Original Article

Role of Vasoactive Drugs in Surgical Patients with Septic Shock

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ABSTRACT

Objective: To assess the effect of vasoactive drugs in the management of septic shock in surgical patients.
Study Design: An Experimental Study.
Place and Duration of Study: Department of General Surgery, Fauji Foundation Hospital Rawalpindi from 1st August 2006 to July 31st 2007.
Patients and Methods: Ninety patients, both males and females were included in this study. All of these patients presented with acute abdomen and having signs and symptoms of generalized peritonitis. Patients were resuscitated and stabilized. Necessary routine investigations were carried out. Operation was done as early as possible. All patients had perforation of the gut with frank purulent fluid in the abdominal cavity or fecal peritonitis. Post operative management was carried out in intensive care unit. Daily progress with vitals were noted. These patients were visited by team of surgeons regularly till they died or discharged from the hospital.
Results: A total of ninety patients were included in this study who presented to the emergency department of Fauji Foundation Hospital. 55 % of the patients were females. Patients were divided into two groups. Group A patients were prescribed vasoactive drugs immediately post operatively with antibiotics, analgesics & IV fluids. Group B was managed exactly in the same way except no vasoactive drug was given as a routine. It has been observed that the mortality was lower in group A where vasoactive drugs were prescribed as routine in immediate post operative period. Patients respond well to vasoactive drugs when their pathology is dealt within 12 hours of the onset of symptoms and the vitals are stable. Those patients who presented after 12 hours and the vitals are deranged then the vasoactive drugs do not show significant favorable response.
Conclusion: In has been concluded in this study that there is more favorable outcome in septic shock patients with peritonitis if vasoactive drugs prescribed in early post operative period. Patients respond well to the vasoactive drugs in septic shock only when the patients report earlier and the primary pathology is dealt within 12 hours of onset of symptoms.
Key Words: Septic Shock, Peritonitis, Vasoactive Drugs.

INTRODUCTION

With a mortality rate near 20 %, septic shock rank first among the causes of death in intensive care units[1]. It accounts for 200,000 deaths each year in United States[2]. Currently septic shock is most frequently triggered by gram positive bacteria followed by gram negative bacteria & fungi[2]. In septic shock, systemic vasodilation & pooling of blood in the periphery leads to tissue hypoperfusion[1]. In later stage, there is decrease cardiac output also which further aggravate tissue ischemia. The ability of diverse microorganisms to cause septic shock even when the infection is localized to one area[3] is consistent with the idea that several microbial constituents can initiate the process of inflammation which result in systemic response. Once macrophages, neutrophils and other cells activated, there is release of inflammatory mediators as well as variety of immunosuppressive factors that modify host response. These mediators combine with the direct effect of microbial constituents on endothelium in a complex way to produce septic shock[4,5,6]. Upon activation, inflammatory cells produce TNF, IL-1, IFN-gamma, IL-12 & IL-18 as well as other mediators like high mobility group box 1 protien[7] (HMGB1) . The complement cascade is also activated by microbial components through the proteolytic activity of plasmin resulting in the production of anaphylotoxins (C3a, C5a) chemotactic fragments (C5a) & opsonins (C3b) that contribute to the pro- inflammatory state[8]. In addition, microbial components such as endotoxins can cause activation of coagulation directly through factor XII & indirectly by altering endothelial function which leads to micro & macro thrombosis in arterioles & capillaries throughout the circulatory system. On the other hand, production of endothelial anti coagulant factors like thrombomodulin & protien C are diminshed[5,6,9] . Septic patients exhibit hyperglycemia & insulin resistant state. Hyperglycemia decreases neutrophil function & which result in further increase in adhesiveness of endothelium[10].

Typically sepsis is manifested by a hyperdynamic state consisting of tachycardia, vasodilatation, decreased cardiac filling pressure, decreased systemic vascular resistance and increased cardiac output, the extreme end of which is adult respiratory syndrome. In this type of shock, tissue hypoxia is further aggravated because the tissue oxygen demand is extremely high and there is

direct impairment of oxygen uptake by the cells also. In addition the capillary wall of the sites of infection becomes leaky due to the endotoxins which later on become more generalized and allowing sodium and water to move from intravascular space to interstitial space and leading to hypovolumia. Warm septic shock occurs as endotoxins are released from strangulated intestine, ischemic peritonitis, leaking esophageal and intestinal anastomosis. It is worth mentioning here that an additional group of secreted bacterial protiens called superantigens also cause syndrome similar to septic shock known as toxic shock syndrome. There is release of high levels of cytokines result in a variety of clinical manifestations ranging from diffuse rash to vasodilation, hypotension & death[11].

The aim of this study was to determine the role of vasoactive drugs like epinephrine, nore epinephrine, ADH, and vasopressin in the management of septic shock due to perforation of the gut in surgical patients. Vasoactive therapy aimed at restoring perfusion and normalizing oxygen consumption. Goals of early resuscitation in patients with sepsis include restoration of tissue perfusion, reversal of oxygen supply and normalization of cellular metabolism. When appropriate fluid resuscitation fails to restore adequate perfusion and arterial pressure, vasopressors are usually necessary to increase mean systemic pressure, cardiac contractility and oxygen delivery. Although many of these agents have the ability to reduce organ flow through their vasoconstriction effect, their utility depends upon the balance between increased organ perfusion pressure and their direct effect on microvasculature. Thus the goal of vasopressor agents is to increase perfusion pressure to the point where flow is optimized. Catecholamine also possess positive ionotropic effects, which increases cardiac output and may be useful in patients with sepsis associated left ventricular dysfunction. Despite its greater vasoconstricting potential, end organ damage may be less prevalent in septic shocked patients treated with norepinephrine as compared with other vasopressors. In short norepinephrine improves systemic blood pressure and does not substantially worsen end organ ischemia in septic patients. Thus norepinephrine can be preferential to other catecholamine as first line therapy for septic shock.

PATIENTS AND METHODS

Written permission from the ethical committee & consent from the patients or their attendants was obtained. This descriptive study include ninety patients with gut perforation or strangulation presenting to the emergency department of Fauji Foundation Hospital Rawalpindi from 1st August 2006 to 31st July 2007. Thorough general examination & routine laboratory tests were carried out in emergency department.

Inclusion criteria:

Patients of either sex above 12 years and below 70 years with septic shock due to acute abdominal pathology were included in this study. Abdominal pathologies like perforation or strangulation of gut leading to peritonitis & septic shock were included. All other surgical pathologies leading to septic shock were excluded.

RESULTS

A total of ninety patients were included in this experimental study. All these patients presented in the emergency department of Fauji Foundation Hospital Rawalpindi with signs and symptoms of peritonitis. Patients were divided into two groups of forty five each. In group A, 24 patients out of 45 (53.3 %) were females & 21 patients were males (46.6 %) . 60% of the total patients were in their 4th and 5th decade of life and mean age of them was 44 years. 25 % of the patients was above 60 years old while 15 % are below the age of 30.

Table No.1: Showing sex distribution & time of presentation.

	Female	Male	Early presentation	Late presentation
Group 1	24	21	29	16
Group 2	27	18	26	19

In group A, 60 % 0f the total were those patients who had perforation of the gut including perforated duodenal ulcer, jejunal and ileal perforations secondary to enteric fever, tuberculosis of abdomen & biliary peritonitis. 29 patients who presented in the emergency department of the hospital within 12 hours of the onset of the symptoms and managed accordingly on merit. Surgical intervention carried out within 6 hours and patients put on vasoactive drugs immediately post operatively with antibiotics, analgesics & IV fluids.

Table No.2: Showing cause of acute abdomen.

	Group 1	Group 2
Perforation of gut	27	30
Anaestomotic leak	5	4
Primary peritonitis	1	1
Strangulated hernias	9	7
Biliary peritonitis	3	3

Group B was also managed in a similar way as far as the operative treatment is concerned except no vasoactive drug prescribed in the immediate post op period as routine. The mortality rate was double in group B where 12 patients died, 4 presented early & 8 presented late. Though all these patients were on dopamine & dobutamine before death but these medicines were given in the resuscitation phase with other measures. 6 out of 45 patients died in group A, all 6 presented late.

Table No.3: Showing % of death in different groups.

Group A. Total 45	Group B. Total 45
Early presentation 29	Early presentation 27
Late Presentation 16	Late Presentation 18
Deaths in early presentation= nil (0 %)	Deaths in early presentation=4 (14.8 %)
Deaths in late presentation=6 (37.5 %)	Deaths in late presentation=8 (44.4 %)

So we see from these results that patients with acute abdomen and in state of septicemia respond well to the effects of surgery and the use of vasoactive drugs effective only when the primary pathology is managed within 12 hours of the onset of symptoms of peritonitis. At the same time the role of vasoactive drugs can be seen reversing the effect of septicemia when instituted early and when the vitals are not deteriorated.

DISCUSSION

It is a common belief that vasoactive drugs can cause peripheral vasoconstriction which can theoretically worsen the effects of shock. Still lot of research is going on all over the world on the use of these medicines so as to find a way to bring the mortality rate down in septic shock patients to acceptable level. The reason is vasoactive drugs are the only group of medicine with proven efficacy in all type of shocks. Most of the intensivist agreed that there are significant risk factors for death among patients with acute renal failure in intensive care units. This need to be identified at an early stage in septic shock[12] & to treat it with the use of dopamine. Infections caused by Gram-negative bacteria constitute one of the major causes of septic shock, which results from the inability of the immune system to limit bacterial spread during the ongoing infection. In the last decade, it has been demonstrated that vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are two endogenous immunopeptides, which together with three G protein-coupled receptors (VPAC1, VPAC2, and PAC1) exert a significant, therapeutic effect attenuating the deleterious consequences of septic shock. There is involvement of PAC1 into the complexities of sepsis and represents an advantage for the design of more specific drugs complementing standard intensive care therapy in severe sepsis, confirming VIP and PACAP as candidates for multi target therapy of septic shock[13].

However different centers got preferences amongst the different medicines. According to Lodha R & his team, fluid refractory shock warrants use of vasoactive drugs. Dopamine is the first choice. Dobutamine and low dose epinephrine are the preferred inotropic drugs while nor-epinephrine is a vasopressor [14]. Another center in Eastern China is more in favor of dopamine and metaraminol. They proved that when dopamine and metaraminol given to the patients with septic shock could effectively maintain the circulatory stability and promote restoration of renal function[15]. Another study done by Nacul FE et. al. confirms the dissociation of the systemic hemodynamic and microvascular alterations in an experimental model of septic shock. Moreover, the results indicate that the use of dopamine, dobutamine, and dobutamine in combination with norepinephrine yields a protective effect on the microcirculation of the intestinal muscular layer in endotoxemic rats[16]. According to our study, if vasoactive drugs are used early, they are much more effective. Same is stated in Br J Pharmacol in 1985 that drugs interfering with complement activation and/or prostaglandin biosynthesis, may be beneficial in endotoxin shock, provided that they are administered at an early stage[17]. There are centers who got special preference of norepinephrine over other medicines & they proved that norepinephrine may not adversely affect the peripheral circulation. In short-term treatment of volume-resuscitation, severe septic shock complicated by pulmonary hypertension and impaired right ventricular performance, norepinephrine may be at least as effective as dopamine[18].

It is usually believed that there is a state of fluid resistant in septic shock. This is also true for children as well as for adults. However, there are some minor differences but role of vasoactive drus cannot be denied even in children & neonates. The hemodynamic patterns of fluid-resistant septic shock by the time children present to the PICU are distinct, depending on cause, with little overlap. If these findings are identified, then target it with the choice of first-line vasoactive infusions in fluid-resistant shock[19].

At the moment, there are lot of other medicines also under clinical trial with the aim to correct the pathophysiology of septic shock like PMX-F, Polymyxin B, ethyl pyruvate e.t.c. Based on this critical review of the published literature, direct hemoperfusion with PMX-F appears to have favorable effects on MAP, dopamine use, PaO2/FiO2 ratio, and mortality[20]. Wang Z & his colleagues proved in an experimental model that in septic shock in ewes, continuous Ethyl Pyruvate infusion in anaesthetized sheeps prolonged time to development of organ dysfunction and markedly prolonged survival. These findings suggest a potential use for EP in the treatment of severe sepsis and septic shock due to fecal peritonitis[21].

Tissue hypoxia, especially in the splanchnic area, is still considered to be an important cofactor in the pathogenesis of multiple organ failure. Therefore, the specific effects of the various therapeutic interventions on splanchnic perfusion and oxygenation are of particular interest. Restoring and maintaining oxygen transport and tissue oxygenation is the most important step in the supportive treatment of patients with sepsis and impaired gut perfusion. Therefore, supportive

treatment should be focused on an adequate volume resuscitation and appropriate use of vasoactive drugs[22].

CONCLUSION

We can conclude that in septic shock, administration of norepinephrine at a low dose should increase the chances of survival but until the results of more randomized trials are available, it should not be routinely used in septicemic patients. We also conclude from this study that vasoactive drugs are more effective if used in septicemic surgical patients within 12 hours of onset of signs and symptoms of peritonitis.

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