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Review Article

Pharmacotherapy of cardiac arrest

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ABSTRACT

Cardiac arrest is the incapability of the heart to pump blood efficiently to essential organs of the frame consisting of lungs, brain, etc. ensuing in lack of cognizance and breathing. Cardiac arrest takes place whilst the coronary heart stops beating. Cardiac arrest is likewise referred to as cardiopulmonary arrest (CPA) or circulatory arrest. It is a main purpose of loss of life worldwide. Cardiac arrest isn't like coronary heart attack. Heart attack takes place whilst an artery wearing oxygen-rich blood to a selected vicinity of the coronary heart is blocked. This results in inadequate delivery of blood to that vicinity and might purpose everlasting harm if the blocked artery isn't reopened. Longer the affected person is going untreated extra may be the harm to coronary heart. Symptoms of coronary heart attack consist of soreness withinside the chest and different components of the higher frame, uneasiness, shortness of breath, +bloodless sweats, nausea and vomiting. In this review the pharmacotherapy of the cardiac arrest has been discussed.

1. Introduction

Cardiac arrest is the inability of the heart to pump blood effectively to vital organs of the body such as lungs, brain, etc. resulting in loss of consciousness and breathing. Cardiac arrest occurs when the heart stops beating. Cardiac arrest is also known as cardiopulmonary arrest (CPA) or circulatory arrest. It is a leading cause of death worldwide. Cardiac arrest is different from heart attack. Heart attack occurs when an artery carrying oxygen-rich blood to a particular region of the heart is blocked. This leads to insufficient supply of blood to that region and can cause permanent damage if the blocked artery is not reopened. Longer the patient goes untreated greater will be the damage to heart. Symptoms of heart attack include discomfort in the chest and other parts of the upper body, uneasiness, shortness of breath, cold sweats, nausea and vomiting. Symptoms of heart attack in women can be different from men. Whereas the latter, occurs due to electrical malfunction of the heart leading to irregular heartbeat (arrhythmia).[1] Death can occur within minutes if the patient is not treated immediately. Cardiac arrest is an electrical problem whereas heart attack is a circulation problem. Heart attack can lead to cardiac arrest. A person suffering from cardiac arrest should be immediately given Cardiopulmonory Resuscitation (CPR) followed by artificial defibrillator (prompt shock). CPR is done to restore spontaneous circulation. This should be followed by drugs to improve the circulation. The survival rate is usually 8-40%, out of which 50-75% have desired neurological outcome whereas 50% survivors show cognitive impairment.

Heart conditions that can lead to cardiac arrest are coronary artery disease, enlarged heart (cardiomyopathy), valvular heart disease, congenital heart disease, electrical

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problems in the heart. Factors that increase the risk of cardiac arrest are smoking, high blood pressure, family history of coronary heart disease, obesity, diabetes.

2. Treatment of Cardiac Arrest

Cardiac arrest is a major health problem with minimal prognosis.[2] Etiology of cardiac arrest could be asystole, pulseless electrical activity (PEA), pulseless ventricular tachycardia (VT), or ventricular fibrillation (VF).

In this paper we will see current pharmacotherapy for cardiopulmonary arrest, safety and efficacy of drugs used for the same. Most common treatment includes vassopressor drugs, antiarrythmics, and other drugs such as atropine, sodium carbonate, magnesium, corticosteroids.

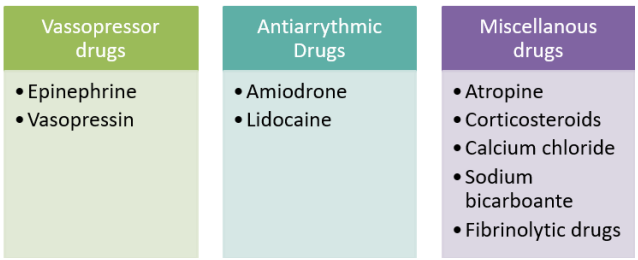

Fig. 1: Classification of drugs used in cardiac arrest.

2.1. Vassopressor drugs

Cardiac arrest is followed by cardiovascular collapse which means that blood flow to vital organs is reduced to zero.[3] CPR can restore this blood flow partially but cardiac output still remains low, about 20% of its normal value. The blood flow to heart is driven by coronary perfusion pressure. The coronary perfusion pressure is defined as the difference between the aortic diastolic pressure and left ventricular end diastolic pressure (LVEDP). This pressure should be maintained during CPR. In a study by Kern et al, it was found that pressure below 20 mm Hg after 20 min of CPR had poor rates of survival in dogs. Coronary perfusion should be higher than 20 mm Hg to increase the chances of survival after cardiac arrest. This was confirmed by a study by Paradis et al. It was found that patients with recovery of spontaneous circulation (ROSC) had higher coronary perfusion rates than that with no ROSC.

Vasopressor drugs have been found to increase aortic diastolic pressure and systemic vascular resistance (SVR) by peripheral vasoconstriction which leads to an increase in coronary perfusion pressure and facilitate ROSC. Also, during cardiac arrest, release of endogenous vasoconstrictors such as amphetamines is reduced. This justifies the use of vasopressor drugs during cardiac arrest. Epinephrine and vasopressin are the most common drugs using in cardiac arrest.[4]

2.1.1. Epinephrine

Epinephrine is also known as adrenaline and is a hormone secreted by medulla of adrenal glands. It is a nonselective agonist of all adrenergic receptors such as $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, and $\beta 3$. Epinephrine is known to increase cardiac output.[5] According to European Resuscitation Council (ERC) guidelines, epinephrine should be given at a dose of 1 mg in patients with pulseless electric activity. This should be repeated every 3-5 min during CPR because epinephrine has short half life of about 2-3 min.

Its action on α receptor causes vasoconstriction whereas on β receptor it causes vasodilation in heart and other vascular beds. Stimulation of α receptor activates phospholipase C pathway, release of IP3 and DAG and smooth muscle contraction. Stimulation of β receptor activates cAMP pathways leading to increased Ca^{2+}release and causing contraction (inotropic effect) in cardiac monocytes. Along with inotropic effect, positive chronotrpic (augmented heart rate) and dronotrpic effect (increased conduction) is also seen. The beneficial effect of epinephrine is due to its action on α receptor during CPR.[6] Its stimulatory effect on β receptor is deletorious and not desired because the heart is already not contracting and cardiac output depends on chest compression. Also this can increase myocardial oxygen consumption and cause an imbalance between oxygen supply and oxygen demand.

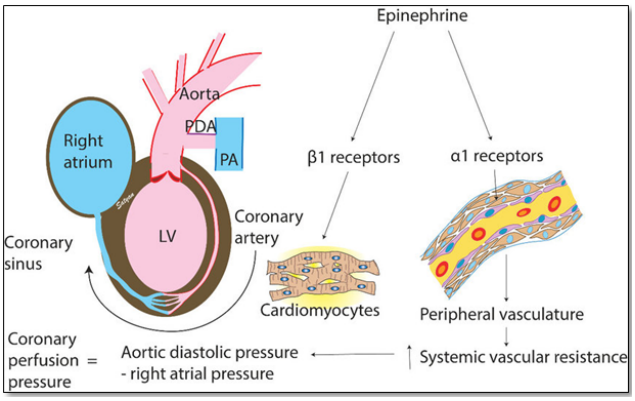

Fig. 2: Mechanism of action of epinephrine

A comparison of standard dose (1 mg) and high dose (15 mg) was done by meta-analysis of studies and it was found that high dose of adrenaline improved recovery of spontaneous circulation (ROSC) by increasing coronary perfusion pressure (CPP) but it worsened post resuscitation myocardial dysfunction. Therefore it was concluded that larger doses of epinephrine is not beneficial because it does not improve long term survival and cause early mortality as compared to standard dose of 1 mg.

2.1.2. *Vasopressin*

Vasopressin is an endogenous nonapeptide hormone having other names such as antidiuretic hormone (ADH), arginine vasopressin (AVP) or argipressin. It is synthesized in hypothalamus and secreted by posterior pituitary gland to maintain the tonicity of body fluids. It is released when atrial blood volume is reduced.

There are three types of vasopressin receptors varying in their location, function and signal transduction mechanism. They are classified as V_1, V_2, V_3. They are G-protien coupled receptors (GPCR).[7] V_1 receptors are located on smooth muscles such as cardiac myocytes, platelets, hepatocytes. They cause vasoconstriction by increasing intracellular Ca^{2+} via phospholipase C pathway. Besides vasoconstriction, V_1 receptor mediates functions such as platelet aggregation, uterine contraction, cardiac hypertrophy. V_2 receptors are found on distal convoluted tubule, vascular smooth muscles. It acts via cAMP pathway and has antidiuretic effect. V_3 receptors are located on anterior pituitary gland and regulate release of prolactin, ACTH and endorphins via PLC pathway.

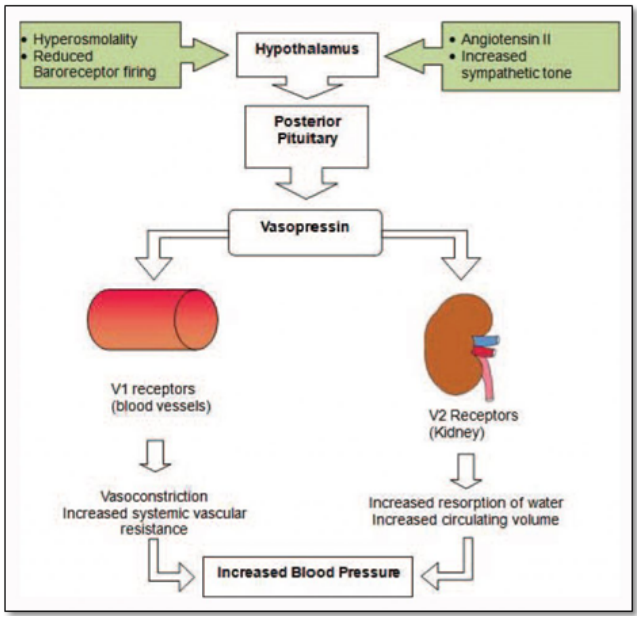

Fig. 3: Effect of vasopressin on heart and kidney

Vasopressin is considered to be an alternative to epinephrine because it was found that vasopressin concentration is higher in patients who were successfully resuscitated. The beneficial effects of vasopressin are mediated through V_1 receptors. The undesired β effects of epinephrine are not seen with vasopressin and therefore the risk of post resuscitation myocardial damage is reduced. The use of vasopressin during CPR was studied on animals and it was found that vasopressin increases blood flow to vital organs, improved cerebral and myocardial blood flow. When epinephrine and vasopressin is combined, coronary perfusion pressure is tripled versus adrenaline and vasopressin used alone. In human trials no benefit of vasopressin over epinephrine is observed. Based on multiple randomized clinical trials and meta-analysis studies it can be concluded that no major difference in the outcome such as ROSC, long-term survival, etc during CPR between vasopressin and epinephrine as first line therapy in cardiac arrest.[8] Moreover the half-life of vasopressin (15 min) is more than that of epinephrine (2-3 min).[8]

3. Antiarrythmic drugs

Antiarrythmics are commonly used during CPR for ventricular fibrillation or ventricular tachycardia (VF/VT). This class of drug exert their effect by blocking potassium, calcium and sodium channels present on cardiac myocytes. There are five phases of cardiac cycle during which there are multiple inward and outward flow of ions leading to generation of action potential specific to each phase of cardiac cycle. Antiarrythmics act on these channels altering the action potential and effective refractory period. Antiarrythmics that are commonly used in cardiac arrest are amiodarone, lignocaine, magnesium.

3.1. *Amiodarone*

Amiodarone is an antiarrythmic drug used to treat various cardiac arrhythmia. It is considered as first choice of treatment in patients with refractory ventricular fibrillation (VF), ventricular tachycardia (VT).[9] Ventricular fibrillation or pulseless ventricular tachycardia (VF/pVT) is considered to be refractory when the patient does not respond to three consecutive shocks.[10] Amiodarone comes under class III of Vaughan Williams classification of antiarrythmic drugs. Amiodarone blocks sodium, potassium calcium channels.[11] It also blocks α and β adrenergic receptors.[12] Amiodarone increases refractory action potential, and cause QT prolongation. It causes coronary artery vasodilation which leads hypotension and bradycardia, possible side effects of this class of drugs. The severity of theses side effects depend upon the infusion rate and solvent used in formulation such as benzyl alcohol and polysorbate 80. The side effects can be reduced by slow infusion and use of aqueous solvents. In a study in animals it was found that amiodarone co-administered with epinephrine improved cardiovascular haemodynamics. Amiodarone has a better survival rate when compared to placebo or lidocaine in out-of-hospital cardiac arrest (OHCA) proved in a double blind randomized clinical trial.

In the ARREST clinical trial, patients were given aniodarone (300 mg i.v. bolus) or placebo. 44% of patients treated with amiodarone survived as compared to 34% of patients treated with placebo.

In the ALIVE clinical trial, patients were randomly given amiodarone (5 mg/kg followed by 2.5 mg/kg of second dose

if required) and lidocaine (1.5 mg/kg). it was found that amiodarone treated patients had better survival of 23% as compared to lidocaine treated patients 12%.

4. Lidocaine

Lidocaine is also called as lignocaine popularly sold as xylocaine. It is a local anaesthetic and commonly used in ventricular tachycardia (VT). Lidocaine prolongs the inactivated fast voltage-gated sodium channels present on the membrane of neurons thereby preventing propogation of action potential. Due to this, the voltage-gated Na^+channel will remain closed and action potential will not be generated. This results in reduction of ventricular automaticity which is increased during cardiac arrest. Lidocaine is considered to be second choice of treatment for refractory ventricular fibrillation and pulseless ventricular tachycardia. Side-effects of lidocaine being paresthesia, hypotension, bradycardia, confusion, arrythmia. These side-effects are dose dependant.[13] It comes under class II b of antiarrythmic drug classification. The maximum tolerated dose of lidocaine is 3 mg/kg. Lidocaine is given when amiodarone is not available.

5. Magnesium Sulfate

Magnesium is an important cofactor for many enzymatic reactions. Extracellular magnesium is present in three forms namely albumin-bound, complexed to phosphate / sulphate and ionized form. Magnesium is a drug of choice for treatment of seizures in pregnant women referred as eclampsia. Magnesium is known to maintain heart's electrical system. Optimum concentration of magnesium is required to maintain cardiac rhythm and conduction. By virtue of these electrophysiological effects of magnesium has led to its utility in cardiac arrest. Magnesium is Na^+/K^+ channel agonist and calcium channel antagonist. It is found to prolong refractory action potential. Magnesium sulfate i.v. is used in torsades de pointes, ventricular tachycardia due to hypomagnesemia and digitalis toxicity. Reduced magnesium concentration is associated with increased risk of cardiac arrhythmia. It can be used in cardiac arrest due to its antiarrythmic action and calcium channel blocking activity leading to vasodilation and improved blood flow to heart.

In two animal studies it was found that when magnesium is given before cardiac arrest or hypoxia induced cardiac arrest resuscitation rate is improved from 15% to 100%. But this benefit of magnesium is not clinically proven in patients with cardiac arrest. In two randomized clinical trial with 2g of $MgSO_4$ and 2-4g of $MgSO_4$ was given to patients with refractory ventricular fibrillation. Both the studies failed to show any improvement in return of spontaneous circulation (ROSC). In a one more randomized clinical trial conducted at the emergency department on out-of-hospital cardiac arrest patients, 5 g of $MgSO_4$ infusion was given and compared to placebo treated patients and no difference in the survival rate of patients was found.

Therefore it can be concluded that the role of magnesium in cardiac arrest is poorly understood due to lack of evidence. No benefit is seen in out-of-hospital and in-hospital cardiac arrest patients. According to American Health Association guidelines, use of magnesium sulfate for cardiac arrest is not recommended.

5.1. Miscellaneous drugs

This class of drugs is used in certain conditions depending upon patients during cardiac arrest. There is no proof that these drugs will improve the rate of survival. Atropine, sodium bicarbonate, calcium chloride and fibrinolytic drugs come under this class.

5.2. Atropine sulfate

Atropine is an anticholinergic drug. It inhibits muscarine acetylcholine receptors (mAchR). Major use of atropine is in pesticide poisoning and to decrease production of saliva during surgery. It is also used in cardiac arrest but to a smaller extent. Atropine is cheap, safe and easy to administer drug.[14] It improves ventricular automaticity by blocking sinoatrial nerve and atrioventricular nerve thereby facilitating atrioventricular conduction. Atropine is commonly used for bradycardia and says asystole. Optimum dose of atropine is 0.6 mg- 3 mg i.v.[14]

According to the guidelines of CPR, routine use of atropine is not recommended. In the SOS KANTO study, it was found that atropine does not have any long-term neurological outcome in out-of-hospital cardiac arrest patients. Atropine is not beneficial to patients with pulseless electrical activity.[15] It's use in cardiac arrest could be due to its vagolytic effect to treat asystole and bradycardia. Common side-effects of atropine are dry mouth, constipation, tachycardia owing to its anticholinergic effects.[16] In multiple studies were carried out to see potential benefits of atropine during CPR, but none showed positive results. Few reports had shown short-term survival without any neurological outcomes in OHCA patients.[17] Hence, atropine is not included in ALS algorithm. Atropine when used alone does not have any neurological benefit but when combined with epinephrine has shown to have an additive effect. When atropine is administered along with epinephrine, it improve the rate of survival in non-shockable OHCA patients.

5.3. Corticosteroids

Corticosteroids are steriod hormones produced in adrenal cortex and also synthesized outside the body. Corticosteroids play an important role in many physiological processes such as immune response, stress,

etc. Some examples of corticosteroids are cortisol, cortisone, corticosteroids. The two most commonly used corticosteroids in cardiac arrest are methylprednisolone and hydrocortisone.

Glucocorticoids function in protein, carbohydrate and lipid metabolism. It is also involved in transfer of glucose during stress conditions. It also maintains electrolyte balance. Endothelial glycocalyx is composed of proteoglycans and glycoproteins. Vascular endothelial has a coating of this glycocalyx. Removal of this coating increases vascular permeability. It is found that glycocalyx plays an important role after cardiac arrest has occurred. This is called as post- cardiac arrest syndrome (PCAS). Also, the components of endothelial glycocalyx are increased significantly in serum post cardiac arrest. Corticosteroids acts on these components of glycocalyx and prevents it shedding.[18]

The level of cortisol is found to be reduced in patients with cardiac arrest or those who couldn't survive to cardiac arrest. This could be one of the reason for use of corticosteroids for treatment of cardiac arrest.[19] There have been various studies carried out to determine the potential benefits of administration of corticosteroids in the treatment of cardiac arrest. In a double-blind randomized clinical trial, the effect of corticosteroids on neurological outcome, survival rate, was studied alone and in conjunction with epinephrine and vasopressin. It was concluded that epinephrine combined with vasopressin and then supplemented with corticosteroids during or after CPR improved survival to hospital discharge, return of spontaneous circulation (ROSC) and favourable neurological outcome and hemodynamics as compared to when either of them given alone. Stress dose of hydrocortisone when given for post resuscitation shock also improved neurological status and survival for hospital discharge. In a pooled analysis it was found that triple therapy of epinephrine, vasopressin and glucocorticoid improved ROSC in in-hospital cardiac arrest patients.

Glucocorticoids act by inhibiting free radical lipid peroxidation, oxidative stress, myocardial apoptosis and reducing inflammation. It prevents breakdown of endothelial glycocalyx thereby providing protection and maintain heamodynamic stability.[18]

5.4. Calcium chloride

Calcium is an important ion and is involved in contraction of smooth muscles, skeletal muscles throughout the body. It is given in cardiac arrest to stabilize the contraction of cardiac muscles caused due to arrhythmia.[20] Calcium is found to improve myocardial contractions when epinephrine has failed. Along with cardiac contractions, calcium also maintains cardiac automaticity.[20] Calcium protects the heart from various metabolic conditions that lead to cardiac abnormalities which arise due to decreased potassium levels, decreased calcium levels or use of calcium-channel inhibitors. Calcium chloride is generally administered intravenously and it should be carefully administered because it carries the risk of tissue necrosis. The side-effects associated with the use of calcium chloride are increasing the acidity of blood and hypotension. So it should be cautiously given to patients whose blood pH is low. Hypotension is observed due to peripheral vasodilation. As seen with other drugs, there is lack of evidence on potential benefits of administration of calcium chloride during cardiac arrest. It is used when other drugs do not respond. It is not recommended to use calcium routinely.

5.5. Sodium bicarbonate

Sodium bicarbonate is also called as baking soda and is frequently used as an antacid, treatment of hyperkalemia and overdose of tricyclic antidepressants. In cardiac arrest, hypoxia leads to metabolic acidosis and impaired myocardial contractions. Previous studies suggest the use of sodium bicarbonate to overcome these effects, but routine use is not recommended because of severe side-effects such as respiratory acidosis, reduction in calcium levels, etc. In a double bind, randomized, placebo-controlled clinical trial, sodium bicarbonate was administered 50 mEq/L. This study was carried out to see whether sodium bicarbonate improves metabolic acidosis without increase in CO_2 burden, improves ROSC and neurological outcome. It was found that no significant difference was found in study and control groups, only 10% patients sustained ROSC and none of the patient survived more than 6 months. Hence, it can be concluded that sodium bicarbonate does not improve ROSC and does not have favourable neurological outcome and survival rate to hospital discharge is also minimum.'[21] According to recent guidelines by American Health Association (AHA) Guidelines, routine use of sodium bicarbonate is not recommended.

5.6. Fibrinolytic drugs

Fibrinolytic drugs are also called as thrombolytic drugs. This class of drugs are used to dissolve blood clots usually found in coronary, cerebral and pulmonary vessels. These blood clots lead to myocardial and pulmonary embolism contributing to myocardial infarction and heart failure. These drugs act by activating plasminogen that forms plasmin after breakdown. Plasmin is known to be a proteolytic enzyme breaking down fibrin which is structural component of blood clots. Therefore, fibrinolytic drugs are also called as plasminogen activators. During cardiac arrest, there is elevation in blood clotting factors leading to formation of microthrombi, which causes obstruction in blood circulation. Fibrinolytic drugs can dissolve these microthrombi and improve blood circulation in heart. Common thromobolytic drugs or plasminogen

activators used during pulmonary embolism and myocardial infarction are alteplase, retaplase and tenectplase. All of them are recombinant forms of tissue plasminogen activators. The use of fibrinolytic agents is associated with increased risk of hemorrhage which limits their use.[22] Thrombolytic treatment is considered in patients confirmed with pulmonary embolism. Routine use of fibrinolytic drugs is also not recommended.[23]

6. Conclusion

During cardiac arrest immediate use of cardiopulmonary resuscitation (CPR) followed by use of defibrillator is the choice of treatment for out-of-hospital as well as in-hospital patients. CPR is done to restore circulation and to maintain the circulation adjuvant therapy is required. This can be fulfilled by use of vasopressor drugs or antiarrythmics. Epinephrine is first-choice drug used during CPR. Arginine vasopressine can be considered alternative to epinephrine. Sodium bicarbonate should be given only when there is complete arterial blood gas analysis or when CPR has failed. Amiodarone can improve short term survival rate. Thrombolytic drugs should be considered only when it is confirmed that cardiac arrest is due to pulmonary embolism and myocardial infarction.

7. Source of Funding

None.

8. Conflict of Interest

None.

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