



Preoperative risk factor analysis in orthotopic liver transplantation with pretransplant artificial liver support therapy

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Supported by the Provincial Natural Science Foundation of Hunan, China, No. 04JJ6017

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Telephone: +86-13875876591

Received: 2005-11-16

Accepted: 2005-12-12

Key words: Liver transplantation; Artificial liver; Sequential Organ Failure Assessment; Risk factors analysis

Yuan JZ, Ye QF, Zhao LL, Ming YZ, Sun H, Zhu SH, Huang ZF, Wang MM. Preoperative risk factor analysis in orthotopic liver transplantation with pretransplant artificial liver support therapy. *World J Gastroenterol* 2006; 12(31): 5055-5059

<http://www.wjgnet.com/1007-9327/12/5055.asp>

Abstract

AIM: To assess the value of pre-transplant artificial liver support in reducing the pre-operative risk factors relating to early mortality after orthotopic liver transplantation (OLT).

METHODS: Fifty adult patients with various stages and various etiologies undergoing OLT procedures were treated with molecular adsorbent recycling system (MARS) as preoperative liver support therapy. The study included two parts, the first one is to evaluate the medical effectiveness of single MARS treatment with some clinical and laboratory parameters, which were supposed to be the therapeutical pre-transplant risk factors, the second part is to study the patients undergoing OLT using the regression analysis on preoperative risk factors relating to early mortality (30 d) after OLT.

RESULTS: In the 50 patients, the statistically significant improvement in the biochemical parameters was observed (pre-treatment and post-treatment). Eight patients avoided the scheduled Ltx due to significant relief of clinical condition or recovery of failing liver function, 8 patients died, 34 patients were successfully bridged to Ltx, the immediate outcome of this 34 patients within 30d observation was: 28 kept alive and 6 patients died.

CONCLUSION: Pre-operative SOFA, level of creatinine, INR, TNF- α , IL-10 are the main preoperative risk factors that cause early death after operation, MARS treatment before transplantation can relieve these factors significantly.

INTRODUCTION

Orthotopic liver transplantation (OLT) is an accepted mode of therapy for selected patients with advanced liver diseases, however, the early mortality after OLT remains relatively high due to the poor selection of candidates with serious conditions. The immediate outcome of OLT is dependent on many factors including pre-transplantation conditions such as renal function and some other organ functions, which indicate that the better preparation for stability or improvement of the previous OLT support, the better immediate outcome for the OLT. It is now widely accepted that the artificial liver support can be of the optional therapy to stabilize patients with liver failure and to gain time for recovery or re-compensation of the liver or to get a suitable donor available^[1]. Although the hybrid biologic method seems theoretically rational, criticism of and arguments against the concept in fear of rejection, transmission of porcine viruses and inducing release of cytokines such as TNF- α and IL-10 probably hinder these methods from gaining a prominent role in future liver support strategies^[2]. A new innovated blood purification system based on hemodialysis named molecular adsorbent recycling system (MARS) has been applied to a wide variety of hepatic failure patients and represents positive effects, the method was shown to be efficient in removing both hydrosoluble substances and strongly albumin-bound substances. The remarkable removal of strongly albumin-bound substances and kinds of metabolic toxins during MARS could therefore reduce the toxic effects and higher concentrations of these compounds exert on liver and kidney, thus could contribute to improvement in encephalopathy, renal and hepatic function and probably survival^[3,4].

The aim of this study is to assess the value of pre-transplant artificial liver support in reducing the preoperative risk factors relating to early mortality after OLT.

MATERIALS AND METHODS

Patients and design

Fifty adult patients undergoing OLT procedures with MARS preoperative liver support therapy in our transplantation institute from September 2002 to June 2003 were studied. The study population consisted of 28 men and 22 women with a mean age of 52.24 years (range 46-68). The indications for liver transplantation were post-hepatic cirrhosis ($n = 11$), fulminant hepatic failure ($n = 6$), alcoholic cirrhosis ($n = 5$), primary liver cancer ($n = 7$), primary biliary cirrhosis ($n = 12$), Wilsons disease ($n = 6$) and post-operative rejection ($n = 3$).

The study contains two parts, the first one is to evaluate the medical effectiveness of single MARS therapy with some clinical and laboratory parameters which were supposed to be the therapeutical pre-transplantation risk factors, the second part is to study the patients undergoing OLT using the regression analysis in preoperative risk factors relating to early mortality (30 d) after OLT.

Our trial was approved by the Ethical Committee of Human Experimentation in China, and was in accordance with the Helsinki Declaration of 1975. All procedures were performed after informed and written consent had been obtained from the patients or their kins.

Treatment and monitoring of clinical and laboratory parameters

Initially, patients were given conventional medical therapy and intensive monitoring or supportive treatment. They were evaluated biochemically and clinically with the prognostic scoring systems including Sequential Organ Failure Assessment (SOFA) score, Glasgow coma score and Hepatic encephalopathy (HE) grade before and after the treatment, no sedatives were administered during treatment, the laboratory variables as Tumor Necrosis Factor α (TNF- α), and Interleukin-10 (IL-10) levels were detected with the flow cytometer (FACSCalibur, Becton, Dickinson and Company, USA).

Those patients who were bridged to OLT were divided into two groups: survival group (survival time ≥ 30 d) and death group (survival time ≤ 30 d). There were different possible risk factors relating to early mortality after liver transplant including pre-operative, inter-operative and post-operative ones. Pre-operative information consisted of age, SOFA, mean artery pressure (MAP), serum Aspartate Transaminase (AST), serum albumin, International Normalized Ratio (INR), serum creatinine level (Cr), serum total bilirubin level, bile acid, serum ammonia, TNF- α , and IL-10.

The extracorporeal liver support system (MARS)

The MARS system (MARS monitor, Teraklin AG, Rostock, Germany) was used with a continuous veno-venous hemofiltration (CVVH) machine (GAMBRO AK 200), The MARS treatment was performed according to the recently published guidelines^[3], a vascular access via a double-lumen jugular central vein line was created, low molecular weight heparine (LMWH) was used for blood anticoagulation for the maintenance of the extracorporeal circuit. The blood

Table 1 Comparison of clinical and biochemical data pre-and post MARS treatment

Parameter	Pre-treatment	Post-treatment	P value
Prognostic scores			
SOFA score (points)	9.72 \pm 1.89	6.98 \pm 2.34	< 0.01
Glasgow coma score (points)	7.23 \pm 1.21	13.34 \pm 2.33	< 0.01
Clinical and biochemical parameters			
MAP (mmHg)	70.5 \pm 12.1	85.1 \pm 10.4	< 0.001
TNF- α (pg/mL)	2.83 \pm 1.7	1.80 \pm 1.39	< 0.01
IL-10 (pg/mL)	7.80 \pm 6.0	4.5 \pm 4.5	< 0.05
ALT	295.7 \pm 1125.4	237.14 \pm 91.82	< 0.036
TBIL (μ mol/L)	341.16 \pm 94.93	232.74 \pm 169.29	< 0.04
TBA (mmol/L)	162 \pm 104	73 \pm 51	< 0.001
Albumin (g/L)	35.5 \pm 35.7	35.7 \pm 6.8	> 0.05
INR	4.66 \pm 3.35	3.98 \pm 3.16	> 0.05
Cr (μ mol/L)	128.67 \pm 87.73	33.21 \pm 22.26	< 0.045
Ammonia (mmol/L)	151.31 \pm 88.99	28.28 \pm 20.19	< 0.028

flow from the dialysis machine and the albumin dialysate circuit flow were equal at a rate of 80-120 mL/min, while the dialysate flow was set accordingly. The time length of each therapeutic session was 6-8 h.

Statistical analysis

Experiment data were presented as mean \pm SD, independent 2-tailed t tests were used to determine whether there were significant differences between the survival and dead group of OLT patients. Pearson's Chi-square statistics were used to test differences in all frequencies. Data with significant difference were entered into a stepwise logistic regression analysis.

RESULTS

In the 50 patients, 80 MARS treatments were performed. Patients who underwent the intended MARS treatment were all remarkably stable without any adverse events or complications except slight chill. All patients showed positive response to the therapy, with respect to remarkable release of severe meteorism, active diet, and significant improvement of liver and kidney functions. SOFA, GSH, MAP, TNF- α and IL-10 were improved significantly, the total bilirubin (TBIL), total bile acid (TBA), ammonia and creatinine (Cr) were shown decreased markedly, however, no difference was found in the markers of alanine-aminotransferase (ALT), albumin and INR before and after the MARS treatments (Table 1). Eight patients avoided the scheduled Ltx due to significant relief of clinical condition or recovery of failing liver function, 8 patients died, 34 patients were successfully bridged to Ltx, the immediate outcome of these 34 patients within 30d observation was: 28 kept alive and 6 patients died.

Comparison between the survival group and the death group showed significant differences in terms of age, SOFA, GSH, MAP, TNF- α , IL-10, INR and serum creatinine level ($P < 0.05$, Table 2). The stepwise logistic regression was used to create the best statistical model

Table 2 Risk factors relating to early mortality after liver transplantation

Group	n	Age ^a	SOFA ^b	GSH ^a	MAP ^a	TNF- α ^a	IL-10 ^a	INR ^a	Creatinine ^b
Survival	28	34.34 \pm 2.45	8.18 \pm 1.23	12.45 \pm 2.26	83.7 \pm 10.01	1.99 \pm 1.4	5.5 \pm 2.0	3.34 \pm 1.89	45.45 \pm 12.12
Death	6	45.56 \pm 2.36	9.88 \pm 1.09	9.88 \pm 2.43	75.0 \pm 12.46	2.34 \pm 1.05	6.2 \pm 2.9	4.77 \pm 2.07	110.34 \pm 23.65

^aP < 0.05, ^bP < 0.01.

Table 3 Stepwise logistic regression analysis

Variables	B	SE	Wald	Df	Sig	R
SOFA	2.638	0.879	5.879	1	0.018	0.224
Creatinine	5.822	1.351	8.345	1	0.002	0.315
TNF-A- α	2.131	0.775	5.664	1	0.019	0.192
IL-10	2.014	0.766	4.784	1	0.025	0.188
INR	3.455	1.335	8.025	1	0.002	0.309

relating to early mortality after transplantation. The factors that had significant independent associations with early mortality after the stepwise procedure were serum creatinine level, INR, SOFA, TNF- α and IL-10, with regression coefficients of 0.315, 0.309, 0.224, 0.192 and 0.188, respectively (Table 3).

DISCUSSION

OLT is a treatment for end-stage liver disease. Early post-operative mortality was below 10% in the world. The mortality remains high in our country. The serious preoperative condition of recipient and the late timing for operation may account for this result. The serious preoperative conditions are due to the poor detoxification ability of the liver, the accumulation of large amounts of toxic substances including hydro-soluble and lipid soluble and various metabolic products, which causing further damage to the heart, brain, kidney and vessels leading to MODS. The accumulation will increase the mortality of OLT^[5]. So, in order to increase the successful rate of OLT, the toxic substances shall be removed as much as possible before operation. The removal of the toxins will help block the vicious cycle and benefit the organ function.

The albumin dialysis MARS is currently the novel cell-free liver support system which enables the selective removal of water-soluble and albumin-bound substances, in which human serum albumin serves as a shuttle based on facilitated diffusion between a blood-sided dialysis membrane on one side and a remove set of sorbent columns and a conventional dialysis unit on the other^[2,3]. MARS has avoided the drawbacks of conventional and bio-artificial liver. It combines the functions of molecular adsorption, hemo-filtration and hemo-dialysis, and can remove the albumin combined toxins quickly and selectively. The hemo-filtration can do nothing to the albumin combined toxins. The hemo-perfusion, whose adsorbents such as carbon or resin will contact with blood directly, cause fibrolysis or activation of complements and systemic

inflammation due to the bio-incompatibility, and also, cause the loss of hepatic cytokines and a large amount of hormones such as T3, T4 and insulin. The plasma exchange has very weak ability to remove toxins and causes loss of useful substances. Attempts to develop an artificial liver were started in the 1950s, today both mechanical devices and hybrid biologic-mechanical devices such as cell-free detoxification methods, whole organ perfusion, hepatocytes transplantation and bioreactor approaches using hepatocytes, however, are with inherent defectiveness and limitations respectively. Although the hybrid biologic methods seem theoretically rational, criticism of and arguments against the concept in fear of rejection, transmission of porcine viruses and inducing release of cytokines as TNF- α and IL-6 probably hinder these methods from gaining a prominent role in future liver support strategies. Many randomized, controlled trials were performed, all reported with statistically significant increases in survival in the MARS group compared with standard care, indications for treatment were hepato-renal syndrome, decompensated chronic disease with intrahepatic cholestasis, post-operative liver failure after heart surgery and cirrhosis with superimposed acute liver injury. The laboratory data of pre- and post-treatment in the 80 sessions on the 50 patients has proved the conclusion of some other researchers. The conclusion is that MARS can remove various toxins and cytokines caused by liver failure, decrease SOFA score and improve multi-organ function.

In this study, we are trying to explore the effects of MARS treatment in post-operative early survival rate. Aiming at this purpose, we analyzed multiple factors which may be related to the post-operative mortality rate. It is different with the bygones. We only analyzed some pre-operative factors which are operable, measurable and curable although the factors are related to the post-operative mortality comprise of not only post-operative factors, but also intra- and post-operative ones such as ischemia time, ahepatic time, bleeding volume and rejection or various complications. Some factors, though very important, can't be controlled or cured, which are not drawn into our study, such as the pathology, former related operation or former transplantation history, ABO blood group, *etc.* The early mortality rate is 17% in the 34 patients in this study. We adopts Logistic regression analysis. The results show that preoperative SOFA, levels of creatinine, INR, TNF- α and IL-10 are the main preoperative risk factors causing early death after operation.

Renal dysfunction is a common dangerous complication in patients with end-stage liver disease. It results from acute tubular necrosis and caused by

hepatorenal syndrome. Literature shows a significant decrease of 43% in glomerular filtration rate (GFR) during transplantation in patients with normal renal function. Both high pre-operative serum creatinine level and inter-operative veno-venous bypass can lead to renal hemodynamic instability during operation. The post-operative nephrotoxic immuno-suppressants can also contribute to the irreversible renal insufficiency, leading to renal failure after liver transplantation. In our study, 2 of 10 patients died of renal failure, who were all along with high preoperative serum creatinine level and hepatorenal syndrome before transplantation. A significant difference found between the survival group and the death group was shown in serum creatinine level ($P < 0.001$), with a mean of 45.45 ± 12.12 and 110 ± 23.65 , respectively. The stepwise logistic regression analysis also showed a statistical independent association with early mortality after liver transplantation, with a regression co-efficient of 0.315. It is also a main risk factor which predicts early mortality after OLT. It is very important to improve renal malfunction before transplantation. If there are indications for hemodialysis, it should be performed without delay, trying to relieve the renal function before operation^[6]. The MARS is a recommended strategy for this kind of case. Because, not only can MARS lower the level of blood creatinine, but also raise mean artery pressure (MAP) and systemic vascular resistance (SVR), for it can lower the blood level of NO which is a vessel dilator to the liver failure patients^[7].

SOFA is currently a popular system applied in ICU for the assessment of multi organ function. SOFA covers the function of multi-system completely including respiratory, hemostatics, hepatic, circulatory, and of brain and kidney. Comparing with the widely used Acute Physiology and Chronic Health Evaluation (APACHE), SOFA has the advantage of daily sequential assessment, and is better than APACHE which is not specific enough to liver function and also better than Child-Turcotte-Pugh (CTP) system which is too specific to liver function^[8]. In this study, the SOFA score is 9.88 ± 1.09 , which is significantly higher than 8.18 ± 1.23 in the survival group ($P < 0.001$). Logistic regression analysis showed that SOFA is related to early mortality in certain extent, its regression coefficient is 0.224. SOFA is one of the main risk factors. It can be regarded as a reference index in choosing operation time.

Though the association between pre- and post-operative level of TNF- α and IL-10 is not so significant as the other risk factors, it still deserves much consideration. A lot of studies show that the systemic inflammatory responses syndrome (SIRS) caused by TNF- α and IL-10 is an important factor to the aggravation of liver failure leading to MODS. Not only does SIRS play an important role in the development of liver failure, but also makes a hormone-like effect, causing hypotension, lung injury, brain edema *etc.* So SIRS may be the common body fluid causing multi-organ injury. If we can remove these factors, theoretically, the MODS caused by the strike of the operation can be relieved, which is beneficial to increasing the success rate of operation. In this study, three patients died of MOF (multi-organ failure). The study showed that

the values of preoperative parameters were lower in the survival group, which may be due to being removed of the cytokine and being blocked of injury to organs by SIRS. The relief of oxygenation of the body will also do benefit to preventing MODS^[9]. Recent studies show that the TNF- α and IL-10 play important roles in mediating the inflammation and immune response caused by rejection. The variability of the cytokine initiator is a risk factor which is related to rejection. Whether the removal of preoperative TNF- α and IL-10 will be of benefit to relieve post-operative rejection is awaits further studies^[10].

In this study, we find that MARS can improve multi-organ function both before and after operation. The improvement is presented as the decreased SOFA score. This is in agreement with some reports in the world. The mechanism may be that MARS has selectively removed a large amount of albumin bound toxins and hydrosoluble toxins including cytokines such as TNF- α , IL-10 and endo-toxin, and repressed or relieved the pathological progress, and also improved the body blood circulation, organ blood dynamics and tissue oxygenation, benefiting the intervention on MODS. Regarding the risk factors, this preoperative MARS treatment will ensure a low post-operative MODS rate and increase the success rate of operation.

Furthermore, INR is an important risk factor related to post-operative early mortality. High preoperative INR is related to disfunction of blood clotting, leading to interoperative bleeding. Large amounts of blood transfusion may develop hemodynamic unsteadiness or even DIC. The long-term hypotension will aggravate the renal failure which has already existed before operation. INR acts as the medium of blood clotting mechanism. Abnormal INR accompanied with previous upper abdominal surgery, or extensive abdominal adhesions, portal hypertension and hypersplenism may develop severe bleeding. It is reported that intra-operative bleeding quantity is related to early mortality after liver transplantation^[11,12]. In this study, INR is not significantly improved by single MARS treatment, possibly because single MARS treatment is not enough to significantly improve of the synthesizing ability of the liver. But it will be improved after sequential treatment. Unlike the other artificial liver treatment, MARS is featured by high bio-compatibility and stable hemo-dynamics. It will not do harm to or initiate the disorder of blood clotting. MARS is very useful in stabilizing INR which is related to the prognosis.

Some other factors such as Glasgow Score (GSH) and mean artery pressure (MAP) showed associations with early mortality after liver transplantation, but the significance is not as high as SOFA and creatinine.

CONCLUSION

After studying the laboratory data of pre- and post-treatment in the 80 sessions on the 50 patients, we think that MARS can be used in transition to OLT. Preoperative SOFA, level of creatinine, INR, TNF- α and IL-10 are the main preoperative risk factors that cause early death after

operation. MARS treatment before transplant operation can relieve these factors significantly.

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S- Editor Wang J L- Editor Ma JY E- Editor Ma WH