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Abstract

Epinephrine has been a standard of care treatment for cardiac arrest for the last century; however, the use of epinephrine began without a significant amount of research. In recent years, many have started to question whether epinephrine is an appropriate treatment for cardiac arrest. While epinephrine causes vasoconstriction of the blood vessels and directs much-needed blood flow to the heart, it has also been shown to harm the microvessels of the brain, causing ischemia and neurological damage. Many trials, studies, and surveys were conducted to determine the correct course of action involving the use of epinephrine during cardiac arrest. Additional trials were performed comparing epinephrine and other treatments, such as vasopressin or basic life support alone. The general conclusion is that epinephrine increases survival in patients at the expense of neurological function. Ultimately, many patients suffer from post-cardiac arrest syndrome and warrant various therapies. For lack of a better alternative, epinephrine will continue to be used at large. This paper is a critical analysis of the available data regarding the use of epinephrine, the numerous related trials, and its long-term effects on quality of life.

Introduction

One of the most common causes of death in the world is cardiac arrest. Within the United States alone, approximately 436,000 Americans die from cardiac arrest each year. Epinephrine, the primary drug used in treating cardiac arrest, has a catch-22 since it is believed to have both beneficial and detrimental effects. The use of epinephrine to treat cardiac arrest has been standard practice since 1906; however, not much has changed in this practice, although medicine continues to progress. Current research brings into question the efficacy of epinephrine in treating cardiac arrest, as well as the potential harm that it can cause.

In order to recognize the effects of epinephrine as a treatment, it is first necessary to understand what cardiac arrest is and what the potential causes are. Cardiac arrest is the failure of the heart to adequately pump blood to all parts of the body, either due to electrical interference or the appearance of a lethal or abnormal rhythm, usually ventricular fibrillation (DeSimone, 2023). Although ventricular fibrillation is the most common cause of cardiac arrest, identified in about 70% of cardiac arrest patients, there are various additional causes, including cardiomyopathy, coronary artery disease, blood loss, lack of oxygen, or electrolyte imbalances which can cause arrhythmias. Both lifestyle and genetic components can increase the risk of one experiencing cardiac arrest. These factors include but are not limited to smoking, abuse of drugs or alcohol, obesity, hypertension, and a family history of cardiac disease or arrest (Chrispin, 2023; Ludhwani, 2022).

Oftentimes, cardiac arrest is sudden and unexpected. Time is critical when dealing with cardiac arrest since every second that the heart is not pumping, there is no oxygenated blood flow to the brain and other vital organs. Most people who have gone into cardiac arrest experienced at least one symptom in the hour prior, and some may even experience symptoms during the week before. These symptoms are often the same as those of a heart attack which can be a direct cause of cardiac arrest. Symptoms can consist of shortness of breath, fatigue, chest pain, or heart palpitations, to name a few. It is imperative that these warning signs not be ignored since studies have shown that those who heed the warning signs and get medical care are 5 times more likely to survive cardiac arrest (NIH). Once someone has already experienced cardiac arrest, the treatment options decrease significantly.

Methods

Databases such as the Touro College Library System, ProQuest, the National Institutes of Health (NIH), and PubMed, among others, were used to review and analyze the information in the following paper. Original articles and peer-reviewed literature were included in this critical analysis of epinephrine and cardiac arrest. Key phrase searches utilized include "cardiac arrest treatments," "epinephrine trials," and "epinephrine vs. vasopressin."

Discussion

A mainstay line of treatment for cardiac arrest is the use of epinephrine administered intravenously. This is due to a clear association between epinephrine and increased return of spontaneous circulation (ROSC) during cardiopulmonary resuscitation (CPR) (Shao & Li, 2017). The first successful use of epinephrine was in a trial done on animals but was soon applied to human cardiac arrest treatment with successful ROSC as well (Loomba et al., 2015). The current protocol for the administration of epinephrine is to administer 1mg of epinephrine every three to five minutes while performing high-quality CPR. As a sympathomimetic catecholamine, epinephrine has pharmacologic effects on alpha and beta-adrenergic receptors. Therefore, the range of effects that epinephrine has on the body is very wide, including increased vascular smooth muscle contraction, increased pupillary dilator and intestinal sphincter muscle contraction, increased heart rate, bronchodilation, and the release of renin (Dalal & Grujic, 2022). Most importantly, when dealing with cardiac arrest, epinephrine's alpha-1-adrenoceptor

agonist effects increase arterial blood flow and coronary perfusion (Callaway, 2013).

The sympathetic nervous system is responsible for the body's fight-or-flight response. Under stressful conditions, the sympathetic nervous system increases the contractile force of the heart and its rate, thereby increasing cardiac output. The sympathetic nervous system achieves this by decreasing metabolic and other functions not significantly required at the moment. The circulation of adrenaline, produced in the adrenal medulla and some neurons of the central nervous system, activates the B-adrenergic receptors of the heart muscle. Once activated, this innervates the internal electrical activity of the heart. Therefore, when coronary circulation is compromised, this process is negatively impacted (Karemaker, 2017). Since the heart's innervation is affected during cardiac arrest, artificial methods are required to stimulate the same response and output. These methods include the administration of epinephrine to potentially help ensure ROSC.

However, the effects of the vasoconstriction properties of epinephrine do not come without a drawback. Although vasoconstriction is beneficial in directing blood flow to the heart, constriction of the microvessels in the brain can cause serious damage long term. In a study done on male pigs, ventricular fibrillation was induced, and CPR was performed. Some of the pigs received epinephrine venous injections, while others did not. After defibrillation, ROSC was achieved in all the pigs, and the results were studied. Using optical miniature sensors revealed that the pigs that received epinephrine had a great decrease in cortical microcirculatory blood flow and distinctly worse brain ischemia (Ristagno et al., 2007).

When applied to the anatomy and physiology of humans, it was discovered that due to the sensitivity of the brain's microvessels, this ischemia has an acute impact on the brain that is not seen in the heart vasculature. Additional adverse effects of epinephrine on the brain include platelet aggregation and thrombosis. On account of these adverse outcomes, those who survive cardiac arrest tend to suffer serious neurologic injury. Unfortunately, among cardiac arrest survivors who make it to the intensive care unit, greater than two-thirds later die from brain injury (Laver et al., 2004). The amount of epinephrine administered directly correlates to the degree of brain damage acquired. The 1 mg dosing of epinephrine does not follow a typical medicine-based pattern. Medications are ordinarily given according to weight since one person's weight can differ greatly from another. Epinephrine, however, is given in 1 mg doses to all adults across the board. This originates from the 1mg adrenaline intracardiac injections given in operating rooms to restart an arrested heart during surgery. In the 1970s, when resuscitation guidelines were first created, they conjectured that 1 mg of epinephrine intravenously would work the same way. Intracardiac injections of epinephrine, while possibly more effective than IV administration, have many risks that generally outweigh the benefits. When doing an intracardiac injection, there's an increased risk of coronary artery laceration, cardiac tamponade, or even a pneumothorax. Another factor to consider is that it would interrupt the performance of chest compressions and external ventilation, which has proven invaluable in ensuring ROSC. So, while it may sound like a good option theoretically, intracardiac epinephrine injections are reserved for open cardiac surgery or when other routes of administration are not possible (Beck & Rand, 1949; Hill, 2000).

After observing a significant return of spontaneous circulation due to epinephrine administration during CPR, medical providers wondered whether higher doses of epinephrine would be more effective. Therefore, studies were done to determine the outcome. High doses of epinephrine were administered to patients in cardiac arrest with similar outcomes to those who received the regular dosing (Stiell et al., 1992). However, studies done on piglets revealed that high-dose epinephrine induces greater vasoconstriction of cortical cerebral blood vessels. Therefore, blood flow is redistributed from the superficial cortex, not supplying enough oxygenated blood to the brain (Gedeborg et al., 2000). Additionally, since epinephrine increases the heart rate and contractility of the heart through its beta-adrenergic effects, there is a parallel increased demand for myocardial oxygenation. When this demand is not met, there is potential for harm to the tissue of the heart as well (Jung et al., 2018).

In contrast, a study was conducted to determine the effect of a lower dose of epinephrine on survival rates and specifically on neurological aftermaths. This study was done over the course of eight years, in which advanced life support (ALS) providers were instructed to administer regular dosing of epinephrine in the first few years, and the data were systematically recorded. In the last four years of the trial, the dose of epinephrine delivered was reduced. The lower dose consisted of 0.5 mg at 4 and 8 minutes, followed by additional doses of 0.5 mg every 8 minutes for shockable rhythms and 0.5 mg every 2 minutes for non-shockable rhythms. The trial included 2,255 patients who experienced non-traumatic out-of-hospital cardiac arrest (OHCA), and the data and analysis were adjusted for age, gender, presence of a witness, bystander CPR, and response interval to ensure the highest level of accuracy possible. Ultimately, this trial indicated that decreasing the amount of epinephrine in cardiac arrest treatment did not result in a greater chance of survival

or better neurological results. Consequently, no changes were made in the dosing of epinephrine (Fisk et al., 2018).

Most studies done on this topic were observational in nature since it is complicated and ethically questionable to withhold a standard of care treatment from patients in a trial. Therefore, trials included observing the difference in outcomes between patients given epinephrine or patients just receiving compressions and defibrillation with ROSC before epinephrine was required. Other trials studied the rates of long-term vs. short-term survival. However, it was not until a placebo-controlled trial was done in Australia that an interventional study was attempted to discover whether epinephrine is actually an appropriate advanced treatment in cardiac arrest. Unfortunately, this trial faded out since they had a difficult time with patient recruitment and politicians protesting the morality of such a trial. The trial was unable to contribute statistical gravity since it was cut short and was not conducted on a large group of participants. In this out-of-hospital cardiac arrest (OHCA) randomized trial, 367 patients received adrenaline, and 481 patients did not receive it. Participating patients were from only one out of the five original ambulances that were going to join the trial. The consensus was that there may be an optimistic link between epinephrine treatment and survival to hospital discharge in patients. Although insignificant, this slightly contradicts the observational trials done prior, which suggested that long-term survival after epinephrine in cardiac arrest is almost nil, but agrees with previous statements on the negative neurological effect (Jacobs et al., 2011).

However, this brought into question whether the rate of survival was majorly affected by the time between epinephrine treatment and cardiac arrest, especially since many cardiac arrests are unwitnessed. Therefore, there is little knowledge on whether the harmful neurologic outcomes are due to the administration of epinephrine or simply due to the amount of time that the patient was down prior to resuscitation. The data for in-hospital cardiac arrest in children was studied and showed an obvious association between a delay in receiving epinephrine and a decreased survival rate. An extension of the study was conducted to determine whether this influences outcomes in out-of-hospital cardiac arrests since there was limited data to analyze. It was a nationwide population-based study done in Japan over the course of many years in which pediatric patients who experienced OHCA with a primary non-shockable rhythm, essentially asystole, were followed. Of the total patient cohort, only 10.2% survived to the 30-day mark, with an average of 26 minutes from the call to the administration of epinephrine. A longer time to delivery of epinephrine correlated with a lower chance of survival and worse neurologic outcomes in the pediatric patients of the study (Fukuda et al., 2018).

Additional factors such as chest compressions and early defibrillation of shockable rhythms play an enormous role in the survival of those who suffer cardiac arrest. When investigating the role of epinephrine in cardiac arrest survival outcomes, it is imperative to ensure that there are no external variables influencing the results. A Norwegian study established that the overall results of cardiac arrest patients who were treated with advanced life support with and without IV drug administration were relatively equivalent. Advanced life support includes epinephrine in addition to basic life support, which is CPR and defibrillation. Further analysis of the study data confirmed that short-term survival is greater with epinephrine, but long-term survival and neurological damage worsened (Olasveengen et al., 2009). This brought into question whether or not the long-established use of epinephrine in treating cardiac arrest is actually constructive.

Although the Australian placebo-controlled trial did not achieve statistical significance, a major breakthrough was accomplished in the PARAMEDIC2 trial done just six years later. The lack of concrete proof about the appropriateness of epinephrine use in OHCA patients up until this point caused concern in the International Liaison Committee on Resuscitation. They directed a placebo-controlled trial to establish the safety and efficacy of epinephrine in such patients. The trial took place in the United Kingdom and was both randomized and double-blind. Included in the trial were 8,014 patients from five National Health Service ambulance services throughout the country. All of the patients received standard care; however, 4,015 patients received epinephrine, while 3,999 patients received a saline placebo. The study had two objectives. Firstly, to determine the primary outcome difference between the groups, which they set at 30-day survival. The secondary outcome studied consisted of hospital discharge with positive neurologic outcomes among the participants. The results of the trial were clear. The primary outcome, 30-day survival, was notably higher with the use of epinephrine. On the other hand, there was no significant difference in favorable neurologic outcomes between the two groups since the percentage of severe neurologic impairment in the group which received epinephrine treatment was almost double that of the group which received the placebo.

The parameter that was set to decide whether neurologic outcomes were favorable in the trial was a score of three or less on the modified Rankin scale (Perkins et al., 2018). The Rankin scale is mainly used to determine the

degree of an individual's disabilities and dependence after suffering a stroke or other brain damage. The scoring ranges from zero, meaning "no symptoms at all," to a six, which indicates death. A three on the Rankin scale stipulates moderate disability requiring some help but being able to walk unassisted (NINDS, 2022). It was through this study that the catch-22 of epinephrine use in cardiac arrest was made abundantly clear to the medical world at large. It proved that epinephrine increases survival in patients at the expense of neurological function. Although the concept was already given some attention in the faded-out Australian trial, through the PARAMEDIC2 trial, it achieved statistical significance due to the enormity of the study (Jarvis, 2021).

Therefore, scientists and physicians began to think in terms of other effective treatment options for cardiac arrest victims. The second drug of choice is vasopressin, also known as antidiuretic hormone (ADH), synthesized in the hypothalamus. Vasopressin is an endogenous peptide which is another vasopressor agent. It causes the contraction of the vascular smooth muscles through the V1 receptors, leading to an increased total peripheral resistance and, thereby, an increased blood pressure (Cuzzo et al., 2022).

Additionally, vasopressin affects the V2 receptors of the blood vessels causing vasodilation which can combat the lack of perfusion to vital organs, as seen with epinephrine administration (Stroumpoulis et al., 2008). The effects of vasopressin on the V1 and V2 receptors are seemingly contradictory; however, in a study performed using the vasculature of rabbits to help clarify which effect dominates, it was discovered that the V1 receptors, which respond with vasoconstriction, superseded the V2 vasodilatory receptors in response to being treated with vasopressin. Therefore, the working theory of vasopressin's advantage in better perfusion is seemingly unfounded (García-Villalón et al., 1996).

When evaluating patients post-cardiac arrest, an interesting observation was discovered. There was a higher level of endogenous vasopressin in the survivors than in the ones who died. This correlation led scientists to hypothesize that vasopressin may increase the chances of cardiac arrest survival (Stroumpoulis et al., 2008). In a study, patients in cardiac arrest were given, at random, either adrenaline or vasopressin in addition to standard emergency care. The trial stipulated that if two injections of the given medication did not work, then an epinephrine injection would be administered. There were approximately 500 adults in each group with similar clinical profiles, yet the trial did include patients in cardiac arrest caused by various means such as ventricular fibrillation, pulseless electrical activity, or asystole. The patients with ventricular fibrillation were only included in the trial if three rounds of defibrillation failed and medication was required. The trial results showed that the total survival rate was the same between the two groups, mainly when it came to ventricular fibrillation and pulseless electrical activity (PEA), but within the data, they noticed something different. Within the group of patients in asystole specifically, the vasopressin survival rate was 4.7%, while the adrenaline rate was only 1.5%. They also noticed that in those whom the vasopressin failed to resuscitate, the additional injection of adrenaline often ensured ROSC. Thereby, they concluded that vasopressin and then a subsequent epinephrine injection may be more effective than solely epinephrine in refractory cardiac arrest treatment. This can be due to vasopressin being a greater vasopressor agent than epinephrine in asystole, leading to better coronary perfusion pressure during resuscitation. (Wenzel et al., 2004).

An additional study was conducted to determine the results of epinephrine and vasopressin given respectively, since evidence was inadequate to make clinical recommendations at the time. The participants consisted of roughly 2,500 adults with OHCA who were separated into two divisions. In the trial, one group received a 1mg injection of epinephrine followed by 40 international units (IU) of vasopressin, and the other group received 1mg of epinephrine, after which they were injected with a saline placebo. If ROSC was not obtained, then they received another set of the original treatment, as well as an added dose of epinephrine if required after that. The patient population all had relatively the same characteristics to ensure the least variation and utmost accuracy in results; however, the study did note that there were more men in the combination group. Unfortunately, the trial concluded that there was no consequential difference between the two groups. The combination of epinephrine and vasopressin did not improve the outcomes of patients in cardiac arrest more than epinephrine. The survival rate of this trial was substantially lower than the Wenzel et al. trial previously mentioned, and this was explained to most likely be due to the high number of patients with asystole. In asystole, it is notoriously hard to achieve ROSC, and the average time to resuscitation of asystole patients in this trial was 45 minutes. Among the participants, there was a considerably low number of patients with ventricular fibrillation, so they could not draw a definite conclusion against using vasopressin in those circumstances.

A burning question regarding vasopressin is whether vasopressin can help resuscitate patients in cardiac arrest without the serious neurological effects that epinephrine

has. The authors reported that since their study contrasting the use of individual vasopressors during cardiopulmonary resuscitation revealed no clear difference in their effects on short-term survival, there is no basis for anticipating an improvement in their effects on neurologic recovery in the long term (Gueugniaud et al., 2008). A systematic review of trial results and literature available regarding cardiac arrest treatment options concluded that giving ordinary dosing of epinephrine or high dose, vasopressin alone, or both adrenaline and vasopressin together all help improve survival rates, but they all do not have very favorable neurological outcomes. The review mentioned that some of the trials and studies cited are from many years prior and may not be useful to present practice (Finn et al., 2019).

The guidelines for advanced cardiovascular life support were updated by the American Heart Association in 2019. Based on the many trial outcomes, they state that vasopressin can be considered in the management of cardiac arrest but does not provide an advantage over epinephrine in any way. Vasopressin, in addition to the epinephrine, may also be considered but does not offer any advantage either. The protocol states that it would be appropriate to maintain simplicity for providers by limiting the primary choice to epinephrine, although ultimately, they are interchangeable. Regarding timing for epinephrine administration, the American Heart Association states that for a non-shockable rhythm, it should be given as soon as possible; however, when treating a patient with a shockable rhythm, it is reasonable to first attempt to defibrillate and only administer epinephrine if that fails. When it comes to cardiac arrest with a non-shockable rhythm due to a reversible cause, such as asphyxia, if the cause can quickly be identified and reversed then the time to epinephrine is adjusted accordingly. It is important to note that the American Heart Association accounted for all of the trials done to date when updating their protocol guidelines. The information available is scarce in comparison to other areas of medicine, and it was mentioned that many of the trials were biased as a consequence of confounding. Essentially, there were additional factors influencing the results, such as the type of rhythm prior to arrest, time to administration of drugs, bystander intervention, gender, age, and more (Panchal et al., 2019).

The confusion and uncertainty surrounding epinephrine and its appropriateness in treating cardiac arrest is greater than ever. For every question answered by the trials performed, more questions arise. As corroborated by the PARAMEDIC2 trial, the primary concern today is that epinephrine increases survival in patients at the expense of neurological function. Many patients resuscitated after cardiac arrest suffer from post-cardiac arrest syndrome (PCAS), an umbrella term including brain damage, myocardial dysfunction, and systemic ischemia–reperfusion injury. Systemic ischemia–reperfusion injury is the damage done to the tissue of the body when oxygenated blood supply returns to the tissue after some time without it. The pathophysiology of ischemia-reperfusion injury is very complex. Essentially, the ATP and pH levels in the cells decrease during extended periods of ischemia as a result of anaerobic metabolism and lactate accumulation. Therefore, the mechanisms for ATPase-dependent ion transport lose function, leading to cell swelling and rupture, necrosis of cells, and calcium overload, among others. The damage is not reversed automatically with reperfusion since, once resuscitated, oxygen levels are re-established, and there is a dramatic increase in species reactive to oxygen. Neutrophils, white blood cells which respond to damaged tissue and pathogen invasion, then invade the ischemic tissue, which exacerbates the ischemic injury already inflicted (Kalogeris et al., 2012). The vasoconstricting effects of epinephrine can exacerbate the inevitable ischemia in patients with cardiac arrest. This can cause serious damage to all organ systems and is often fatal (Cunningham et al., 2022).

Another focal issue associated with post-cardiac arrest syndrome is adrenal insufficiency as a result of anoxia and elevated concentration levels of epinephrine during intervals in CPR and cardiac arrest as a whole. When a patient is resuscitated after cardiac arrest, their body undergoes many hemodynamic disturbances. During this time of distress, they require higher levels of cortisol; however, if they're suffering from adrenal insufficiency, they will not receive an adequate amount of cortisol, which prevents healing at best or can possibly lead to death. Oftentimes, adrenal insufficiency as a result of cardiac arrest is overlooked. A major issue is that unless diagnosed early on, patients with untreated adrenal insufficiency, along with ischemia and other detrimental results of cardiac arrest, will suffer refractory shock (Chalkias & Xanthos, 2012).

Another major component of post-cardiac arrest syndrome is myocardial dysfunction, often caused by ischemia-reperfusion injury. An additional cause of myocardial dysfunction post arrest is cardiovascular toxicity as a result of inflated levels of inflammatory cytokine activation and catecholamines such as epinephrine. Low cardiac output or ventricular systolic or diastolic dysfunction both fall under the category of myocardial dysfunction. Around two-thirds of patients who are resuscitated post-cardiac arrest have impaired left ventricular systolic function. Additionally, hypotension and shock necessitating the use of vasopressors are also frequent after cardiac

arrest. The presence of preexisting cardiac pathologies, of course, increases the likelihood of developing myocardial dysfunction post-cardiac arrest (Jentzer et al., 2015).

The fourth element of post-cardiac arrest syndrome is a persistent precipitating pathology, the pathology that most likely caused the cardiac arrest to occur or contributed to it. Diagnosing and controlling the underlying condition is imperative in managing a patient post arrest. Some of the most common persistent participating pathologies of cardiac arrest are acute coronary syndrome, infection leading to sepsis, various lung pathologies, hemorrhage, or toxic syndromes caused by chemicals. While some of these conditions require very specific treatment plans to reverse, such as an antidote for a drug overdose or temperature control for hypothermia, many others require an all-inclusive approach to manage along with the rest of the post-cardiac arrest complications involved (Neumar et al., 2008).

In order to improve results in patients with post-cardiac arrest syndrome, suitable therapies need to be utilized as soon as possible post arrest (Cunningham et al., 2022). The time after cardiac arrest was meticulously broken down into intervals for clarity in treatments and analysis. The first twenty minutes after achieving ROSC are considered to be the immediate post arrest phase. The twenty-minute mark until 6-12 hours later is described as the early post arrest phase. It is during this period that early interventions may be most successful. From then until the 72nd hour is the intermediate phase. During this time, there is still activity in the injury pathways, and powerful treatments are attempted. Lastly, the recovery phase is after the first three days, when a clearer picture can be gleaned and a more accurate prognosis made (Neumar et al., 2008).

The measures taken to manage patients post arrest vary from the very basics to advanced therapies specific to their individual needs. Of course, patients are monitored extensively post-cardiac arrest, as they would for any patient in the intensive care unit (ICU). In general, patients who are post-cardiac arrest are typically hemodynamically unstable, presenting with dysrhythmias, hypotension, and a low cardiac index. The sooner these are managed, the greater the chances are for improved long-term outcomes. Although this is widely accepted as sensible, this motion has not been researched and studied at length yet. Ventilation is another extremely important intervention usually required after resuscitation. It is common to provide 100% oxygen flow to prevent hypoxemia, but evidence has shown that hyperoxia in the beginning phases of reperfusion can cause harm as well. Hyperoxia can harm neurons by generating excessive oxidative stress post-ischemia. Therefore, the post-cardiac arrest care protocol was adjusted to advise maintaining an oxygen saturation of 94% to 96%. Clinical trials are still required to study modulated reoxygenation more thoroughly.

Furthermore, if the cause of cardiac arrest is determined to be an ST- elevation myocardial infarction (STEMI), they should immediately receive coronary angiography and percutaneous coronary intervention (PCI) if warranted. A STEMI is caused by a blockage of a major coronary blood vessel and is initially determined by an electrocardiogram reading. Some hold that since the precipitating pathology of cardiac arrest is frequently an acute coronary syndrome (ACS), such as a heart attack, it is reasonable to consider coronary angiography right away in any patient who is even suspected of having ACS. Routine management of ACS should be kept as well.

Of all the possible therapies considered in post-cardiac arrest treatment, mild therapeutic hypothermia is the only one to have solid evidence indicating increased survival rates. In four separate studies, hypothermia was proven to increase outcomes in comatose cardiac arrest survivors. There remains a lot to explore in this regard, such as ideal temperature, length, and rewarming rate. From the trials performed, the consensus was to rewarm at around 0.25 to 0.5 degrees celsius per hour. It is imperative that great care is taken during this period since hemodynamic conditions, electrolyte balances, and metabolic pace can fluctuate swiftly. Nevertheless, if hypothermia is inaccessible or unable to be done for various reasons, then at the very least, it is vital to avert pyrexia. For every degree of body temperature above 37 degrees celsius, there is an increased risk of inferior neurological outcome.

Further measures, including sedation, tracheal intubation, and mechanical ventilation, may be necessary if there are no significant signs of awakening five to ten minutes after ROSC is established. Prevention of seizures, glucose control, and hemodialysis for renal failure may be required depending on the extent of the damage acquired during and post arrest (Bernard et al., 1997; Neumar et al., 2008).

An interesting notion has been suggested regarding cardiac arrest care. Life-saving therapies, including therapeutic hypothermia or PCI, are not always obtainable in many hospitals to which post-cardiac arrest patients are brought. On that account, it was proposed to establish "regional cardiac arrest centers" parallel to the idea of level-one trauma centers (Lurie et al., 2005).

Conclusion

With all of the precariousness surrounding cardiac arrest, its treatment, and its aftermath, it is fair to question the status quo and expect change. When a trial is

performed, there is a minimum clinically important difference (MCID) required to adopt the suggested treatment. This is the minimum threshold value needed to actually enforce change. In most of the trials done regarding the treatments for cardiac arrest, there has been scarce evaluation for MCID. Therefore, there has been an accordingly limited room for change. An international survey was conducted involving emergency physicians or other practitioners of acute cardiovascular exploration to establish the MCID for outcomes post-cardiac arrest. The conclusion was that the MCIDs constantly change depending on the outcomes. When outcomes were positive, the MCID increased and vice versa. The conductors of the survey reflect that defining a clear MCID for survival post arrest would help hasten the rate of evidence-based change in cardiac arrest care (Nichol et al., 2016).

When putting the statistics of epinephrine results up against other interventions, some clarity is gained. According to the PARAMEDIC2 trial, for every 112 patients given epinephrine, there was one more survivor than in the placebo group. Contrasting this with the numbers from other basic interventions, such as early defibrillation with an impact of five survivors or bystander CPR with an increase of 15, tells providers where the real influence lies. Community awareness and intervention are major components of positive cardiac arrest outcomes (Jarvis, 2021).

As of now, the evidence shows epinephrine to be the most effective resuscitative measure when CPR and defibrillation alone are not enough. The evidence has shown that neurological outcomes suffer significantly as well. As a result of a lack of concrete medicine-based alternatives, epinephrine continues to be the standard of care treatment in OHCA. Many providers argue that epinephrine is not a life-saving method but a method of prolonging death. The real question is of an ethical and moral nature. It boils down to whether or not patients would prefer to avoid risking poor neurological outcomes and a decreased quality of life rather than resuscitation with epinephrine. When community commentary was sought during the PARAMEDIC2 trial, 95% of the studied population picked long-term favorable neurological results rather than short-term survival, which was specified as several hours to days. While the trial has definitely shown that the present standard dosing and use of epinephrine may not be perfect, it also may not warrant an all-or-nothing approach (Welsford et al., 2019). One unanimous conclusion from the myriad of trials, studies, and surveys performed is that there is still an incredible amount of work to be done in this area.

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