 30.5%, p=0.65). Conversely, vasopressin was associated with higher rates of hospital admission in those with asystole as the initial rhythm (29% vs. 20.3%, p=0.02); this also translated to a higher rate of hospital discharge in those receiving vasopressin (4.7% vs. 1.5%, p=0.04).[9]

In a corresponding viewpoint, the editorialist commented that these "advances should be translated into a new standard of care without delay." One should balance this enthusiasm with the fact that the greater benefit of vasopressin in asystole was based on a post hoc analysis, and that the overall rate to hospital discharge remained low and associated with poor neurologic outcomes.[10]

A population-based registry used multiple sources to collect every case of sudden cardiac death (SCD) in Paris and its suburbs and covering a population of 6.6 million. It showed that epinephrine dose greater than 3 mg (OR 0.05, 95 % CI 0.03-0.08) was inversely associated with survival.[11] A study randomly assigned 650 patients who had cardiac arrest either in or outside the hospital to receive up to five doses of high-dose (7 mg) or standard-dose (1 mg) adrenaline at 5-minute intervals according to standard protocols. High-dose adrenaline was not found to improve survival or neurologic outcomes in adult victims of cardiac arrest.[12] A Japanese study of cardiac arrest patients found that those given epinephrine who survived were less likely to survive a month. In addition, in patients with long QT syndrome (LQTS), when epinephrine is given as a bolus infusion, paradoxical lengthening occurs in the QT interval which may increase the chance of SCD.[13]

Adrenaline has good bioavailability following tracheal delivery if administered appropriately.[14] Although the optimal dose of epinephrine for tracheal delivery is unknown, a dose that is at least 2 to 2.5 times the peripheral IV dose may be needed.[15] Intracardiac administration should be used only during open cardiac massage or when other routes of administration are unavailable.[16] Intracardiac injections increase the risk of coronary artery laceration, cardiac tamponade, and pneumothorax. Intracardiac injections also cause interruption of external chest compression and ventilation.[16]

The flip side of Adrenaline is that it may cause serious side effects in severely compromised patients. Adrenaline increases myocardial oxygen demand as it increases blood pressure and heart rate and this may cause myocardial ischemia.[17] Most studies have documented that enhanced dosage does not improve survival or neurologic outcome.[18] Importantly, high doses may contribute to post resuscitation myocardial dysfunction. It has potent pro arrhythmic effects and high doses may lead to

complex ventricular tachyarrhythmias.[4]

To conclude, based on the current evidence, use of Adrenaline can still be recommended but considering the potential side effects the dose should be limited to just 1 mg. It may be prudent to consider switching to other medicines that have already been approved in the guidelines. In the scenario of pulseless VT or VF, the most important step is to institute early CPR and perform defibrillation/shock as soon as possible.

REFERENCES

1. Thel MC, O'Connor CM. Cardiopulmonary resuscitation: historical perspective to recent investigations. Am Heart J 1999;137:39-48.
2. Yakaitis RW, Otto CW, Blitt CD. Relative importance of alpha and beta adrenergic receptors during resuscitation. Crit Care Med 1979;7:293-6.
3. ACLS-Algorithms.Com. 2010-2015 ACLS guidelines [Online]. 2010 [cited on 2013 July 10]. Available from URL: https://acls-algorithms.com/2010-acls-guidelines
4. Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. Resuscitation 2014;85:732-40.
5. Perkins GD, Cottrell P, Gates S. Is adrenaline safe and effective as a treatment for out of hospital cardiac arrest? BMJ 2014;348:g2435.
6. Kern KB, Lancaster L, Goldman S, Ewy GA. The effect of coronary artery lesions on the relationship between coronary perfusion pressure and myocardial blood flow during cardiopulmonary resuscitation in pigs. Am Heart J 1990;120:324-33.
7. Kaji AH, Hanif AM, Bosson N, Ostermayer D, Niemann JT. Predictors of neurologic outcome in patients resuscitated from out-of-hospital cardiac arrest using classification and regression tree analysis. Am J Cardiol 2014;114:1024-8.
8. Woodhouse SP, Cox S, Boyd P, Case C, Weber M. High dose and standard dose adrenaline do not alter survival, compared with placebo, in cardiac arrest. Resuscitation 1995;30:243-9.
9. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105-13.
10. McIntyre KM. Vasopressin in asystolic cardiac arrest. N Engl J Med 2005;350:179-81.
11. Bougouin W, Lamhaut L, Marijon E, Jost D, Dumas F, Deye N, et al. Characteristics and prognosis of sudden cardiac death in Greater Paris: population-based approach from the Paris Sudden Death Expertise Center (Paris-SDEC). Intensive Care Med 2014;22:846-54.
12. Bos JM, Ackerman MJ. Arrhythmias: adrenalinee test for sudden cardiac death--is it too early? Nat Rev Cardiol 2012;9:675-6.
13. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA 2012;307:1161-8.
14. Quinton DN, O'Byrne G, Aitkenhead AR. Comparison of endotracheal and peripheral intravenous adrenaline in cardiac arrest. Is the endotracheal route reliable? Lancet 1987;329:828-9.
15. Roberts JR, Greenberg MI, Knaub MA, Kendrick ZV, Baskin SI. Blood levels following intravenous and endotracheal epinephrine administration. JACEP 1979;8:53-6.
16. Aitkenhead AR. Drug administration during CPR: what route? Resuscitation 1991;22:191-5.
17. Perkins GD, Nolan JP. Early adrenaline for cardiac arrest. BMJ 2014;348:g3245.
18. Behringer W, Kittler H, Sterz F, Domanovits H, Schoerkhuber W, Holzer M, et al. Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome. Ann Intern Med 1998;129:450-6.