

Epinephrine, the standard of care in cardiac arrest in ACLS. Does it increase survival and improve neurological outcomes?

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A Capstone project submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements for the degree of Master of Physician Assistant Studies
Physician Assistant Studies, University of Manitoba, Winnipeg
Submitted: May 15, 2019

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ABSTRACT

Background

During cardiopulmonary resuscitation (CPR), epinephrine administered intravenously every 3-5 minutes is the recommended drug of choice per ACLS guidelines determined by the International Liaison Committee on Resuscitation (ILCOR), citing greater likelihood of ROSC (1)(2)(3). However, recent evidence implies there may be impaired neurological outcomes when administering epinephrine to cardiac arrest patients out of hospital (3)(4).

Objective

To evaluate if epinephrine has the ability to increase return of spontaneous circulation, increase survival to discharge, and promote functional neurological outcomes in patients who sustain an out of hospital cardiac arrest event. Furthermore, to determine whether initial cardiac rhythms during cardiac arrest respond differently to epinephrine administration.

Methods

A literature review of randomized controlled trials was conducted using PubMed, Google Scholar and Cochrane Library databases. Key words used include but were not limited to: cardiac arrest, epinephrine, adrenaline, and out of hospital cardiac arrest. A total of 15 5 were selected based on inclusion criteria.

Results

Three of the five RCTs demonstrated an increased likelihood for ROSC however there was conflicting results as to whether epinephrine increased survival to discharge. One RCT

found epinephrine administration worsened neurological outcomes. There were inconsistent findings to discern whether different cardiac arrest rhythms respond differently to epinephrine administration.

Conclusion

The justification of epinephrine's use in ACLS is based on inconsistent data limited to trials with small enrollment. Further large scale high quality RCTs are needed to determine whether help or harm is being done to patients are in imminent danger of death.

INTRODUCTION

Cardiac arrests are a serious medical emergency which requires prompt medical management in order to increase chances of survival. The Canadian Heart and Stroke foundation estimates that approximately 35,000-45,000 Canadians die each year from cardiac arrests, with 80% of them occurring either at home or in public places (5). Globally, out of hospital cardiac arrest (OHCA) survival rates remain low at approximately 8-11% (6). Epinephrine (adrenaline) has been an integral component of modern advanced cardiovascular life support (ACLS) since its integration into guidelines in 1961 (7) and is accepted today as a standard of care for cardiac arrest (3). Multiple published studies have indicated that epinephrine results in greater return of spontaneous circulation (ROSC) which is the first step towards survival and functional neurological outcomes (8). However, conflicting research suggests that greater ROSC may not equate a greater likelihood of survival (2)(3). Moreover, recent evidence implies there may be impaired neurological outcomes when administering epinephrine to cardiac arrest patients out of hospital (3)(4). These events led to the following research questions: does epinephrine improve ROSC and survival to discharge with favorable neurological outcomes among patients who cardiac arrest out of hospital? Furthermore, do different initial cardiac rhythms respond differently based on epinephrine administration?

Epinephrine background

Epinephrine is a naturally occurring catecholamine that is stored in chromaffin cells of the adrenal gland. Epinephrine is derived from methylation of norepinephrine and is released in greater quantity (80% vs 20%) during adrenal medulla stimulation. When released into circulation, epinephrine interacts with alpha and beta receptors with an affinity for beta receptors at low doses and alpha receptors at high doses (9). Stimulation of α_1 receptors on vascular smooth

muscles increase aortic diastolic pressure and coronary perfusion pressure as a direct result of vasoconstriction, which is believed to increase chances of ROSC(2)(4)(10). Epinephrine also increases cardiac output via β_1 activation of myocardium inducing increased contractility and the rate of contraction. Furthermore, β_1 activation of renin receptors in the kidney induce the renin angiotensin aldosterone system which causes increased blood pressure through potent vasoconstriction (9).

It is widely believed that adverse effects of epinephrine are largely due to decreased microvascular cerebral blood flow possibly increasing the risk for cerebral injury(2)(4)(10). Adrenergic α_1 stimulation induces platelet activation, promoting thrombosis and further impeding microvascular blood supply to the brain, worsening cerebral ischemia during resuscitation (4). β_1 adrenergic stimulation increases myocardial demand though increased inotropic and chronotropic activity of the myocardium, creating a possible supply/demand imbalance and induce ischemia. The potential for serious adverse effects of epinephrine led to the addition of vasopressin (anti-diuretic hormone) to the ACLS cardiac arrest algorithm, however it was removed in the 2015 update as studies demonstrated no additional benefit with the administration of both epinephrine and vasopressin (11).

Current Management of Cardiac Arrest

Cardiac arrest results from four cardiac rhythms: pulseless ventricular tachycardia (pVT), ventricular fibrillation (VF), pulseless electrical activity (PEA but also known as electromechanical dissociation), and asystole. Ventricular tachycardia is a condition where the ventricles contract at a rapid pace to the point where the atria cannot fill the ventricles, resulting in the absence of a pulse. Ventricular fibrillation occurs when there are disorganized, rapid

ventricular contractions that have no association with atrial contractions, resulting in a quivering heart that cannot produce a uniform contraction. Asystole arises when there is no evidence of electrical and mechanical cardiac activity. Pulseless electrical activity refers to a group of electrical rhythms that are associated with insufficient mechanical ventricular activity (11). These rhythms do not generate adequate perfusion sustainable for life and require immediate intervention.

Current management of cardiac arrest requires basic life support and ACLS. The first step in cardiac arrest requires activation of EMS and the initiation of CPR with supplemental oxygen and the use of a cardiac monitor/defibrillator at the earliest convenience. If the initial cardiac rhythm is not shockable (i.e. asystole or PEA) the healthcare providers will continue CPR for 2 minutes, establish IV access and administer epinephrine 1mg IV every three to five minutes. The patient is then reassessed for a cardiac rhythm after two minutes, if there is no change the process will repeat until either the cardiac rhythm is shockable, ROSC is achieved, or until the patient is declared dead. If the rhythm is shockable (i.e. pVT or VF) a biphasic 120-200J or monophasic 360J shock can be delivered to the patient. The patient should be reassessed after two minutes for changes to cardiac rhythm. If there are no changes, the cycle continues. According to ILCOR, epinephrine 1mg IV can be administered every three to five minutes. Amiodarone can be given in a 300mg IV bolus followed by a second dose of 150mg bolus after the first two epinephrine administrations (12). For ROSC to be accomplished there must be either a return blood pressure and pulse, abrupt sustained increase in $P_{ETCO_2} > 40\text{mmHg}$, or spontaneous arterial pressure waves with intra arterial monitoring (12).

OBJECTIVE

The purpose of this literature review is to evaluate randomized clinical trials to determine whether epinephrine improves ROSC, and functional neurological outcomes on discharge among patients who experience out of hospital cardiac arrest (OHCA). Additionally, this literature study seeks to determine whether epinephrine affects ROSC and neurological outcomes differently based on the initial cardiac rhythm during the cardiac arrest.

METHODS

To evaluate the objective of this literature review, searches were conducted in PubMed, Cochrane, and Google Scholar. Search terms used but were not limited to the following: cardiac arrest, ventricular fibrillation, pulseless electrical activity, ventricular tachycardia, out of hospital cardiac arrest, epinephrine, adrenaline, neurological outcomes. Furthermore, the bibliographies of previous systematic reviews were assessed for eligible trials. In total, 15 randomized controlled trials were identified for screening, yielding 5 RCTs eligible for evaluation

Inclusion Criteria

Studies that were included for this literature review met the following criteria: randomized controlled trials, trials published in English, trials conducted in 1st world countries belonging to ILCOR, patients over 18 years of age, cardiac arrest out of hospital, cardiac arrest presumed to be cardiac in etiology, randomized controlled trials, and an intervention compared to the standard of care based on ACLS guidelines at the time of the trial.

Exclusion Criteria

Exclusion criteria included animal studies, patients who had known or apparent pregnancy, pediatric patients, arrest due to trauma or anaphylaxis, or patients who had received epinephrine prior to being deemed eligible for the trial.

Data Extraction

A summary of the following was extracted from the reviewed RCTs: author, intervention, control, number of patients, primary and secondary outcome (Table 1). Figures 1-3 depict graphical representation of primary outcomes of ROSC and functional neurological outcomes on discharge (Figures 1-3). Figure 4 Depicts a flowchart for the 2015 ACLS cardiac arrest algorithm

RESULTS

Standard dose epinephrine vs placebo (0.9% normal saline)

With the need to understand the benefit of epinephrine in cardiac arrest, Jacobs et al. (3) performed the first randomised placebo controlled trial. This single centre study occurred in Western Australia from 2006 to 2009 with the primary outcome of the trial being survival to hospital discharge. Secondary outcomes included pre-hospital ROSC (defined as greater than 30 seconds), and neurological outcomes based on the Cerebral Performance Category (CPC) defined as follows:

CPC 1: Good cerebral performance: conscious, alert, might have mild neurological or psychological deficit

CPC 2: Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment

CPC 3: Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis

CPC 4 Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/ awake cycles. Cerebral unresponsiveness.

CPC 5: Brain death- apnea, areflexia, EEG silence

A large obstacle precluding this trial from being undertaken involved the ethics of not providing the standard of care for ACLS to patients who have experienced cardiac arrest. The scope of practice for Paramedics of Western Australia are determined by St John Ambulance Western Australia (SJA-WA) based on guidelines from the Australian Resuscitation Council (ARC); who are a council of ILCOR. With that said the trial was allowed to commence as SJA-WA had a policy allowing no drug administration based on the lack of evidence for improved survival and risk for adverse effects due to compromised uninterrupted chest compressions (3). The study was designed such that all out of hospital cardiac arrests (OHCA) would be attended by paramedics who received a two-day continuing education training course in the trial protocol and cardiac arrest simulations. Inclusion criteria for the trial included all patients aged 18 or above who suffered an arrest from any cause. Patients were randomized when it became apparent IV epinephrine would be required either after the third unsuccessful defibrillation or after IV access in the case of non-shockable rhythms. Epinephrine 1:1000 (i.e. 1 mg) and normal saline were prepared in identical 10ml vials distinguishable by randomization number only. Epinephrine or NS were administered per guidelines in increments of 1ml with a maximum dose

of 10ml (10mg adrenaline or 10ml normal saline). During pre-hospital resuscitation, there were no other medications administered through intravenous route only. Resuscitation efforts were terminated in the field if patients remained asystole for a minimum of twenty minutes. 4426 patients were planned to be included in the trial based on a survival rate to hospital discharge of 5%, improvement of survival in 2%, and power of 80%(3). Of the 4103 cardiac arrests that were attended to, 601 patients were eligible for randomization of which 262 patients received epinephrine and 262 patients received the placebo administration. When comparing patient characteristics amongst the treatment groups, cardiac etiology was identified in greater than 90% of the patients (49.2% placebo vs 42.9% epinephrine, $p = 0.39$) with nearly 50% of all patients receiving bystander CPR. Average ambulance interval response time was nearly identical (10.2 min placebo vs 10.1 epinephrine, $p= 0.76$). Median volume of trial drug and fluids given were identical at 5ml and 500ml ($p=0.13$ and $p=0.28$)(3).

In terms of outcomes, ROSC was achieved prior to hospital in 23.5% of patients who received epinephrine vs 8.4% of patients who received the placebo (OR 3.4, CI 2.0-5.6, $p<0.001$). Of those patients in which ROSC was successful, 25% of patients who received epinephrine were admitted to hospital compared to 13%. (OR 2.3, CI 1.4-3.6, $p<0.001$). There was no significant difference in survival to discharge (epinephrine 4% vs 1.9%, OR 2.2, CI 2.2 (0.7-7.3), $p=0.15$) and neurological outcomes comparing when comparing treatment groups (placebo 100% vs 81%, $p=0.31$) (3).

When comparing patient outcomes based on initial cardiac arrest rhythms, patients were twice as likely to achieve ROSC if given epinephrine (27% epinephrine vs 13% placebo, OR 2.4 (1.2-4.5), $p=0.009$). Of the patients who initially had a non-shockable rhythm, 21% of patients receiving epinephrine achieved ROSC compared to 3.7% of patients receiving the placebo (OR

6.9 (2.6-18.4), $p < 0.001$). There was no statistically significant difference in survival to hospital discharge based on initial cardiac rhythm.

This study is unique in that it is the first double blind randomized placebo controlled trial of epinephrine in cardiac arrest patients. Jacobs et al. (3) determined that the use of epinephrine in OHCA patients was successful in achieving ROSC but did not demonstrate a benefit in survival to hospital discharge. That being said, there are multiple limitations to this study. Over 4000 patients were anticipated to be included in the trial however only 601 were eligible to be randomized resulting in an underpowered study. The trial was initially designed to be multi centered however four of the 5 ambulance services withheld from participation despite ethics approval, citing ethical concerns of not providing the standard of care in cardiac arrest patients. In addition, neither the quality of CPR or timing of intervention administration were assessed to determine their influence on primary and secondary outcomes. Lastly, participation by the paramedics was on voluntary basis resulting in the possibility of selection bias as well as contributing to the lower sample size.

Standard dose epinephrine 1mg vs placebo (0.9% normal saline)

Due to continuous studies demonstrating conflicting evidence concerning epinephrine in cardiac arrest, the International Liaison Committee on Resuscitation called for placebo controlled experiments to determine the effectiveness and safety of epinephrine in cardiac arrest. Perkins et al. (4) developed the Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC2) trial. The PARAMEDIC2 trial was conducted across five national EMS services in the UK from December 2014 to October 2017. This trial was unique in that it was multicentered, randomized, placebo

controlled, and double blind (4). Due to the nature of cardiac arrest being sudden and the need to comply with European legislation on consent, informed consent was obtained after resuscitation or a legal representative if the patient was deemed unable to make informed health decisions. Inclusion criteria included all adult patients who sustained OHCA and received ACLS by paramedics trained in the trial process. Exclusion criteria included patients under 16 years of age, arrest due to trauma, known or apparent pregnancy, arrest due to anaphylaxis or asthma, or if epinephrine was administered prior to arrival of a trial trained paramedic (4).

Patients were randomized based on failed initial attempts of CPR and defibrillation to receive either 1mg epinephrine or 0.9% saline in prefilled syringes administered IV/IO every three to five minutes. The primary outcome of this trial was survival at 30 days, with secondary outcomes including survival until hospital admission, length of hospital stay, three month survival rate at discharge, and three month neurological outcomes using the modified Rankin Scale (favorable deemed a score of three or less) (13):

0: No symptoms

1: No significant disability, can carry out ADL with minimal symptoms

2: Slight disability, can attend to affairs but cannot perform all activities

3: Moderate disability- can walk unassisted but requires help

4: Moderate severe disability: cannot perform ADL or walk without assistance

5: Severe disability: requires constant care and attention, bedridden and incontinent

6: Dead

Perkins et al. (4) planned for a total population of 8000 patients, estimating the risk ratio for the epinephrine group at 1.25, corresponding to a survival of 6% in the placebo group and 7.5% in the epinephrine group. In total 10,623 patients were screened with 8016 patients enrolled

in the study; 3999 patients received the placebo treatment compared to 4015 patients receiving the epinephrine treatment. There was no significant difference between patient treatment groups regarding patient characteristics including age, sex, initial cardiac rhythm, cause of arrest.

The treatment group receiving epinephrine demonstrated a greater percentage of patients achieving ROSC when compared to the placebo treatment (36.3% vs 11.7%) as well as survival to hospital (50.8% vs 30.7%). Thirty-day survival was seen in 3.2% of patients receiving epinephrine vs. 2.4% of the placebo group (OR 1.39, 95% CI 1.06 to 1.82, $p=0.02$). The number needed to treat to prevent death at 31 days was found to be 112. The epinephrine group also performed marginally but not significantly better in terms of survival to discharge with a favorable neurological outcome (2.2% vs 1.9%, OR 1.18, 95% CI, 0.86 to 1.61). However, there were more patients with poor three-month neurological outcomes in the epinephrine group compared to placebo (0.7% vs 0.2%; aOR 1.408, 95%CI, 1.071-1.852). There were no statistical differences between treatment groups on the impact of admission to hospital, or length of stay. Ultimately, Perkins et al. (4) found that epinephrine significantly impacted survival at 30 days (NNT= 112) however there was no difference in terms of rate of survival with a favorable neurological outcome as there were slightly more patients who survived with severe neurological impairment in the epinephrine group. Limitations to this study include the lack of monitoring for CPR quality, lack of baseline neurological status documented, and the lack of early administration of epinephrine.

Epinephrine vs no drug administration

Olasveengen et al. (14) conducted a randomized control trial from May 2003 to April 2008 to understand whether the administration of intravenous drugs (epinephrine) affected

survival and neurological outcomes. Olasveengen et al. believed that successful ACLS was largely based on the importance of high quality CPR, and that the administration of drugs would shift valuable time and focus towards less successful treatments. Thus, the trial sought to compare outcomes who received standard ACLS with IV drug administration (control) to patients receiving standard ACLS without IV drug administration (intervention). The primary outcomes of this trial were survival to hospital discharge. Secondary outcomes included neurological outcomes (CPC 1-4), 1 year survival, successful ROSC, and CPR quality (14). The trial occurred in Oslo, Norway using an ambulance crew carrying two trained paramedics and an anesthesiologist who would be dispatched when available.

Inclusion criteria for this RCT included patients older than 18 suffering a nontraumatic out of hospital cardiac arrest. Patients were randomized by EMS on site- sealed envelopes were opened to further direct whether drug administration would be given. If ROSC was achieved in the non-intravenous group, IV access was deemed to be performed after 5 minutes and with possible drug administration if necessary. Exclusion criteria were witnessed arrests by EMS, interruptions by non-team members, and arrest due to asthma or anaphylaxis. The decision to waive informed consent for inclusion was determined by Oslo regional ethics committee, however consent would be required for 1 year follow up survivors.

Over the course of this study 1183 patients were recruited with 851 patients eligible for randomization with 481 patients receiving no epinephrine and 367 patients receiving epinephrine. There was no significant difference in ROSC between treatment groups (24% no epinephrine vs 29% epinephrine, $p=0.12$) (14). Patients receiving epinephrine were found to have an increased likelihood of admission to hospital compared to patients receiving no epinephrine (48% vs 27%, OR 2.5, 1.9-3.4, $p<0.001$). Moreover, patients who received

epinephrine were less likely to be discharge with a favorable neurological outcome (5% vs 11%; OR 2.4, 0.2-0.7, $p < 0.001$), less likely to be discharged alive (7% vs 13%, OR 0.5, 0.3-0.8, $p = 0.006$), and less likely to survive 1 year after cardiac arrest (6% vs 12%; OR 0.5, 0.3-0.8, $p = 0.004$) (14).

Patients with an initial shockable rhythm (VF/pVT) who received epinephrine were less likely to be discharged alive (12% vs 33%, OR 0.3, 0.1-0.5, $p < 0.001$) and less likely to experience favorable neurological outcomes on discharge (12% vs 33%, OR 0.3, 0.1 to 0.5, $p < 0.001$). Patients with an initial non shockable rhythm (asystole or PEA) who received epinephrine were more likely to achieve ROSC (OR 5.1, CI 3.2 to 8.1) however there was no statistical difference survival to discharge or survival with a favorable neurological outcome (14).

There are multiple limitations to this study. The possibility of paramedic bias cannot be ruled out despite proper training. Furthermore, 25% of cases did not assess CPR quality and timed medication administration was unreliable. Third, this trial was single centered making it difficult to extrapolate to other major cities and countries. Lastly, the study is underpowered due to low enrollment in the trial.

Standard dose epinephrine vs single initial high dose epinephrine

Experimental animal studies on swine and dogs in the 1980s demonstrated improved myocardial and cerebral blood flow along with improved rates of resuscitation in subjects receiving altered doses of vasopressors, leading to uncontrolled human trials in the late 1980s. Brown et al. (15) conducted a randomized, double blind, multicentered trial with a goal to compare the effectiveness of high dose epinephrine (0.2mg/kg) compared to the standard dose

per AHA guidelines (0.01 to 0.02 mg/kg). Patients for this study were selected across six states in the USA with the trial being conducted from October 1989 to Dec 1990. Inclusion criteria included patients over 18 years of age with a cardiopulmonary arrest, patients with an initial shockable rhythm and remained in that rhythm despite three electrical shocks, patients with an initial shockable rhythm which converted to asystole after the initial shock, or if the initial tracing indicated asystole or PEA. Exclusion criteria included arrest pregnant women, arrest due to non-cardiac causes (ex. overdose, drowning, hypothermia), primary respiratory arrest, signs of irreversible cardiac arrest, or failure to establish intravenous access.

Patients were randomised to receive either the standard or high dose epinephrine via numbered and coded syringes packaged in random order by the manufacturer to each study centre. The syringes were identical in appearance and prefilled to 20ml (1:1000 standard epinephrine vs. 1:10,000 high dose epinephrine). Patients were treated according to 1990 AHA guidelines with the exception that the first dose of epinephrine was either standard or high dose. Primary outcomes of this trial were slightly different than the other trials identified in this study but included ROSC, successful resuscitation to hospital, admission to hospital, survival to discharge, and neurological outcomes at discharge. Neurological outcomes were graded retrospectively based on the CPC scale with a score of 1-3 deemed as conscious.

Brown et al. (15) included 1280 patients in this trial with 632 patients receiving the standard dose epinephrine and 648 patients receiving high dose epinephrine. Patient characteristics involving age, sex, presenting rhythm, response time were similar amongst the treatment groups, however not all data was collected for each patient, affecting the results. In terms of primary outcomes, ROSC was achieved in 30% of patients receiving standard dose epinephrine compared to 33% of patients who received high dose epinephrine (99% CI, -10 to 3)

(15). Successful resuscitation and mission to hospital were identical at 22% for each treatment group (99% CI, -7 to 5). Of those patients who were admitted to hospital, 4% of patients in the standard dose group and 5% of the high dose group were discharged from hospital (99% CI, -4 to 2) with nearly identical favorable neurological outcomes at 92% and 94% respectively (99% CI, -20 to 16) (15). Subgroup analysis found when epinephrine was administered within 10 minutes of cardiac arrest, survival to discharge improved in the high dose group compared to the standard dose group (23% vs 11%, 95% CI -28 to 3) (15). Patients with an initial rhythm of PEA were also increasingly likely to achieve ROSC when given high dose epinephrine (47% vs 33%, 95% CI -26 to -2) (15). Brown et al. (15) found similar results in primary outcomes when comparing standard epinephrine to high dose epinephrine. There were no outcomes demonstrating a statistically significant benefit to suggest altering the epinephrine dose impacts morbidity in cardiac arrest. With that said, there are multiple limitations to this study. First, the study sample is small resulting in a low power and the increased likelihood of a type 2 error. Neurological outcomes were recorded via chart reviews which affects the results in that minor improvements may not be recorded. Furthermore, functional neurological outcomes were scored from CPC 1-3 where a score of three indicates a severe disability, questioning whether it is a functional outcome. Therapies to improve neurological status are not commented on or accounted for in this study. Additionally, confounders such as quality of CPR were not accounted for nor addressed in this study.

Standard doses of epinephrine vs repeated high doses of epinephrine

Gueugniaud et al. (16) conducted a prospective multicentered double blind randomized controlled trial to investigate the effectiveness of repeated high doses of epinephrine (5mg)

compared to repeated standard dose epinephrine (1mg). This study involved 12 centres across France and Belgium and was performed from September 1994 to September 1996. Inclusion criteria were all patients over 18 years of age with sustaining a cardiac arrest event whether it be ventricular fibrillation or asystole/PEA. Exclusion criteria included pediatric patients, traumatic cardiac arrest, obvious irreversible cardiac arrest, or patient who received epinephrine prior to study protocol (16). The study was designed with the intention to follow ACLS protocol as per European Resuscitation Council and AHA guidelines with the exception of epinephrine doses. With ethics approval, patients were randomly assigned to receive either standard epinephrine dose (1mg) or high epinephrine doses (5mg) every three minutes with a maximum of fifteen doses. Treatment groups could receive medication through intravenous access or endotracheal if IV access could not be established. EMS personnel were blinded to this study as both treatment doses were packaged identically in 5ml ampules, where each patient would receive a package set of 15 ampules. Primary outcomes of this study were sustained ROSC for at least one minute, admission to admission, and discharge from hospital. Secondary outcomes included survival and neurological outcomes. Neurological function was assessed during admission and initially based on the Glasgow Coma Scale for the first week, and assessed via the CPC scoring system on discharge (16).

By the time this trial had concluded, 3946 patients had been included for investigation. Of these patients 580 were excluded based on exclusion criteria or lost to follow up, and 39 packages were improperly used resulting in a total population of 3327 patients; 1650 patients receiving standard epinephrine doses and 1677 patients receiving high dose epinephrine. In terms of the study patients, there were similar characteristics between both study groups, with the

exception that the high dose epinephrine group required less doses of epinephrine for ROSC to be achieved (5.8 vs 6.1, $P=0.04$)(16).

The high dose epinephrine group also demonstrated a statistically significant increase in ROSC compared to the standard dose epinephrine group (40% vs 36.4%, $P = 0.02$). In terms of witnessed arrests, ROSC was achieved in 45% of patients receiving high dose epinephrine compared to standard dose epinephrine (40%, $P=0.009$). ROSC was also achieved with greater frequency in patients with witnessed cardiac arrests with suspected cardiac cause (42.8% vs 37%, $p = 0.02$)(16) . However, survival to discharge remained similar in both treatment groups (2.8% standard dose vs 2.3% high dose, $p = 0.34$), as well as regardless of whether the cardiac arrest was witnessed or as a result of cardiac cause. Functional neurological outcomes amongst the percentage of discharged patients with a CPC score of 1 were statistically insignificant regardless of treatment group (57% standard dose vs 68% high dose group, $P = 0.95$).

In terms of outcomes based on cardiac rhythm, ROSC was achieved in 37% of patients in the high dose group whose initial EKG rhythm was asystole compared to 32% of patients receiving standard epinephrine dose ($p=0.01$). This resulted in an increase of patients admitted to hospital (25% high dose vs 20% standard dose, $P=0.004$), however there was no improvement nor difference in survival to discharge (13% high dose vs 18% standard dose, $P=0.38$). In patients where PEA was the initial cardiac rhythm, ROSC was achieved with greater success in patients receiving high dose epinephrine vs standard dose epinephrine (55 vs 45%, $P = 0.09$), however there was no clinically significant data to support improved survival to hospital or survival to discharge. Patients who arrested with an initial cardiac rhythm of ventricular fibrillation demonstrated no statistical difference in ROSC, admission to hospital, or survival to discharge regardless of the epinephrine dose administered (16).

DISCUSSION

Epinephrine has a longstanding history of being the standard of care for drug administration in cardiac arrest since the 1960s despite conflicting evidence based on randomized controlled trials and prospective observational studies. This literature review evaluated randomized controlled trials evaluating whether epinephrine (in various doses) affects ROSC, survival, and functional neurological outcomes. In terms of evaluating ROSC, Jacobs et al. (3) and Perkins et al. (4) evaluated the use of standard dose epinephrine against 0.9% normal saline. Jacobs et al. (3) and Perkins et al. (4) both found that epinephrine was statistically significant in ROSC when compared to normal saline. Olasveengen did not find a significant difference in ROSC standard dose epinephrine was compared to no IV drug administration. Brown et al. (15) did not see any benefit of increased ROSC with an initial high dose of epinephrine, however Gueugniaud et al. (16) found that repeated high dose epinephrine was successful in achieving ROSC with greater frequency.

In terms of survival to discharge, Perkins et al. (4) found that epinephrine was statistically significant in increasing survival to discharge.. On the other hand, Olasveengen et al. (14) found that patients receiving epinephrine were less likely to survive to discharge compared to patients who did not receive IV medication. Jacobs et al.(3), Brown et al. (15), and Gueugniaud et al. (16) did not find any benefit of epinephrine increasing survival to discharge.

In terms of neurological outcomes based on interventions, Olasveengen et al. (14) determined that patients receiving epinephrine suffered worse neurological outcomes on discharge compared to patients who did not receive IV drug administration. The other four randomized controlled trials evaluated in this literature review did not see any clear benefit based on intervention. In terms of evaluating whether epinephrine affects primary outcomes based on

initial cardiac rhythm, Jacobs et al. (3) found that patients with non-shockable rhythms were more likely to achieve ROSC however there was no increased survival to discharge or change increased likelihood of functional neurological outcomes. Olasveengen et al. (14) found that patients with non-shockable rhythms who received epinephrine statistically fared worse in achieving ROSC however there was no significant difference in terms of survival or discharge with favorable neurological outcomes. Furthermore, Olasveengen et al. (14) discovered that patients with shockable rhythms who received standard dose epinephrine were found to be less likely to survive until discharge, and more likely to have worse neurological outcomes. Gueugniaud et al. (16) found that high dose epinephrine was more successful in achieving ROSC in patients with a non-shockable rhythm, however there was no benefit in neurological outcome on discharge. Brown et al. (15) did not identify any statistical significance of epinephrine affecting outcomes based on initial cardiac rhythms.

CONCLUSION

Cardiac arrest is a serious emergency that continues to have poor prognosis despite advancements in pharmacology, imaging modalities and interventions. Based on the randomized controlled trials evaluated in this literature, epinephrine does appear to increase the chances of ROSC however there does not appear to be any tangible benefit in terms of increased survival or functional neurological outcomes on discharge. With that said, there currently isn't enough evidence to suggest that patients suffer worse neurological outcomes if they receive epinephrine. Regardless of the initial cardiac rhythm, there is no clear pattern to suggest epinephrine improves chances of survival or functional neurological outcome. Although ROSC is the critical first step to survival to discharge and functional neurological outcomes, one must begin to question how much longer we should continue to administer a medication that is proving to provide little

benefit in the long term. At what point do you consider the adverse effects of epinephrine? Would certain population groups be more likely to benefit from epinephrine and its possible adverse effects on microvascular circulation? Further high quality multi centered RCTs with adequate power are required to assess whether epinephrine should remain as a part of the cardiac arrest algorithm in ACLS.

TABLES

Table 1. Summary of RCTs

Trial	Intervention & Control	Number of Patients	Primary Outcome	Secondary Outcome
Jacobs et al.	I: 1mg epinephrine C: 0.9% NS	I: 272 C: 262	1. Survival to hospital discharge	1. ROSC 2. Neurological outcomes
Perkins et al.	I: 1mg epinephrine C: 0.9% NS	I: 4015 C: 3999	1. Rate of survival at 30 days	1. Rate of survival until hospital discharge 2. ROSC 3. Neurological outcomes
Olasveengen et al.	I: No IV Drugs C: 1mg epinephrine	I: 481 C: 367	1. Survival to hospital discharge	1. ROSC 2. Survival to hospital admission 3. Neurological outcomes
Brown et al.	I: 0.2 mg/kg C: 0.02 mg/kg	I: 648 C: 632	1. ROSC 2. Admission to hospital 3. Survival to discharge 4. Neurological Outcomes	

Gueugniaud et al.	I: 5mg epinephrine C: 1mg epinephrine	I: 1969 C: 1938	1. ROSC 2. Discharge from hospital	1. Neurological outcomes
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Figure 1. Comparison of ROSC based on intervention and control. Note- * denotes statistical significance

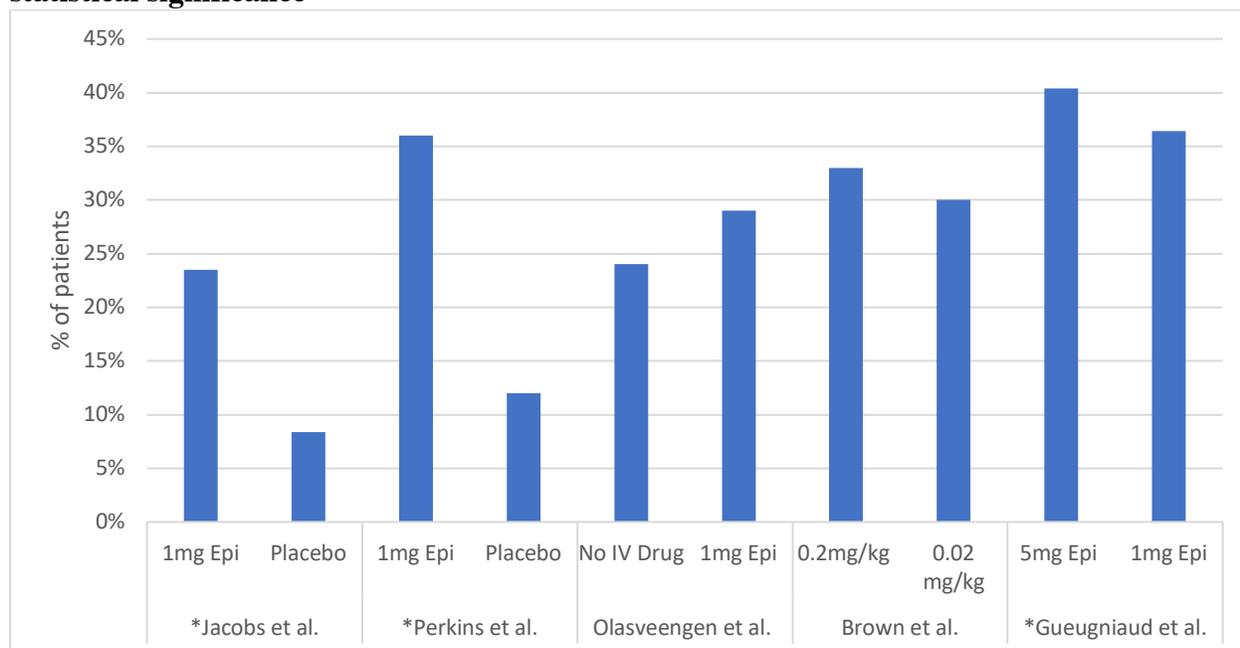


Figure 2. Comparison of Neurological outcomes based on intervention and control. Percentages are based on number of patients with good neurological outcome/ number of patients surviving to discharge. Note* denotes statistical significance

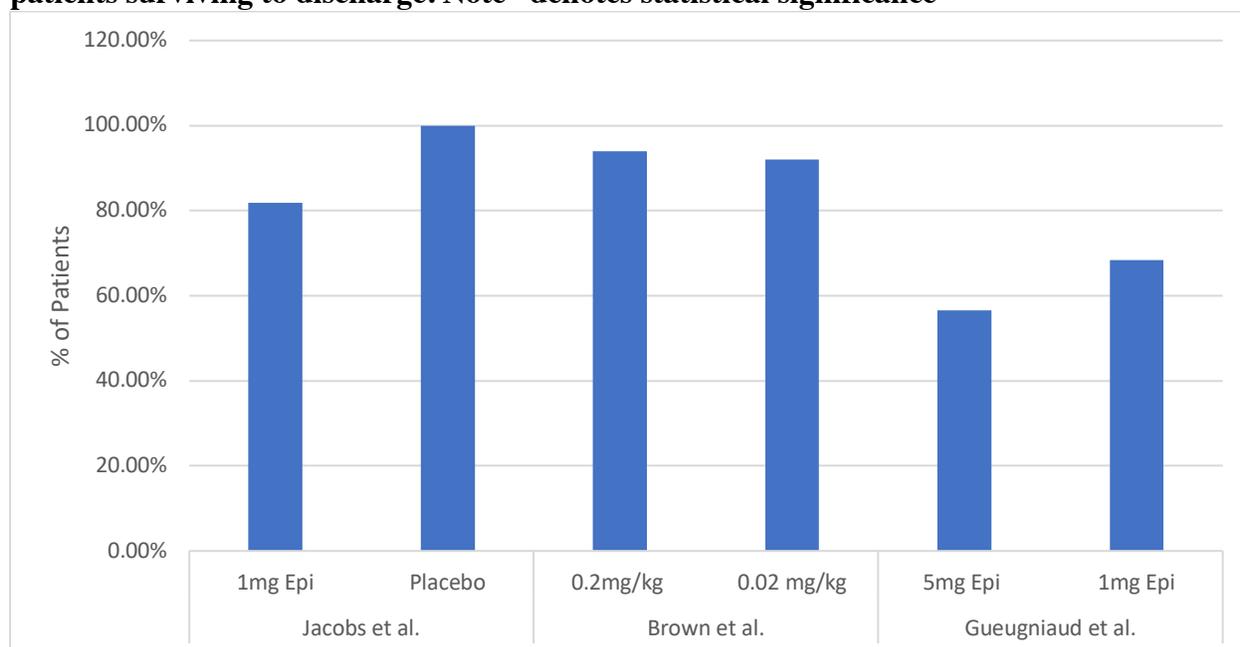


Figure 3: Comparison of Neurological outcomes based on intervention and control. Percentages are based on percentage of patients with good neurological outcomes/total patients in treatment group. Note* denotes statistical significance

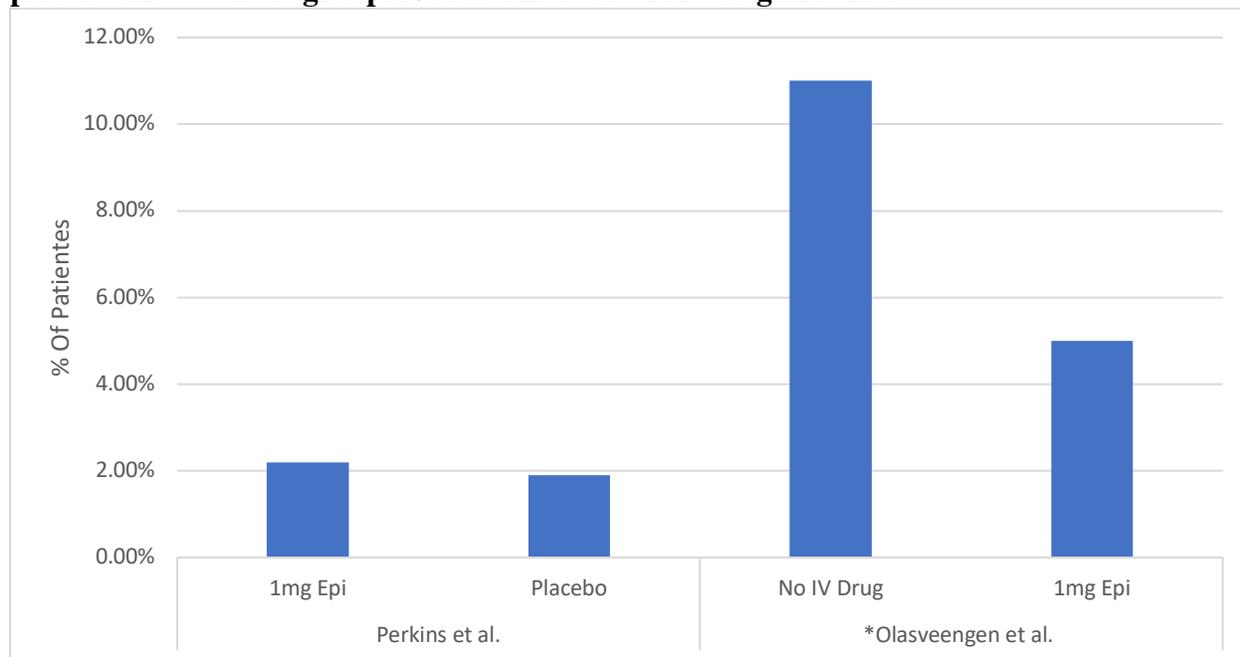
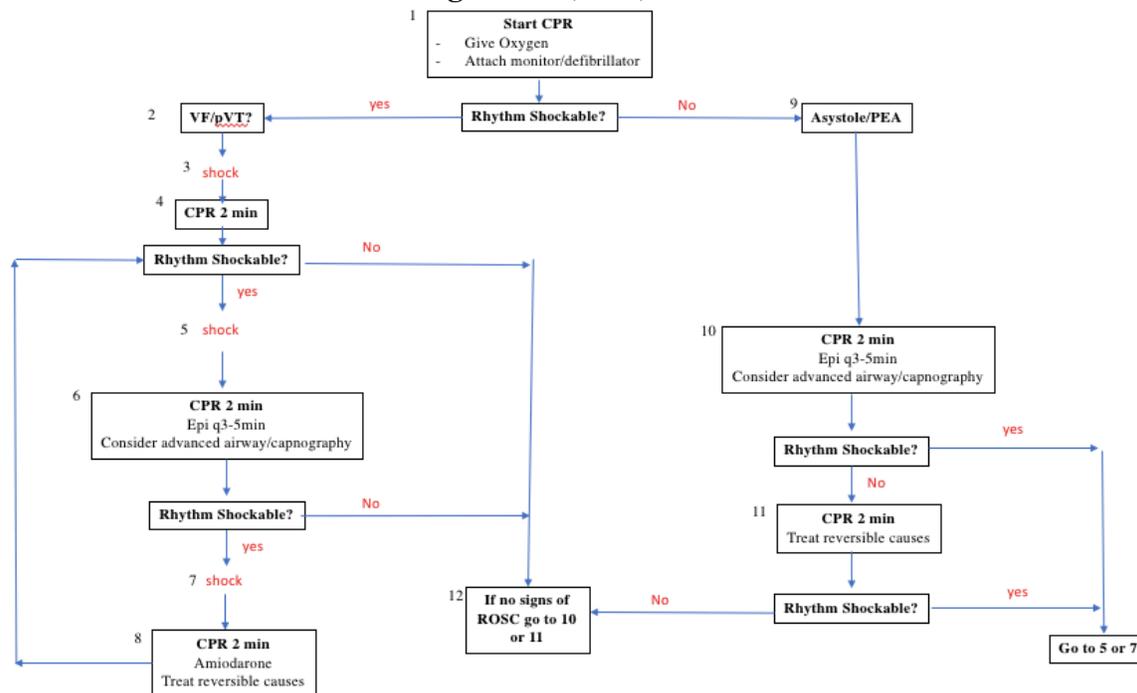


Figure 4. Current ACLS Cardiac Algorithm (2015)



REFERENCES

1. American Heart Association. 2015 American Heart Association guidelines : update for CPR and ECC. 2015;2015.
2. Dumas F, Bougouin W, Geri G, Lamhaut L, Bougle A, Daviaud F, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? *J Am Coll Cardiol*. 2014;64(22):2360–7.
3. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation* [Internet]. 2011;82(9):1138–43. Available from: <http://dx.doi.org/10.1016/j.resuscitation.2011.06.029>
4. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, et al. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. *N Engl J Med* [Internet]. 2018;2018:NEJMoa1806842. Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1806842>
5. Foundation H and S. Position statement on CPR [Internet]. [cited 2019 Nov 27]. Available from: <https://resuscitation.heartandstroke.ca/guidelines/position/CPR>
6. Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP, et al. Epinephrine for out of hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled trials. *Resuscitation* [Internet]. 2019;136(6):54–60. Available from: <http://dx.doi.org/10.1016/j.resuscitation.2014.03.008>
7. Nolan JP, Perkins GD. Is there a role for adrenaline during cardiopulmonary resuscitation? *Curr Opin Crit Care*. 2013;19(3):169–74.
8. Hagihara A, Abe T. Prehospital Epinephrine Use and Survival Among. *Jama*.

- 2012;307(11):1161–8.
9. Karen W. Pharmacology. In: Journal of Chemical Information and Modeling. 6th ed. Philadelphia, PA: Wolt; 2015. p. 77–95.
 10. Finn J, Jacobs I, Ta W, Gates S, Gd P. Adrenaline and vasopressin for cardiac arrest (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. Cochrane Database Syst Rev. 2019;(1).
 11. Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(SUPPL. 3).
 12. Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, et al. Part 7: Adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(18):S444–64.
 13. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke. 2017;48(7):2007–12.
 14. Olasveengen TM, Wik L, Sunde K, Steen PA. Outcome when adrenaline (epinephrine) was actually given vs. not given - post hoc analysis of a randomized clinical trial. Resuscitation [Internet]. 2012;83(3):327–32. Available from: <http://dx.doi.org/10.1016/j.resuscitation.2011.11.011>
 15. Brown CG, Martin DR, Pepe PE, Steuven H, Cummins RO, Gonzalez E, et al. A comparison of standard-dose and high dose epinephrine in cardiac arrest outside the hospital. Drug Ther (NY). 1994;327(15):1051–5.

16. Gueugniaud P-Y, Mods P, Goldstein P, Pham E, Dubien P-Y, Deweerdt C, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. *New Engl Med J* [Internet]. 1998;339(22):1595–601. Available from: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa003289>

ACKNOWLEDGMENTS

The author would like to Nancy Luxa-Le Blanc for her encouragement and mentorship in the completion of this capstone project, as well as the MPAS faculty for their unwavering support and guidance.