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Release of Neopterin, PMN Elastase and Terminal Complement Complexes by Orthotopic Liver Transplantation with and without the Use of Veno-venous Bypass

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Summary

Aim: The aim of the study was to determine whether orthotopic liver transplantation leads to the activation of macrophages, neutrophils and complement.
Patients and methods: Twenty-four patients undergoing orthotopic liver transplantation were studied. 12 were operated on with and 12 without the use of a veno-venous bypass. Blood samples for neopterin, PMN elastase and terminal complement complex (SC5b-9) determinations were drawn preoperatively, 1 minute before perfusion of the grafted liver and 2-5 and 30-60 minutes after the start of perfusion of the grafted liver. Comparisons were made between patients with or withour a veno-venous bypass and with or without postreperfusion syndrome (PRS). PRS was defined as hypotension with $\geq 30\%$ reduction of systemic mean arterial blood pressure during at least 1 minute after reperfusion of the grafted liver.
Results: Release of neopterin was observed 2-5 and 30-60 minutes after the start of perfusion of the grafted liver in patients operated upon with and without the use of a veno-venous bypass. There were no significant differences in neopterin concentration between patients developing PRS and those without circulatory instability. Increased PMN elastase and SC5b-9 concentrations ($p<0.05$) were found 2-5 and 30-60 minutes after the start of reperfusion in both patients operated upon with and without a veno-venous bypass. The plasma concentrations of neopterin, PMN elastase and SC5b-9 were higher in patients with PRS compared with those without ($p<0.05$, respectively).
Comments: This study indicates that orthotopic liver transplantation leads to the activation of macrophages, neutrophils and the complement cascade. There is no major difference regarding the activation between patients operated upon with and without the use of a veno-venous bypass.

Key words: Complement activation, Elastase, Extracorporeal circulation, Liver transplantation, Pteridines, Terminal complement complex

Introduction

Orthotopic liver transplantation is often associated with circulatory instability (postreperfusion syndrome) in association with reperfusion of the grafted liver and with the development of a systemic inflammatory response syndrome (1,2,3). The etiology behind these complications may be activation of macrophages, polymorphonuclear neutrophil granulocytes and the complement system (4). Patients undergoing orthotopic liver transplantation with postoperative

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multiple organ failure have a longer hospital stay and higher mortality than patients without postoperative multiple organ failure (5).

During orthotopic liver transplantation recipient hepatectomy and implantation of the liver graft is performed during the anhepatic phase. The anhepatic phase is initiated by clamping of the portal vein and the suprahepatic and infrahepatic inferior caval vein, leading to congestion of the mesenteric and lower body venous circulation. The use of a veno-venous bypass technique during the anhepatic phase has been suggested for abdominal and lower extremity venous decompression, improved haemodynamic stability and decreased intraoperative blood loss (6). However, the use of veno-venous bypass during the anhepatic phase does not result in normal perfusion of the abdomen and lower extremities, probably because of inadequate venous return to the bypass pump (6).

The immune system is composed of both humoral and cellular factors. The main function of the immune system is to protect its host from both pathogenic (i.e. virus, bacteria and foreign material) and neoplastic invasion. The humoral factors comprise the antibodies and the complement system, while the cellular factors comprise the lymphocytes and the phagocytes (7). These immunological factors remain in a relatively unactivated stage until activated by foreign molecules. Activation of the immunological system during normal conditions is beneficial to the host. In organ transplantation, septic, multiple traumatised, or critically ill surgical patients, the host response to stress is more extensive and, as a result, the extensively activated immunological factors could create complications in the host like the adult respiratory distress syndrome (ARDS) and multiple organ dysfunction (MOF) (8,9,10).

The phagocytes include polymorphonuclear phagocytes (neutrophils), eosinophils and basophils. The polymorphonuclear leukocytes play a key role in the non-specific inflammatory mechanisms. Organ transplantation, extracorporeal circulation, septic situations and trauma lead to a variety of immunological disorders (8,9,10). If the surgical trauma or the septic event is large enough, complications like organ dysfunction, multisystem organ failure or adult respiratory distress syndrome may ensue. The polymorphonuclear leukocytes serve for recognition, ingestion and killing of invading micro-organisms or transplanted tissue. Important cells in the inflammatory response are the phagocyte cells. The non-specific host defence mechanism leads to phagocytosis and intracellular killing of invading organisms. Phagocyte cells are able to recognise and eliminate invading organisms, injured tissue or non-compatible tissue. They are also able to release substances which will further stimulate the inflammatory response. Such substances are the lysosomal enzymes, free oxygen radicals, histamine and cytokines (11,12,13).

Human monocytes and macrophages release neopterin when activated, a mechanism believed to be dependent on stimulation with interferon-gamma from activated T-lymphocytes (14). Neopterin is a pyrazinopyrimidine compound which is biosynthesised from guanosine triphosphate and involved in the pathway of tetrahydrobiopterin, the coenzyme of the enzymatic hydroxylations of phenylalanine, tyrosine and tryptophan (15). Increased urinary neopterin excretion has been demonstrated in patients with diseases in which the cellular immune response is known to participate, e.g. viral and bacterial infections, acute cellular graft rejection and acquired immune deficiency syndrome (16). High levels of neopterin in serum and urine from patients with various malignancies such as multiple myeloma, cervical cancer, ovarian cancer, prostate and hepatocellular carcinoma have been demonstrated (17).

Complement split products are important in the chemotactic and in the opsonisation response. Opsonisation is a process whereby the foreign tissue or invading micro-organism is coated with immunoglobulins or complement split products. This makes the phagocytosis process more effective. The adherence of leukocytes to the endothelium is crucial in the process of inflammation. It is also of fundamental importance to migration, phagocytosis and killing of invading micro-organisms. If the response is excessive, it may lead to a general inflammation with the development of circulatory instability or organ failure. Leukostasis has been demonstrated to occur in the lung, liver or kidneys after organ transplantation, sepsis, multitrauma and the use of extracorporeal circulation (18,19). Leukostasis may be induced by hypoperfusion, changes of the endothelial function and activation of the leukocytes. Split products of the complement cascade are able to activate the leukocytes. Cytokines (TNF-α, IL-1, IL-6 and IL-8), endotoxin and bacteria are activators of polymorphonuclear neutrophils.

Macrophages, T-lymphocytes and B-lymphocytes are necessary for the specific immune response mechanism. Different types of immune reactions occur between these immunological

cells. The mononuclear phagocyte system is composed of intravascular monocytes and tissue macrophages. The macrophages play a key role in the development of the specific immune response mechanism. A foreign antigen has to be taken up and processed in a proper way before the macrophages can stimulate the T cells (T helper cells). The T cells are of different types and with specific activity. There are helper cells, cytotoxic cells and suppresser cells.

Several studies have demonstrated that cytokines are released by organ transplantation, sepsis, ischaemia, and trauma (20,21). Cytokines are classified as pro-inflammatory cytokines (e.g. TNF-α, IL-1, IL-6 and IL-8) while some have anti-inflammatory properties (IL-4 and IL-10). Rejection of transplanted organs is also accompanied by increased release of cytokines. Cytokines are formed in patients undergoing dialysis and extracorporeal circulation (22,23).

The aim of the study was to determine whether orthotopic liver transplantation leads to the activation of macrophages, neutrophils and complement and whether there is a difference in the activation between patients developing circulatory instability after reperfusion of the grafted liver compared to those without circulatory instability and whether the use of veno-venous bypass influences the activation process.

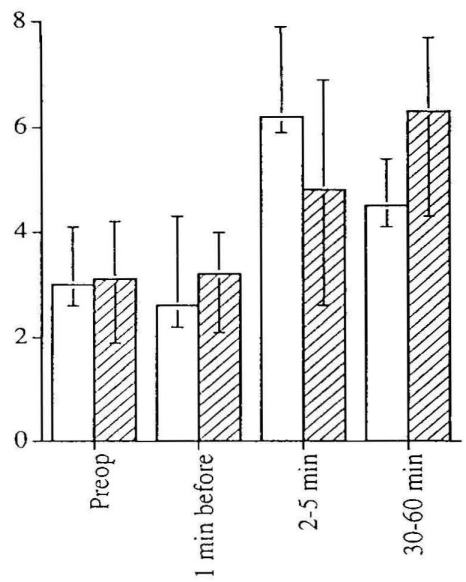

Figure 1. Neopterin in patients undergoing orthotopic liver transplantation. Concentrations in patients operated upon the use of a veno-venous bypass (open bars) and those without a bypass (filled bars). The results are given as median and 25th-75th percentiles.

Material and methods

The study was approved by the Human Ethics Committee of Göteborg University. All patients received immunosuppression with antithymocyte globuline (Fresenius AG, Bad Homburg, Germany), azathioprine (Imurel®, The Wellcome Foundation Ltd; London, UK) and corticosteroids. cyclosporin A (Sandimmun®, Sandoz Pharma Ltd, Basel, Switzerland) was given given orally only and started when the renal function was stable, usually on the 5th to 7th postoperative day. University of Wisconsin solution (Via Span®, Du Pont Pharmaceuticals Ltd, Hertfordshire, UK) was used as the preservation fluid.

Patients

Twelve consecutive patients (median age 41 years, range 32-52 years) with acute or chronic liver disease undergoing orthotopic liver transplantation with the use of a veno-venous bypass were included in the study. The veno-venous bypass technique was performed with the use of a nonocclusive centrifugal pump (model 540 Bio-Medicus®, Medtronic, Kerkrade-West, Holland), heparin-bonded 3/4 inch diameter shunt tubing (Medtronic, Kerkrade-West, Holland) and 16 Fr. to 32 Fr. heparin coated insert probes (Carmeda AB, Täby, Sweden). A combined caval and portal bypass was used. The bypass circuit was primed with 500 ml of Ringer's acetate at room temperature. Blood was drained from the portal and femoral veins and returned to the patient through a shunt tube inserted into the axillary vein.

Liver transplantation was also performed in twelve consecutive patients with a surgical technique without the use of a veno-venous bypass during the anhepatic phase.

The anhepatic phase was defined as the period between clamping and declamping of the portal vein. Before declamping the portal vein the liver was flushed with Haemacel® (Behringwerke AG, Marburg, Germany) 1000 ml at 370 °C via the portal vein.

Anaesthesia

Anaesthesia was achieved with thiopentone sodium (Pentothal® sodium, Abbott Laboratories, North Chicago, Illinois, USA), fentanyl citrate (Leptanal®, Janssen Pharmaceutica, Illinois, USA) in oxygen/air. Pancuronium bromide (Pavulon®, Organon Teknika, Boxtel, Holland) was used for

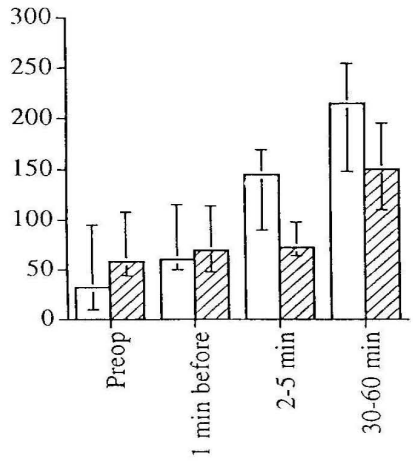

Figure 2. PMN elastase in patients undergoing orthotopic liver transplantation. Concentrations in patients operated upon the use of a veno-venous bypass (open bars) and those without a bypass (filled bars). The results are given as median and 25th-75th percentiles.

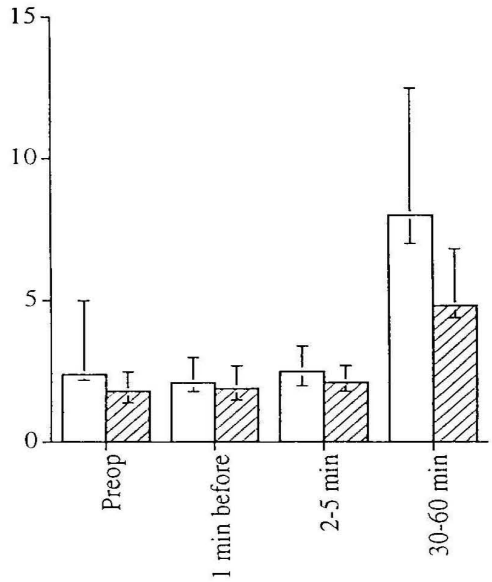

Figure 3. Terminal C5b-9 complement complex (SC5b-9) in patients undergoing orthotopic liver transplantation. Concentrations in patients operated upon the use of a veno-venous bypass (open ars) and those without a bypass (filled bars). Teh results are given as median and 25th-75th percentiles.

muscle relaxation. All patients received a continuous infusion of 3 microgram/kg/min dopamine (Intropin®, Hässle AB, Mölndal, Sweden). Ulcer prophylaxis with omeprazol (Losec®, Astra Lä kemedel AB, Södertälje, Sweden) was started preoperatively.

Postreperfusion syndrome (PRS)

Postreperfusion syndrome, PRS, was defined as hypotension with ≥30% reduction of systemic mean arterial blood pressure during at least 1 minute compared with base-line during the anhepatic phase and/or need for intensified treatment with sympathomimetics during the first five minutes of the reperfusion. Eight of 12 patients operated upon without the use of a veno-venous bypass fulfilled the criteria for PRS.

Determinations

Blood samples for neopterin, PMN elastase and terminal complement complex (SC5b-9) determinations were drawn peroperatively, 1 min before perfusion of the grafted liver and 2-5 and 30-60 minutes after the start of perfusion of the grafted liver. Arterial blood for neopterin, PMN elastase and SC5b-9 determinations was drawn into tubes containing 0.34 M ethylene diamine tetraacetic acid in a quantily of 0.054 ml per 4.5 ml of blood. The tubes were centrifuged to remove the cells. The samples were frozen within 30 minutes in individual tubes for each determination and stored at -80 °C until the analyses were performed. All assays were performed in duplicate. The results are all given as means of duplicate determinations.

The neopterin concentration was determined by an enzyme-linked immunoassay (ELISA) procedure (Henning Berlin GMBH, Berlin, Germany) with a sensitivity of 2.0-250 nmol/l. The standard deviation of duplicate determinations of neopterin was less than 7% and the inter-assay coefficient of variation was 8%. PMN elastase was determined as an α_1-antiprotease-elastase complex and determined by the PMN Elastase IMAC® immunoassay (E Merck, Darmstadt, Germany. The standard deviation of duplicate determinations of PMN elastase was less than 6% and the interassay coefficient of variation was 4%. The plasma concentration of the terminal C5b-9 complement complex was determined by an ELISA.

Statistics

Median values and 25%-75% percentiles are given. The significance of difference within the groups was analysed with Wilcoxon's test. The Mann-Whitney U test was used for statistical analysis of difference between the hypotensive and nonhypotensive groups.

Results

The results of the plasma neopterin determinations are given in Table 1. The concentration of neopterin was in both groups elevated 2-5 and 30-60 minutes after the start of reperfusion ($p<0.05$ for both groups). No significant changes in the neopterin concentration were observed before the start of reperfusion. The plasma neopterin concentrations were not higher in patients with PRS after the start of perfusion of the grafted liver compared with those without PRS.

The results of the PMN elastase determinations are given Table 1. The PMN elastase concentrations were elevated in both groups 2-5 and 30-60 minutes after the start of reperfusion compared with the levels found preoperatively and 1 minute before the start of reperfusion ($p<0.05$). No significant changes were observed before reperfusion. The PMN elastase concentrations were higher in patients with postreperfusion syndrome compared with those without PRS at 2-5 and 30-60 minutes ($p<0.05$).

The concentrations of SC5b-9 were elevated in both groups at 2-5 and 30-60 minutes after the start of reperfusion compared with the levels found before the start of reperfusjion ($p<0.05$). The SC5b-9 concentrations were higher in patients with postreperfusion syndrome compared with those without PRS at 2-5 and 30-60 minutes ($p<0.05$) (table 1).

Discussion

Orthotopic liver transplantation with and without the use of a veno-venous bypass leads to activation of macrophages, neutrophils and complement This is confirmed by the results of the present study. Neopterin was determined as an indicator of macrophage activation while PMN elastase was determined for evaluation of neutrophil activation For evaluation of complement system activation, the terminal complement complex (SC 5b-9) was analysed.

Several studies indicate that extracorporeal circulation leads to activation of leukocytes and of the complement system. However, in the present study similar degrees of activation of macrophages, neutrophils and complement were observed in patients operated upon with and without the use of a veno-venous bypass. Thus, these systems become activated independently of the bypass procedure in connection with orthotopic liver transplantation. The plasma levels of neopterin were not very high in the circulation during the first hour of perfusion of the grafted liver. There was a significant increase of neopterin compared with the levels found before reperfusion. We have in an earlier study demonstrated high neopterin concentrations in plasma 6 and 24 hours after re-

Table 1. Neopterin, PMN elastase and terminal complement complex (SC5b-9) in patients undergoing liver transplantation operated upon with and without a veno-venous bypass. Mean values and 25th-75th percentiles are given

	Preop	1 min before start of reperfusion	2-5 min after start of reperfusion	30-60 min after start of reperfusion
Without veno-venous bypass				
Neopterin				
PRS	3.3 (2.6-5.0)	4.1 (2.8-5.3)	4.3 (2.7-7.0)	4.9 (4.1-6.4)
non-PRS	2.0 (1.4-4.8)	2.1 (1.4-3.2)	6.6 (2.8-8.5)	6.8 (6.6-6.9)
PMN elastase				
PRS	64 (48-97)	72 (50-1070	81 (76-88)	162 (129-269)
non-PRS	64 (39-106)	77 (49-107)	78 (67-134)	109 (99-174)
SC5b-9				
PRS	1.5 (<1.0-2.0)	1.1 (<1.0-2.8)	1.4 (1.0-2.5)	6.7 (3.9-6.9)
non-PRS	<1.0 (<1.0-5.5)	1.7 (1.1-5.6)	1.7 (<1.0-4.2)	2.8 (2.6-5.3)
With veno-venous bypass				
Neopterin				
PRS	3.3 (2.3-5.0)	2.8 (2.4-5.4)	6.6 (5.2-15.2)	4.1 (3.7-8.0)
non-PRS	2.8 (2.6-3.2)	2.3 (2.1-3.0)	4.8 (3.5-5.6)	4.6 (2.9-5.1)
PMN elastase				
PRS	36 (17-85)	71 (55-93)	134 (85-206)	238 (158-325)
non-PRS	<30 (<30-252)	55 (33-141)	151 (129-154)	166 (152-201)
SC5b-9				
PRS	2.7 (2.5-6.7)	1.9 (1.5-2.6)	2.8 (1.9-3.9)	8.3 (3.8-14.4)
non-PRS	5.3 (2.4-8.2)	7.6 (2.3-12.9)	3.2 (2.4-4.0)	7.1 (5.2-9.1)

perfusion (24). This study clearly indicates that neopterin starts to be released within 60 minutes after the start of reperfusion.

Several investigators have discussed the relationship between activation of macrophages, neutrophils and the complement cascade and the development of complications like shock, adult respiratory distress syndrome and multisystem organ failure in connection with transplantation, trauma and sepsis. Circulatory shock, ARDS and MOF are complications often seen in connection with liver transplantation (2.5). Release of pro-inflammatory cytokines and formation of complement derived anaphylatoxins and other inflammatory products may initiate pathophysiological events that lead to the development of circulatory insufficiency. Studies using broncho-alveolar lavage have shown that neutrophils accumulate in the lungs and that C5a accumulates in alveolar fluid early during the course of ARDS (26). Robbins and co-workers have demonstrated that the concentrations of the chemotactic factor inactivator are higher in broncho-alveolar lavage fluid from patients with ARDS compared with those without ARDS. They could also show that the functional activity of chemotactic factor inactivator was reduced in ARDS broncho-alveolar fluid (27).

In an earlier study, we demonstrated that patients undergoing liver transplantation develop metabolic acidosis during the anhepatic phase. This indicates that hypoperfusion of the gut secondary to clamping of the portal and inferior caval veins may trigger the complement activation during liver transplantation (28). The mechanisms mediating this activation may include formation of immune complexes reacting with injured endothelial cells and translocation of bacterial endotoxins through the gut mucosa (29). In agreement with earlier studies, more than 50% of the patients in the present study suffered from the PRS. Hypothermia, hyperkalaemia, acidosis, impaired sympathetic activity, changes in the rate of venous return and the release of vasoactive substances from the gut during reperfusion of the grafted liver may be factors influencing the PRS.

This study showed, in accordance with earlier studies, an association between the release of PMN elastase and the activation of complement and development of profound hypotension upon reperfusion of the grafted liver. Neopterin, on the other hand, was not increased after the start of reperfusion in the patients with circulatory instability as compared with blood pressure stable patients. In a study by Himmelreich and co-workers, an elevated concentration of neopterin was found in the perfusate released from the grafted liver dujring the flushing procedure before the reperfusion phase (30). This indicates that it was released from the grafted liver. In addition, earlier studies indicate that hypoperfusion of the intestine will also influence activation of inflammatory mediators. In a study by Rϕnholm and coworkers, it was demonstrated that the portal vein contained higher concentrations of complement anaphylatoxins than the hepatic artery or the radial artery during the intial reperfusion of the grafted liver (31). Elevated concentrations of neopterin and cytokines have been observed in patients with septic shock and in critically ill patients (32). In addition, in a study by Delogu and coworkers, it was demonstrated in septic patients that neopterin may be used as a predictor of circulatory shock as a consequence of sepsis. They also showed that neopterin exceeded the soluble IL-2 receptor as a prognostic indicator (33).

This study indicates that orthotopic liver transplantation leads to the activation of macrophages, neutrophils and complement cascade. There is no major difference regarding the activation between patients operated upon with and without the use of a veno-venous bypass.

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