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Terlipressin in norepinephrine resistant hyperdemic shock post cardiac surgery

Thesis

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By

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Khaled Mohamed Abdelnaeem

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ACE	angiotensin-converting enzyme
AVP	Arginine Vasopressin
CABG	coronary artery bypass grafting
CI	cardiac index
CO	cardiac output
CVP	central venous pressure
ECMO	extracorporeal mechanical oxygenation device
HR	heart rate
IHD	ischemic heart disease
ITA	internal thoracic artery graft
LAD	left anterior descending artery
MAP	mean arterial pressure
OPCAB	of pump coronary artery bypass
PAOP	pulmonary artery occlusion pressure
PCI	Percutaneous coronary intervention
PVR	pulmonary vascular resistance
ROOBY	The Randomized On/Off Bypass
SAP	systolic arterial pressure
SIRS	systemic inflammatory response syndrome
STEMI	ST segment myocardial infarction
SV	stroke volume
TP	Terlipressin
VS	Vasoplegic syndrome

Introduction

Vasoplegic syndrome following cardiopulmonary by pass (CPB) is a relatively common and well-recognized syndrome. Several patient-dependent and procedure-related risk factors can predict the development of this syndrome. It usually affects about 5% of patients undergoing (CPB) and is associated with a mortality rate reaching 25% **(Mejia et al.,2017)**

Standard treatment options for severe refractory vasoplegic syndrome are extremely limited and include vasopressor support and systemic corticosteroids. Norepinephrine and phenylephrine are the most commonly used drugs to treat post cardiac surgery hypotension. However, catecholamine refractory vasoplegia can occur and has high morbidity and mortality rates. VP, methylene blue and terlipressin have been used to treat catecholamine-resistant vasoplegia, but more studies are needed to evaluate these drugs in the treatment of this complication **(Omar et al.,2015).**

In cardiac surgery patients, the use of CPB is associated with the release of inflammatory vasodilators and impairment of the arginine-vasopressin system that results in a decreased sensitivity to catecholamines and a hemodynamic state mimicking sepsis. Preoperative left ventricular dysfunction and the use of renin-angiotensin-aldosterone system (RAAS) inhibitors are associated with a higher incidence of postoperative vasoplegia in post-surgical patients. Patients with shock often have relative adrenal insufficiency, hyperglycemia and hypocalcemia (**Carel T et al .,2013)**

Norepinephrine is a potent α-1 agonist which is responsible for vasoconstriction more than β adrenoreceptors; therefore its main clinical effect would be increase in SVR and blood pressure. On the other hand, the cardiac output is often decreased or unchanged due to baroreceptor reflex through vagal activation **(Dabbagh *et al .,2018).***

Norepinephrine is recommended and is commonly used for treatment of hypotension in volume-resuscitated hyperdynamic septic shock, and is also used to correct hypotension in the vasodilatory shock syndrome after cardiac surgery with a cardiopulmonary bypass. Resistance to norepinephrine and other catecholamines may develop in vasodilatory shock. Adrenergic receptor downregulation as well as endogenous vasodilators may contribute to the diminished vascular responsiveness to norepinephrine **(Nygren et al.,2009) .**

Terlipressin (triglycyl lysine-vasopressin) is a synthetic analogue of vasopressin with a stronger selectivity for V1 vasopressin receptors and a longer half-life. The main clinical indication for terlipressin administration are hepatorenal syndrome and esophageal variceal bleeding. A limited number of randomized trials have investigated the role of terlipressin in the context of vasodilatory shock. Terlipressin can be more effective than vasopressin in improving hemodynamic parameters, however an excessive splanchnic vasoconstriction, decrease in cardiac output and oxygen delivery, especially following bolus injection, may be detrimental **(Belletti et al .,2015).**

Aim of Work

The aim of study is to evaluate the effectiveness of terlipressin given in bolus doses in management of refractory vasoplegic shock unresponsive to nor-epinephrine post cardiac surgery. As regard improvement of mean arterial blood pressure and subsequent vasoplegic shock state which was reflected on length of ICU stay

Complications and adverse effects of cardiac surgery :

The Randomized On/Off Bypass (ROOBY) trial showed that, among low-risk patients, the rate of death or major adverse events at 30 days after surgery was similar with off-pump and on-pump CABG, but off-pump CABG was associated with a higher rate of incomplete revascularization at 1 year ***(Mejia et al, 2017)***.

The early period after CABG is of crucial importance for long-term outcomes because many events with potentially unfavorable impact on late outcomes take place soon after surgery. For example, platelet or coagulation cascade activation, both of importance in promotion of early thrombus formation (i.e., major mechanism of early venous grafts failure), are also crucial early steps in vein graft intimal hyperplasia, venous wall pathology that predominates throughout the post-CABG follow-up period up to 1 year. Moreover, early adverse events after CABG have been linked to a significantly decreased late survival ***(Perek et al., 2016)***.

Manipulation of ascending aorta is one of the most important factors associated with embolism. Partial clamping of ascending aorta for anastomosing saphenous vein on aorta leads to create 28% of embolisms during operation. Acute renal failure occurs on more than 40% of patients and leads to dialysis in 1% of patients. Development of acute renal failure is associated with a rise in mortality risk, hospitalization period, need for further medications and increase in total cost. In post CABG patient several pathophysiological mechanisms are involved in the development of acute renal failure

Postoperative adverse events:

- **Prolonged use of inotropics (>12 h)** This refers to the use of use of epinephrine, norepinephrine, milrinone, amrinone, dobutamine, dopamine, levophed and/or levosimedan for > 12 h after surgery.
- **IABP** This refers to postoperative insertion of an intra-aortic balloon pump device.
- **ECMO** This refers to intra- or postoperative insertion of an extracorporeal mechanical oxygenation device.
- **Resternotomy for bleeding** This refers to any reoperation for hemostasis/removal of hematoma in presence of excessive bleeding with or without hemodynamic problem.
- **Resternotomy for hemodynamic problems**
- **Sternal and leg wound infections**
- **Postoperative atrial fibrillation**
- **Postoperative stroke**
- **Type 5 myocardial infarction** (CABG related MI <48hrs after procedure defined by elevation of cTn values >10 times of the 99th percentile URL in patients with normal baseline values)
- **Delirium**
- **Blood loss 12 h after surgery**
- **Hemoglobin and Hematocrit nadir during the operation day**
- **Acute kidney injury *(Biancari et al. 2015)***.

Over the past 20 years, there has been an increase in the incidence of vasoplegic syndrome, which affects more than 5% of patients undergoing cardiopulmonary bypass (CPB) and is associated with a mortality rate approaching 25%. Standard treatment options for severe refractory vasoplegic syndrome are extremely limited and include vasopressor support and systemic corticosteroids ***(Mehaffey et al,2017)***.

Cardiac surgery with cardiopulmonary bypass (CPB) leads to acute changes in the composition and volume of body fluid compartments. CPB dilutes serum proteins, decreases the plasma colloid osmotic pressure and reduces endothelial integrity. This causes fluid shifts from the intravascular to extravascular space and leads to a 33% increase in extravascular fluid space and tissue edema. Depending on the severity, inflammatory response can cause cerebral, myocardial, pulmonary and renal dysfunction ***(Mazandarani et al. 2012)***.

Arginine Vasopressin supplementation is safe in supporting patient hemodynamics while reducing the requirements and potential toxicities of high-dose catecholamines in the setting of septic shock. A similar pathophysiologic vasodilatory state (vasoplegia) complicates 10% of cardiac surgery patients after cardiopulmonary bypass (CPB). Retrospective and prospective studies examined the use AVP in this type of vasodilatory shock with varying results. Many surgical centers already routinely use AVP for the treatment of refractory vasodilatory shock; however, the data suggest that it can be used early and even routinely after CPB ***(Kunkes et al, 2019).***