Value of Serum Procalcitonin In Diagnosis and Management of Non-Viral Infection Post Living Donor Liver Transplantation

Thesis

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Introduction: Infection is the most common life-threatening complication observed after organ transplantation and a primary goal in liver transplantation programme is the prevention, early detection, and effective treatment of infection. The aim of the present study is to evaluate the role of serum procalcitonin(PCT) as an innovative infection parameter in diagnosis and management of non-viral infection post living donor liver transplantation. Patients and methods: The study enrolled 50 adult recipients of right lobe living donor liver transplantation who were followed up post operatively during their hospital stay for 30 ± 14 days (range 13 -74). Clinical, laboratory, bacteriological, and histopathological data were analyzed. CRP, PCT, LDH, and WBCs were compared in patients with and without infection. Serum PCT was measured at 1st and 3rd post-operative days to determine its normal pattern after surgical trauma, and at first clinical, laboratory or imaging suspicion of infection (which was confirmed by positive cultures), then after 12 hours, then after 48 hours of antimicrobial treatment to correlate its level to the clinical response. Results: The cohort consisted of 47 males and 3 females with a mean age of 49.1±8 years (range 19-64). Patients were categorized according to bacteriological and histopathological data into infection group (n=25) and rejection group (n=25). Among the 25 patients with proven infection only 3(12%) patients had normal PCT level , 6 (24%) had PCT level (0.5 – 2 ng/ml), 11 (44%) had PCT level (2 – 10 ng/ml) , and 5 (20%) patients their PCT levels were very high (> 10 ng/ml). On the other hand all the 25 patients with rejection had a PCT level < 2 ng/ml. At cut off value of 2 ng/ml PCT had a sensitivity of 64% and specificity of 100% for diagnosis of systemic infection (P = .0001). Laboratory data in infection and rejection groups revealed that the mean total leukocytic count was not statistically different between the two groups, however immature (band) form showed a significant difference between them, also mean CRP value was (36.96 ± 29.17) in infection and (14.16 ± 7.32) in rejection (P< .01) and 18 was the best cut off value of CRP to diagnose infection with sensitivity 72% and specificity 68%. (P=.000). As regards PCT levels done after 48 hours of antimicrobial treatment, data revealed a significant relation to clinical improvement which was not demonstrated with follow up CRP. Conclusion: Both PCT & CRP have the ability for diagnose infection but PCT had higher specificity (100% vs 68%) and only PCT had a prognostic ability with early evaluation of treatment response.

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RECOMMENDATIONS

- Serum PCT is a rapid reliable test for systemic infection with good diagnostic and prognostic ability and should be part of bed side evaluation of patients with suspected infection.
- Further large scale studies are needed with close follow up of serum PCT in recipients with persistently unexplained high levels in the immediate post operative period for more evaluation of its significance and relation to mortality.
- The use of small graft in LDLT should be discouraged as it may be associated with earlier and more profound susceptibility to infection. Further studies are needed to define the critical limit for the graft size.
- More attention should be directed in post operative management of cases with known risk factor for infection as low GRWR.
- As infection whether viral or bacterial became a global burden, more studies are recommended to evaluate a newer biomarkers of infection as proadrenomedullin, Neopterin, soluble CD14 subtype, leukocyte antisedimentation rate, and endotoxin assays.

LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ALP	Alkaline Phosphates
ALT	Alanin Amino Transferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate Amino Transfearse
CBC	Complete Blood Count
CEA	Carcino-embryonic Antigen
CMV	Cytomegalo Virus
CRP	C – reactive protein
CT	Computed Tomography
CTP	Child-Turcotte-Pugh
EBV	Epstein-Barr Virus
ESR	Erythrocyte Sedimentation Rate
FHF	Fulminant Hepatic Failure
GGT	Gamma Glutamyl Trans peptidase
GRWR	Graft Recipient weight ratio
HAR	Hyper acute Rejection
HAT	Hepatic artery thrombosis
HAV	Hepatitis A Virus
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocytic Antigen
HSV	Herpes Simplex Virus
HTN	Hypertension
ICU	Intensive Care Unit
IL-6	Interlukin 6
INR	International Normalized Ratio
LDH	Lactate dehydrogenase
LDLT	Living Donor Liver Transplantation
LTx	Liver Transplantation
MELD	Model for End Stage Liver Disease
MODS	Multiple organ dysfunction syndrome
MRI	Magnetic Resonance Imaging

MRSA	Mecithilin resistance staphylococcus aureus
NICE	National Institute of clinical excellence
NIH	National Institute of Health
No.	Number
OLT	Orthotopic Liver Transplantation
OPTN	Organ Procurement and Transplantation Network
PBC	Primary Biliary Cirrhosis
PCP	Pneumocystis carinii pneumonia
PCR	Polymearse Chain Reaction
PCT	Procalcitonin
PSA	Prostatic Specific Antigen
PSC	Primary Sclerosing Cholangitis
PTLD	Post Transplant Lympho proliferative Disease
PTT	Partial Thromboplastin Time
RNA	Ribonucleic acid
RSLT	Reduced-size Liver Transplantation
RSV	Respiratory Synciteal Virus
SCCM	Society of Critical Care Medicine
SIRS	Systemic inflammatory response syndrome
SLT	Split Liver Transplantation
SLV	Standard Liver Volume
TB	Tuberculosis
TIBC	Total Iron Binding Capacity
TIPS	Transjugular intra hepatic porto-systemic shunt
TNF	Tumour necrosis factor
UNOS	United Network of Organ Sharing
UTI	Urinary tract infection
VRE	Vancomycin Resistant Enterococci
VZV	Varicella Zoster Virus
WBCs	White Blood Cells

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INTRODUCTION

The high prevalence of viral hepatitis B and C, and its associated chronic complications has led to the need for liver transplantation ***(Chui, et al., 2003).***

The shortage of organ donors and the increasing number of patients waiting for liver transplantation are serious and difficult problems for transplant clinicians ***(Grazi, 2001).*** Over the last 10 years, the number of patients awaiting liver transplantation has increased more than 15-fold. During the same period, the number of liver transplants increased less than twofold. The median waiting time has increased dramatically, increasing numbers of patients on the waiting list (approximately 10% each year) are dying while waiting for a donor liver ***(Eghtesad, et a., 2003).***

Several innovative techniques have been developed to enlarge the utility of the relative constant pool of organs and to meet the growing needs of recipients. One recently advanced procedure utilizes a part of the liver as an allorgraft. Splitting cadaveric livers for two recipients has benefited the pediatric population, but the adult recipient pool has not experienced the same benefit ***(Malago, et al., 2001).***

Another approach to enlarge the donor pool is living donor liver transplantation (LDLT), an extension of reduced-size liver transplantation. ***(Eghtesad, et al. 2003).*** It gives an increasing number of patients with end-stage liver disease the opportunity for effective

treatment in the face of a critical shortage of cadaveric organs. ***(Ryan, et al. 2002).***

The issue of differentiating patients after liver transplantation with severe bacterial sepsis from others with similar non-specific symptoms and signs has generated interest in identifying useful laboratory markers of infection. The "unconventional" inflammatory markers such as fibronectin, interleukin 6, tumour necrosis factor, and β integrins, have been used as research tools but not gained widespread acceptance in routine practice ***(De Werra, et al. 1997).***

Because the diagnosis of "possible sepsis" has implications for antibiotic usage and hospital stay, management strategies have evolved based on a combination of clinical and laboratory information. Although laboratory markers of infection might aid in differentiating the type of infection, opinions vary on the interpretation of tests such as the leukocyte count, neutrophil count, and C reactive protein concentration ***(Browne, et al. 1997).***

A polypeptide identical to a prohormone of calcitonin, procalcitonin, was initially described as a potential marker of bacterial disease by ***Assicot, et al. (1993).*** Procalcitonin (PCT) is a 116 amino acid protein with a sequence identical to that of the prohormone of calcitonin (32 amino acids). Under normal metabolic conditions, hormonally active calcitonin is produced and secreted in the C-cells of the thyroid gland after specific intracellular proteolytic procession of the prohormone procalcitonin. In severe bacterial infections and sepsis, however, intact

procalcitonin is found in blood. Current research indicates that the origin of procalcitonin in these conditions is extra-thyroidal. C-cells of the thyroid are not believed to be the source of bacterial infection induced PCT. It is synthesized by leukocytes, neurocrine cells of internal organs such as the lung and the intestine as well as other cell types including macrophages and monocytic cells of various organs (such as liver). ***(Oberhoffer, et al. 1999).*** It is almost undetectable under physiological conditions, but rises to very high values in response to bacteraemia or fungaemia, and appears to be related to the severity of infection ***(Assicot, et al., 1993).*** This response can be duplicated by in vivo endotoxin administration, which results in a rapid rise in procalcitonin, paralleling that of tumour necrosis factor and interleukin 6 ***(Dandona, et al. 1994).***

Sequential measurements in patients with bacteraemia have shown a rapid fall within 48 hours of antibiotic administration ***(Assocot, et al. 1993)***. It has been postulated that procalcitonin measurement might be superior to commonly used tests, such as C reactive protein measurement, as an aid to the early diagnosis of bacterial sepsis ***(Raynard, et al. 1997).***

The usual signs of sepsis cannot be used to differentiate between severe hepatic necrosis and bacterial infection. Procalcitonin (PCT) has been reported to be a selective inflammatory marker that rises in bacterial infection but not in non-infection related inflammation ***(Jackson, et al. 2000).***

Kuse, et al. (2000) studied the effect of procalcitonin level in differentiation between infection and rejection after liver transplantation