Student Contribution

THE USE OF VASOPRESSIN IN THE TREATMENT OF CARDIAC ARREST – A CASE STUDY

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INTRODUCTION

Despite widespread use, current methods of treatment for cardiac arrest in many settings yield poor results. Historically, adrenaline has been used for decades as a primary pharmacological agent in the treatment of cardiac arrest. The drug is still used today, although a lack of tangible evidence pertaining to its benefit exists. In fact, the use of adrenaline, is supported only by animal studies and anecdotal case reports. (Chugh, et al, 1997)

The primary aim in using adrenaline as the front line drug treatment of cardiac arrest is to produce selective vasoconstriction, in an attempt at maintaining vital organ perfusion during Cardiopulmonary Resuscitation (CPR).

The use of adrenaline in this situation is less than ideal as it creates its own set of potential problems including increased myocardial oxygen demand. Based on the poor survival rates following CPR, researchers have gone further afield in an attempt to identify a pharmacological agent which produces the main beneficial effect of adrenaline without the potentially damaging or harmful side effects.

This paper discusses the use of *vasopressin* in the treatment of cardiac arrest, as a somewhat controversial alternative to adrenaline. Within the context of this paper, I will review relevant literature and based on current evidence, evaluate the most appropriate drug therapy for the treatment of cardiac arrest. Readers are encouraged to access the journal articles and additional readings if more in depth information is required.

CASE PRESENTATION

Paramedics were called to a 42 year old male patient, unconscious and not breathing. No cardiopulmonary resuscitation had been initiated prior to SA Ambulance arrival. The downtime was estimated to be a few minutes. The presenting rhythm was ventricular fibrillation (VF), which did not revert following three defibrillations. CPR was initiated.

On arrival of a second crew, the patient was intubated and an intravenous (IV) line was established. CPR was continued by paramedics until a further 3 shocks were given. The patient remained in ventricular fibrillation.

IV adrenaline was administered in 1mg boluses every couple of minutes in support of CPR and defibrillation. A further 2 shocks were administered resulting in *Return of Spontaneous Circulation (ROSC)* for a short time (45 seconds) before reverting back to a VF rhythm, CPR was continued, as was increments of IV adrenaline. IV Lignocaine was used without success. Resuscitation continued for a further 28 minutes which was interlaced with short periods of unsustained ROSC. The rhythm became asystolic and efforts were ceased.

A total of 8mg of intravenous adrenaline, 16 defibrillations and around 50 minutes of CPR failed to produce a sustained return of spontaneous circulation.

CARDIAC ARREST

The survival rates of cardiac arrest and resuscitation, particularly in the pre-hospital setting remain poor, despite significant advances in other areas of pre-hospital emergency care. Many factors influence the rate of cardiac arrest survival, which may include, but are not limited to age, pre-existing disease, length of time until intervention, presenting rhythm and cause of the arrest.

ADRENALINE IN CARDIAC ARREST

Adrenaline is an adrenergic agonist, which is employed in cardiac arrest for the effect it has on the α_1 receptor of selective vasoconstriction. However, like many pharmacological agents, adrenaline also targets other receptor sites including α_2 , β_1 and β_2 . Stimulation of some of these other receptor sites may have a detrimental effect on the outcome of cardiac arrest, in particular the β_1 effects.

Although adrenaline is recommended by many resuscitation councils throughout the world for the treatment of cardiac arrest, its use is more recently being reconsidered due to other, theoretically harmful effects including increased myocardial oxygen demand (β_1), ventricular arrhythmia's (β_1), ventilation perfusion mismatch (α_1 , β_1 , β_2), post-resuscitation myocardial defects and unfavourable neurological recovery. (Wenzel, et al, 2000)

Another potential side effect of the use of adrenaline is that it induces a potent platelet aggregation, so much so that it is commonly used as an aggregator in platelet function tests. (Poullis, M, 2000) This idea in itself would suggest that the use of adrenaline in the arrested patient may prove interesting, particularly in those patients with significant coronary artery narrowing.

Babbs, et al, (2001) writes that "*routine use of initial and repeated doses of epinephrine has not definitively improved survival outcome in adult victims of cardiac arrest*"

What then would be the ideal drug for use in cardiac arrest? Would it be a potent vasoconstrictor, which would **not** increase myocardial oxygen demand, would **not** promote platelet aggregation, and still provide vital organ perfusion? This would require a selective α agonist, or at least the principle behind it. Hence the idea of using *vasopressin* as an alternative to adrenaline has been put forward.

VASOPRESSIN IN CARDIAC ARREST

In recent years, vasopressin has received considerable interest as an alternative to adrenaline as it generates a similar pattern of vasoconstriction, however it is less likely to increase myocardial and cerebral oxygen demand.

Vasopressin is an important endogenous hormone released from the posterior pituitary gland, which increases in levels, during the time of cardiac arrest and during CPR. The drug is a powerful vasoconstrictor, which targets mainly V_1 receptors in smooth muscle.

Since 1992, a link has been identified between the level of endogenous vasopressin and outcome of cardiac arrest. One paper (Babbs, et al, 2000) writes that in 60 victims of out of hospital cardiac arrest, the endogenous plasma levels of vasopressin were significantly higher during CPR in patients with a return of spontaneous circulation (ROSC). Alternatively plasma adrenaline concentrations were significantly higher in those patients that died.

Laboratory studies have suggested that vasopressin is a moderately selective stimulator of V_1 receptors, resulting in intense peripheral vasoconstriction of skin, skeletal muscle, fat, intestine and relatively less constriction of coronary, renal and cerebral blood supply. Some animal studies have confirmed that vasopressin increased vital organ perfusion under CPR in comparison to adrenaline. Vasopressin produces little increase in myocardial oxygen demand in states of ventricular fibrillation or after resuscitation. (Babbs, et al, 2000)

ACTH & Cortisol

Vasopressin is also a potent stimulus for *Adrenocorticotropin Hormone* (ACTH) secretion and as a result, plasma cortisol levels are increased. Higher levels of stress hormones e.g. ACTH and cortisol are associated with successful defibrillation and ROSC. These hormones may enhance myocardial function and prevent irreversible circulatory collapse. This may be one reason why improved outcome is seen in animal models of CPR when vasopressin is used over adrenaline.

One study by Kornberger, et al, (2000) found that ACTH and cortisol levels during cardiac arrest and CPR were higher in the vasopressin group versus the adrenaline group. In this study on swine cardiac arrest, 7/7 of the vasopressin pigs survived cardiac arrest where as only 1/7 of the adrenaline treated pigs survived.

To enable ROSC, only one defibrillation was required in each of the vasopressin animals, whereas in the single surviving adrenaline treated animal, six shocks were required. Interestingly, the only surviving adrenaline treated pig, had higher levels of ACTH and cortisol, than the other adrenaline treated pigs that died.

The clinical significance of the ACTH and cortisol concentrations remains unclear. The levels of these hormones have been low in failed resuscitation attempts.

Vasopressin use in prolonged or shock-refractory cardiac arrest

As of April 2001, there were three published clinical studies, which supported the use of vasopressin use in *human* cardiac arrest.

In one hospital study, 8 patients with shock-refractory arrest (6 in VF, 2 with pulseless electrical activity (PEA) were given vasopressin 40 units IV (failing all other attempts at resuscitation). As a result all 8 patients had a return of spontaneous circulation and 3 of those patients (2 in VF and 1 with PEA) survived to hospital discharge. (Babbs, et al, 2000)

In the second study by Morris, et al, (1997) in Detroit USA, 10 patients were given vasopressin 1U/kg after traditional resuscitation methods with adrenaline failed to produce ROSC. This did not produce ROSC, however it demonstrated an increase in coronary perfusion pressure in 4 patients. The average total resuscitation time was 39.6 minutes prior to vasopressin use. The total time, included pre-hospital and in-hospital resuscitation time. These patients were deemed non-salvageable. This study may demonstrate that earlier use of vasopressin could be more beneficial in producing ROSC.

The third study compared 40 units of vasopressin with 1 mg of adrenaline for “pre-hospital”, shock-refractory, VF arrest in adults. This study involved 40 patients (20 for each drug) and showed encouraging trends in **ROSC - (to hospital admission)**: 70% vasopressin versus 35% adrenaline ($p=0.06$) **24 HOUR SURVIVAL**: 60% versus 20% respectively ($p= 0.02$) and **SURVIVAL TO DISCHARGE**: 40% vasopressin versus 15% adrenaline ($p= 0.16$). (Lindner, et al, 1997)

It must be noted, that of the published human clinical studies evaluating the use of vasopressin for cardiac arrest, no significant long-term survival benefits, or neurological outcome advantages have been demonstrated by its use.

Another potential downfall of the research is that, of the 27 animal studies supporting the use of vasopressin in cardiac arrest, all but two of the studies modeled VF. Therefore benefits of using vasopressin for other cardiac arrest rhythms, remains largely unknown. Some of the studies compared adrenaline with vasopressin and showed haemodynamic improvement with vasopressin over adrenaline. Several studies showed that vasopressin significantly improved haemodynamic variables, vital organ blood flow and cerebral oxygen delivery when compared with high dose adrenaline.

When compared with a placebo and high dose adrenaline in one study, vasopressin not only improved haemodynamics, but also demonstrated a ROSC advantage. Another study on an adult pig model of cardiac arrest showed repeated doses of vasopressin improved coronary perfusion pressure, improved the rate of successful defibrillation, and sixty minute survival rates when compared with adrenaline (Babbs, et al, 2000)

Combination of vasopressin and adrenaline

Some studies have looked at a combination of both adrenaline and vasopressin in the treatment of cardiac arrest. Simultaneous administration of the two drugs was thought to improve vital organ blood flow by targeting both adrenergic and non-adrenergic receptor sites. (Wenzel, et al, 1998)

As a result of this study it was thought that adrenaline may diminish the vasodilating effect of vasopressin on the cerebral blood flow due to the reduced perfusion observed when both were combined when compared to vasopressin alone. Vasopressin alone has been described as beneficial during CPR with regard to neurological outcome (Lindner, et al, 1996 and Lindner, et al, 1997)

It should be noted that one of the potential limitations of animal studies is that there are different vasopressin receptors in pigs (lysine vasopressin) and humans (arginine vasopressin) which may alter haemodynamic responses with exogenously administered arginine vasopressin. In addition to this, animal studies are conducted on healthy animals with healthy hearts and vasculature, whereas, in humans with pre-existing cardiac and vascular disease, similar results may not be seen.

Paediatric arrest

In paediatrics, vasopressin has been reported to exert vasopressor effects on children with vasodilatory shock, however no human studies on neonatal or paediatric cardiac arrest with vasopressin has been undertaken. One animal study compared the use of vasopressin Vs adrenaline Vs a combination of both drugs on a paediatric porcine model of asphyxial cardiac arrest. In this model, adrenaline was seen to be superior in improving myocardial blood flow and ROSC. (Voelckel, et al, 2000)

One possible explanation for these results, may be that the vasopressin receptor sites may not be fully developed in the piglets, as the blood pressure response of vasopressin was around 50% of that seen in adult pigs. Therefore, researchers continue to recommend the use of adrenaline for paediatric cardiac arrest, however, the optimal dose remains unclear.

Longer ½ life

Another potential downfall of vasopressin use could be the extended ½ life (10-20 minutes in intact circulation and around 5 mins under CPR) of the drug when compared to that of adrenaline. Hence the need to possibly reverse the vasoconstrictive effects of vasopressin once ROSC has been achieved, in order to prevent ischaemic injury.

One study comparing vasopressin with adrenaline identified that the vasopressin group had a higher aortic BP and increased systemic vascular resistance and worse cardiac function 15 minutes after resuscitation. (Hilwig, et al, 2000) On the upside of this, the long ½ life of vasopressin reduces the number of administrations in the pre-hospital arrest setting, although there is no real benefit, as drug administration is not overly time consuming.

Currently, there is no specific data relating to the 'ideal' dose, number of administrations or intervals between administrations of vasopressin. This itself, demonstrates that further studies are needed. The dose of vasopressin for cardiac arrest is the same for each route and can be given IV, intra-bronchially and intra-osseously.

Current use of vasopressin

The use of vasopressin has been acknowledged by the Emergency Cardiac Care Committee guidelines 2000 by the American Heart Association. The guidelines allow for the use of vasopressin, for the treatment of adult shock-refractory VF as an alternative to adrenaline. (Babbs, et al, 2000) They also recognize that vasopressin may also be effective, in patients with asystole or PEA, however recommend that further research is undertaken in this area.

The committee suggests a dose of 40u vasopressin, once only in the event of shock-refractory adult cardiac arrest following three initial defibrillations.

Wenzel et al, (1998) suggests that vasopressin may be the superior drug for successful defibrillation and that adrenaline may be carefully titrated to maintain pressures after ROSC.

A Canadian study which compared the effectiveness of adrenaline versus vasopressin on patients with in-hospital cardiac arrest, failed to identify any survival advantages of using vasopressin over adrenaline. The study involved 200 patients, and of those, 104 patients received vasopressin and 96 patients received adrenaline. (Stiell, et al, 2001)

A large-scale trial, is being planned by scientists at the University of Innsbruck, on the use of vasopressin vs. adrenaline for treatment of human cardiac arrest in the pre-hospital setting, the outcome of which may not be known for many years.

More recently, the Pittsburgh Business Times reported on 5th March 2003 that emergency medicine researchers from the University of Pittsburgh School of Medicine, in conjunction with city paramedics are embarking on a 1 year study to determine if the use of vasopressin will improve survival rates of out of hospital cardiac arrest. It is estimated that a total of 324 cardiac arrest patients will be enlisted in the study, and of those, half will receive vasopressin.

Cost is another issue, which puts limitations into ongoing studies on the use of vasopressin as an alternative to adrenaline. When you consider the cost of 1 ampoule of adrenaline is around 85 cents compared with 1 ampoule (20 units) of vasopressin is around \$70 retail

It should be noted that the major hospitals, in Adelaide, continue to use adrenaline as front line pharmacological intervention in the treatment of cardiac arrest.

SUMMARY

The survival outcomes of cardiac arrest are poor. Historically adrenaline has been used in the treatment of cardiac arrest for its α effects of peripheral vasoconstriction to promote vital organ perfusion. Unfortunately adrenaline, like many other pharmacological agents, targets other receptor sites which can have a detrimental effect on the patient in cardiac arrest.

Vasopressin is an endogenous hormone, which may be an ideal alternative to adrenaline in the setting of cardiac arrest. Vasopressin, like adrenaline, also promotes selective but potent vasoconstriction of smooth muscle, without the potentially harmful side effects of increasing myocardial workload and therefore increasing oxygen demand and subsequent worsening of cardiac function.

Many studies on the use of vasopressin in cardiac arrest have been undertaken with promising results. This has led to the recommendation of the use of vasopressin, as an alternative to

adrenaline in the treatment of adult shock-refractory VF cardiac arrest. Benefits of vasopressin have also been demonstrated in prolonged cardiac arrest, when mainstream drug therapy has failed.

These studies, are however, laced with limitations. The majority of studies have been conducted on healthy animal specimens, in controlled situations. In human situations, there are many variables, which need to be considered, that may affect outcomes.

Further human trials are required to identify relevant clinical indicators, not only in terms of ROSC but also long-term survival statistics and quality of life.

In paediatric animal studies, adrenaline has been shown to be more beneficial over vasopressin.

Cost is an inhibiting factor at current market values. A significant clinical benefit would need to be demonstrated to cost-justify the routine substitution of adrenaline with vasopressin in cardiac arrest.

RECOMMENDATIONS

Given the poor results yielded from traditional methods of treating cardiac arrest, I feel that it is important to investigate alternatives. As a result of my research, I feel that vasopressin possibly does have a place in the treatment of cardiac arrest in some circumstances, including shock refractory VF and in prolonged events of resuscitation, where appropriate.

Having said that, however, I believe that vasopressin may be more effective, if given early in cardiac arrest, prior to the onset of severe hypoxia.

Until further human studies are conducted demonstrating that patients have improved survival rates and improved post-arrest recovery, I am not able to recommend the implementation of vasopressin into SA Ambulance Service practice at this time.

I believe that more research is needed on the use of vasopressin, particularly in humans, to enable its full benefits as an alternative to adrenaline in cardiac arrest to be realized.

I also feel that the use of vasopressin as an alternative to adrenaline would be difficult to promote given adrenaline's historical use and acceptance in the setting of cardiac arrest.

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Additional Readings

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