DOES TERLIPRESSIN ACETATE REDUCE THE COMPLICATIONS OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME ?

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Systemic Inflammatory Response Syndrome (SIRS) which may be seen after cardiopulmonary bypass is associated with systemic hypotension and decreased systemic vascular resistance (SVR) resistant to vasopressor therapy. We investigated the effects of terlipressin acetate (TA) in prophylaxis of SIRS.

Thirty patients who were considered to have the risk of SIRS were divided into two groups randomly. In the control group (group I, n=15 patients) standard cardiopulmonary bypass procedures were done. Additionally in study group (group II, n= 15 patients) 5 mg/kg IV terlipressin acetate was administered preoperatively and half of the initial dose TA (2.5 mg/kg/ h) continously infused. SVR, cardiac index, systolic mean arterial pressure (SAP) values were measured perioperatively. Also TNF-a, IL-6, IL-8 and arginin- vasopressin levels were measured.

Preoperative mean SVR was 957± 38 dynes/sec/cm-5, cardiac index was 3.7± 0.21 lt/min/m^2 and SAP was 109.6 ± 6.7 mmHg in group I and consecutively 953± 37 dynes/sec/cm-5, 3.6± 0.24 lt/min/m^2 and 108.7 ± 6.9 mmHg in group II ($p>0.05$). Contrary to group I (67± 8 mmHg) no significant decrease in SAP was occured in group II (98± 5 mmHg) while weaning from CPB ($p=0.0001$) SVR was significantly decreased to 574± 32 mmHg at postoperative$_{\frac{1}{2}}$ th hour in group I, but no significant decrease was observed in group II. The necessity of inotropic support and IABP were significantly different between two groups. TNF-a levels peaked at postoperative$_{\frac{1}{2}}$ th hour, IL-6 and IL-8 peaked at the 3rd hour in group I but slight increases were occured in group II ($p<0.0001$).

SIRS is a rare but dramatic complication after cardiopulmonary bypass. We suggest that prophylactic administration of terlipressin acetate reduces cathecolamine pressor requirements and increases MAP without decreasing SVR and Cardiac index.

Key words: Systemic inflammatory response syndrome (SIRS), Terlipressin acetate

Since 1955, cardiopulmonary bypass (CPB) has been a widely used technique for the cardiac surgery. Lots of complications may occur during the CPB by using pump oxygenators. CPB have various types of damaging effects

on the human being. In the early 1980's Kirklin et al first described the damaging effects of the complements (1). Various types of factors (hypotermia, surgical trauma, ischemia- reperfusion) which may induce complex inflammatory responses including the release of cytokines, and the complement activation called systemic inflammatory response syndrome (SIRS). SIRS is associated with increased cardiac index and reduced systemic vascular resistance. This massive inflammatory response induces multiple organ failure.

The aim of this study was to clarify the importance of SIRS after cardiac surgery in patients who have risk factors and the effects of terlipressin acetate in the prophylaxis of SIRS.

MATERIAL AND METHODS

Thirty patients who were considered to have the risk of SIRS (severe left ventricular dysfunction, cerebrovascular disease, history of long term calcium channel bloker intake or ACE inhibitors, severe cachexia, insülin dependent diabetes mellitus, acute heart failure and renal failure) were divided into two groups randomly. There were 10 males in group I and the mean age was 59.4±8 years. In group II, 11 males and the mean age was 60.7±8 years. 11 patients in group I and 12 patients in group II had history of smoking. 4 patients in group I and 3 patients in group II had chronic hypertension. ECG revealed chronic MI in 5 patients in group I and 6 patients in group II. Two patients in each group had coronary artery disease (CAD) combined with cerebrovascular disease. Seven patients in group I and 8 patients in group II had severe left ventricular dysfunction (Table I).

Dideco (D 708 simplex III) adult type hollow fiber membrane oxygenator and heparin coated tubing set were used for the bypass circuit. In both groups routine CPB protocols such as; CI: 2lt/min (at 28-30°C) with non-pulsatile flow, mean perfusion pressure: 55-65 mmHg, heparinazation with 4mg/kg dose) were done. Sarns Delphin II centrifugal pump was used in all patients and during thermoexchange period a-stat strategy were followed. Additionally in group II (study group, n=15 patients) single dose 5 mg/kg IV prophylactic terlipressin acetate was administered just before CPB and half of the initial dose (2.5 mg/kg/h) were infused for consecutive 4 hours. Cardiopulmonary bypass was initiated with a temperature of 28 C. Antegrade St. Thomas II cardioplegia was infused with topical iced saline slush simultaneously with the dose of 10 ml/kg and repeated every 20 minutes with the half of initial dose.

Routine blood, tumor necrosis factor-a (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8) samples were taken preoperatively. DPC Immulite immunanalyser techniques were applied to determine TNF-α, IL-6, IL-8 (Diagnostic Products Corporation, Los Angeles, USA). Blood samples were taken at postoperatively 1 , 3, 6,12, 24 and 48 hours consecutively to detect TNF-α, IL-6, IL-8 concentrations and also plasma arginin-vasopressin (AVP) concentrations were measured at the preoperative and postoperative period by Correlate-EIA arg8-Vasopressin Enzyme Immunassay Kit (Assay Designs, Inc, Ann Arbor, Michigan, USA). Anesthesia was induced with midazolam and fentanyl. After induction of anesthesia, termodilution catheter (Biosensor International, Model TD 1504 HX, Singapore)

Table 1. Preoperative characteristics of the patients.

	Group I (n=15)	Group II (n=15)	P value
Mean age(year)	59.4±8	60.7±8	NS
Sex(M/F)	10/5	11/4	NS
Hx of smoking	11	12	NS
Hypertension	4	3	NS
Chronic MI	5	6	NS
LMCA disease	3	3	NS
Hypertension + LMCA disease	-	1	NS
Hx of long term Ca++ channel bloker intake	4	5	NS
Severe left ventricular dysfunction	7	8	NS
Severe cachexia	1	-	NS
Insulin dependent DM	-	1	NS
CAD+ cerebrovascular disease	1	1	NS
Insulin dependent DM + CAD + cerebrovascular disease	1	1	NS

Table 2. Preoperative values of the patients.

	Group I	Group II	P value
CI (lt/min/m2)	3.7± 0.21	3.6± 0.24	NS
SVR (dynes/sec/cm-5)	957± 38	953± 37	NS
SAP(mmHg)	109.6 ± 6.7	108.7 ± 6.9	NS

was inserted through internal jugular vein and the cardiac index (CI), the systemic vascular resistance (SVR) and systolic arterial pressure (SAP) values were analyzed preoperatively (Table II). Also SVR, CI datas were repeated at postoperative ½, 3, 6, 12, 24, and 48 hours. Cardiac output was measured by Gould Statham SP1435 apparatus. SAP was observed by Hewlett Packard MP 1166A Model 68S monitoring system continuously. Prophylactic single dose Terlipressin acetate (2mg/kg IV) was administered to group II patients just before cardiopulmonary bypass. Daily urine output was measured in two groups.

Datas were analyzed with the use of SPSS 9.05 for Windows. All datas are expressed as mean±SD. All datas for the 2 groups were compared by Mann Whitney U test. Regarding the categorical data, the comparison between the groups was performed with the Fisher's exact test.

RESULTS

No significant differences were observed between the two groups in aortic cross clamp time and perfusion times. Number of grafts used in aortocoronary bypass are similar in both groups (Table 3). During CPB; SVR was decreased to 568± 34 dynes/sec/cm-5 in group I whereas it was stable in group II patients. MAP also decrased to 45± 3 mmHg in group I but 59± 4 in group II (during aortic cross clamp). During the weaning period, 11 patients in group I required therapeutic inotropic support (> 10 μg. kg-1. min-1 of dopamine and 3 μg. min-1 of adrenalin) in order to increase the SVR and the MAP and in six of eleven patients intraaortic balloon counterpulsation (IABP) was necessary. Daily urine output was similar in two groups (p=0.560). One of the patients (with severe left ventricular dysfunction who required inotropic support in group I) died at the postoperative 39th hour due to the left ventricular dysfunction.

Systolic arterial pressure (SAP) was the significantly decreased to 67± 8 mmHg at the postoperative 1th hour. In spite of the inotropic agents (> 10 μg. kg-1. min-1 of dopamine and 3 μg. min-1 of adrenalin), no improvement was observed until the postoperative 1st hour (71± 6 mmHg), then high dose terlipressin acetate (10-15 mg/kg/h) was begun to be infused and SAP tended to increase at the postoperative 2nd hour (p=0.0001). Observing the increase of SAP at the postoperative 2nd hour, low dose terlipressin was infused (2.5 mg/kg/h) till the postoperative 12th hour. Contrary to group I no significant decrease was occured in group II (Fig I). CI was significantly increased to 5.2 ± 0.32 lt/min/m^2 at postoperative 1 hour in group I. After the infusion of Terlipressin acetate CI was decreased to 4.7±0.24

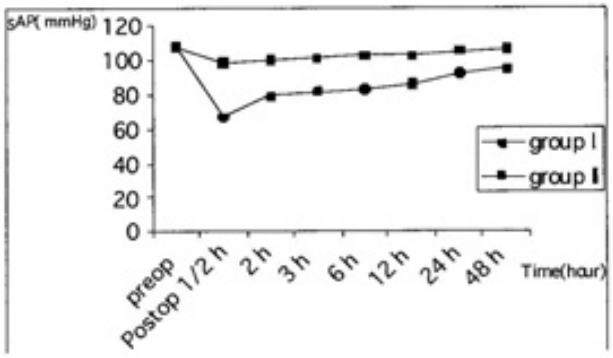

Fig 1. Systolic arterial pressure in group I and group II.

Table 3. Peroperative characteristics of patients.

	Group I	Group II	P value
Cross clamp time(min)	78±7	81±8	NS
Perfusion time(min)	91.3±14	88.5±11	NS
No of grafts	3.2±0.3	3.4±0.3	NS
Operation			
CABG*	9	8	NS
CABG+MVR*	1	2	NS
AVR*	1	2	NS
CABG+LVA*	1	1	NS
Inotropic support	11	2	0.001*
IABP	6	-	0.013**
Date of ICU	4.75±0.6	2.3±0.3	0.0001
Date of discharge	13.9±0.3	8.15±0.4	0.0001
Urine output (ml/24 h)	1752±470	1797±450	0.560
Early exitus	1	-	0.473**

CABG: Coronary artery bypass grafting MVR: Mitral valve replacement AVR: Aortic valve replacement LVA: Left venricular aneurysmectomy

* Categorical data, the comparison between the groups was performed with Chi-square test

**Categorical data, the comparison between the groups was performed with Fisher's exact test.

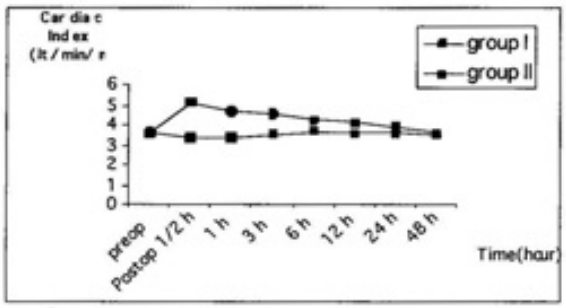

Fig 2. Preoperative and postopreative Cardiac index values in group I and group II.

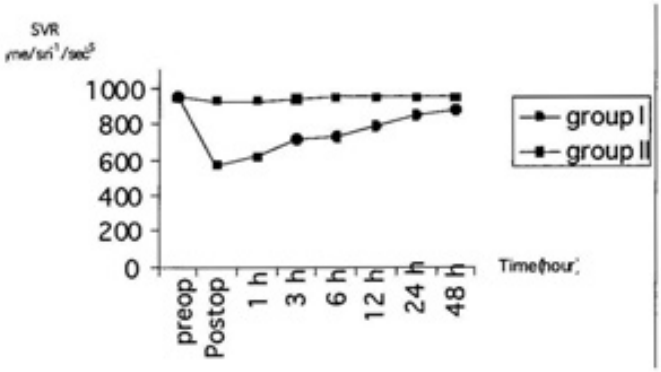

Fig.3. Preoperative and postoperative systemic vascular resistance differences in two groups.

lt/min/m2 at 2nd hour, 4.6±0.22 lt/min/m^2 at 3rd hour 4.3±0.27 lt/min/m2 at 6th hour, 4.1±0.26 lt/min/m^2 at 12th hour, 3.9±0.22 lt/min/m^2 at 24th and 3.9±0.23 lt/min/m2 at 48th hour whereas preoperative CI (3.6±0.24 lt/min/m^2) was stable at postoperative period in group II (Fig 2). Preoperative SVR was significantly decreased to 574± 32 mmHg at the postoperative 1th hour and 607± 29 mmHg at the postoperative 1st hour in group I whereas stable in group II during the early period (p=0.0001). SVR began to increase at the postoperative 3rd hour after the infusion of terlipressin acetate in group I (Fig 3).

There was no significant differences between two groups in pulmoner vascular resistances (PVR) during the perioperative period. Preoperative mean PVR was 183± 32 dynes/sec/cm-5 in group I and 192 ± 28 dynes/sec/cm-5 in group II. During the postoperative initial 24 hours the mean PVR was measured and no significant difference was observed between the two groups (178±37 dynes/sec/cm-5 in group I and 186 ± 34 dynes/sec/cm-5 in group II).

Blood samples (TNF-a, IL-6 and IL-8) were analyzed perioperatively and 1 , 3, 6,12, 24, 48 and 72 hours after CPB consecutively. Tumor necrosis factor-a (TNF-a); significantly peaked at postoperative 1th hours in group I and returned to normal at the 6th hour. Contrary to group I, no significant increase was observed in group II (p=0.0001) (Table 4).

Preoperative IL-6 levels were similar in two groups (p=0.891). IL-6 was reached its peak level at the postopreative 1 hour whether the peak level was higher in group I than group II. The level tended to decrease at the postoperative 3rd hour and at postoperative 6th hour, the level was decreased to half of its peak level.

Correlate-EIA arg8-Vasopressinn Enzyme Immunassay Kit was used to determine preoperative and postoperative (at 1st hour) AVP concentration in both groups. Preoperative mean AVP concentrations were 6.1± 0.4 pg/ml in group I and 5.9 ± 0.6 pg/ml in group II(p=0.551). At the postoperative 1st hour plasma AVP samples were repeated and mean AVP concentrations were significantly different between two groups (postoperative mean AVP concentration was 7.1±0.6 pg/ml in group I and 24.9± 1.2 pg/ml in group II) (p=0.0001).

COMMENT

Systemic Inflammatory Response Syndrome

Table 4. TNF-a, IL-6, IL-8 levels of two groups

	TNF-a (pg/ml)		P value	IL-6(pg/ml)		P value	IL-8(pg/ml)		P value
Group	**I**	**II**		**I**	**II**		**I**	**II**	
Preop	4.1±0.38	4.4±0.65	0.317	7.3±0.98	7.4±0.87	0.891	41.9±5.43	46.3±3.77	0.027
Postopreative									
_ h	13.9±2.23	5.4±1.26	0.0001	9.1±1.50	13.3±1.93	0.0001	56.8±5.11	52±3.44	0.010
3 h	13.7±1.49	5.1±0.80	0.0001	33.7±3.50	13.6±1.75	0.0001	103±11.3	61±7.64	0.0001
6 h	8.9±1.24	4.9±0.75	0.0001	28.2±5.67	9.2±1.83	0.0001	85±6.45	51±3.83	0.0001
12 h	5.25±1.21	4.69±0.85	0.195	15.8±3.32	8.3±1.43	0.0001	63±11.64	49±3.42	0.002
24 h	4.75±0.96	4.53±0.77	0.550	9.66±2.57	7.92±1.50	0.056	51.9±4.42	48±3.46	0.022
48 h	4.33±0.77	4.46±0.77	0.684	7.66±2.38	7.61±1.55	0.949	45.5±5.68	47.7±3.11	0.430

(SIRS) is one of the most serious complications of CPB. James K. Kirklin and his colleagues first described the damaging effects of complements during cardiopulmonary bypass about two decades ago (1) but the knowledge of the reason was unclear until one decades ago. Systemic Inflammatory Response Syndrome was first described by Society of Critical Care Medicine and the American College of Chest Physicians during the conferense with the definition of: "The response to a variety of severe clinical insults (either infectious or non-infectious) such as temperature >38° or <36° C, heart rate >90 beats/min, respiratory rate > 20 breaths/min, pCO_2 < 32 mmHg, white cell count > 12,000/mm^3 or < 4,000/mm^3, or > 10% immature forms (2-4). During CPB, endotoxins, ischemia-reperfusion cascade, complement activation cascade activates and these all stimulate cytokines to induce cellular activation, so oxygen free radicals, nitric oxide, endothelins increase vascular permeability and may cause tissue injury and multiple organ failure (5). During CPB the release of endotoxins induces the release of cytoxines from various types of cells including activated monocytes, tissue macrophages, lymphocytes and endothelial cells (6). According to Bone SIRS develops in three stages. In stage I cytokines are produced in response to injury or infection. In stage II cytokines are released into the circulation to evoke acute phase response but it is not pathological. Macrophages and platelets are recruited and growth factor production is stimulated. At normal conditions the wound is healed and homeostasis is restored. In stage III, if homeostasis is not restored, massive systemic reaction begins. Cytokines become destructive. Cytokines spill out into the distant organs and multiple organ dyfunction and death occur (7). Decrease of systemic vascular resistance occurs due to vascular permeability changes and systemic vasodilation. The mediator response can be divided into four phases such as induction, stimulation of cytokine synthesis, occurence of cytokine cascade and cellular injury (8). Tumor necrosis factor-a (TNF-∝), IL-1, IL-6 and IL-8 are the most known cytokines which may cause SIRS during cardiopulmonary bypass. So many observations has been done for the levels, effects of cytokines during cardiopulmonary bypass. Some authors suggest that cytokines are elevated during the early period of cardiopulmonay bypass. Mc Bride et al. suggested that TNF-∝, IL-1 were elevated during the early postoperative period and IL-6, IL-8 elevating later(9) and also Menasché et al observed the increased levels of cytokines (10) whereas some authors observed slightly increased levels of cytokines or increases in some cytokines. Steinberg measured the levels of TNF-∝, IL-1,IL-2, IL-4 and IL-6 levels during CPB and observed no significant increases excluding IL-6 (11). Frering et al observed only IL-6 and IL-8 elevations (12). Some factors influences the extent of SIRS during CPB. Left ventricular dysfunction (13) and long term insulin dependent diabetes mellitus (14) are the most known preoperative causes that may cause SIRS. Hemodynamic instability is one of the factors that may cause to SIRS during the perioperative period (15). Additionally heart-lung transplantation and long term ischemia time induce SIRS (16). Shear stress can activate SIRS by increasing hemolysis (17). Normotermic cardiopulmonary bypass also stimulates SIRS (18).

Owing to its importance of mortality and morbidity many authors tried various types of experiments to prevent or manage SIRS. Heparin coated circuits, hemofiltration, leukocyte depletion by leukocyte-spesific filters were tried to prevent the risk factors of SIRS. According to Bidstrup et al and Levi et al high dose aprotinin reduces the blood loss and blood use, thus suppresses the inflammatory response (19-20). Besides the effect of reducing the blood loss Wachtfogel et al studied the antiinflammatory effects and decreasing of complement activation with aprotinin (21). Pentoxifylline which is a phosphodiesterase inhibitor was studied by several authors to determine the effects of inhibition of TNF-∝, reduction of endotoxin and cytokine activation. Jansen et al and Andersen et al studied the inhibitory effects of corticosteroids on endotoxemia and reperfusion phenomena during CPB (22-23).

In the recent years, endopeptidase (protease) inhibitors were used to reduce the myocardial injury during cardiopulmonary bypass (24).

Terlipressin acetate is a synthetic analogue of vasopressin that is metabolized into vasopressin in vivo slowly. Thus lower vasopressin levels and reduced cardiotoxicity or vasoconstriction are occured. The pressor and antidiuretic effects of terlipressin acetate are lower than arginine vasopressin and also the side effects of terlipressin are lower. Abdominal discomfort or pain, headache may have been seen. Terlipressin acetate can be used in portal hypertension, acute esophageal variceal hemorhage, cirrhosis. In our study single dose 2mg/kg IV prophylactic terlipressin acetate was administered just before CPB to the study group patients who were under the risk of systemic inflammatory response syndrome (severe left ventricular dysfunction, cerebrovascular disease, long term calcium channel bloker intake, severe cachexia). Considering the side effects of terlipressin acetate the patients with insulin dependent diabetes mellitus, acute infection, renal failure, acute cardiac failure were excluded from the study. There was a decrease in SVR and SAP without any decrease of CI. When compared to group I patients there was no elevation of TNF-$\propto$, IL-6,IL-8, levels. No complications related to terlipressin administration were observed.

As a result; in spite of many advances in technology and pharmacolgy the occurence of SIRS is not prevented completely . The reason, prevention and the treatment of SIRS is still contreversial. Heparin coated circuits, hypotermic cardiopulmonary bypass, warm blod cardioplegia, hemofiltration, leukocyte depletion filters can be used to reduce the occurence of SIRS. SIRS is a rare seen but dramatic complication after cardiopulmonary bypass due to vasopressin deficiency. We suggest that prophylactic administration of terlipressin acetate reduces cathecolamine pressor requirements and increases MAP without decreasing SVR and cardiac index and can be used in patients under the risks of SIRS effectively.

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