Therapeutic Apheresis in Liver Transplantation

Therapeutic apheresis has been used for ABO-incompatible liver transplantation and for liver support therapy during liver transplantation. The receiver operating characteristics (ROC) curve analysis of the clinical indicator of the post operative liver failure concluded that the bilirubin between postoperative day (POD) 4 and 28 (a short-term follow-up period) might be the best predictor of liver prognosis (length of hospital stay > 100 days, re-transplantation, or death). Liver transplantation patients whose post operative liver failure was treated with apheresis after their bilirubin raised above 22.3 mg/dL maintained the increase of bilirubin after apheresis, while apheresis before the bilirubin levels were below 22.3mg/dl ameliorated the increase of bilirubin. In order to treat the post operative liver failure, the inclusion criteria of apheresis might be recommended to be around 20 mg/dl bilirubin, because the bilirubin level where apheresis therapy might be effective was considered under 22.3mg/dl and the inclusion criteria should include safety margin from 22.3mg/dl. There are several possible mechanisms that apheresis can improve liver function during liver transplantation. One is to supply the essential proteins which can ameliorate the patients’ entire condition. Second mechanism is the removal of the many toxic substances, such as bilirubin, ammonium, cytotoxic substances, inflammatory cytokines, and antibody. Artificial and bioartificial liver support devices have been developed. In the clinical use of these devices, the same inclusion criteria, that is around 20mg/dl bilirubin, can be applied.

Key words: plasma exchange, apheresis, living related liver transplant, progressive liver failure, bilirubin

Therapeutische Apherese in der Lebertransplantation

Die therapeutische Apherese wird für die ABO-inkompatible Lebertransplantation und zur Unterstützung der Leber während Lebertransplantation eingesetzt. Aus der Analyse der Receiver Operating Characteristics (ROC)-Kurve des klinischen Indikators des postoperativen Leberversagens ergab sich, dass das Bilirubin zwischen postoperativem Tag (POD) 4 und POD 28 (eine kurze Follow-up) der beste Prädiktor für die Leberprognose sein könnte (Dauer des Krankenhausaufenthaltes > 100 Tage, erneute Transplantation oder Tod). Um das postoperative Leberversagen zu behandeln, könnten als Einschlusskriterien für eine Apherese Bilirubin-Werte um 20 mg/dl empfohlen werden, da die Bilirubin-Spiegel, bei denen eine Apheresebehandlung effektiv sein könnte, unter 22,3 mg/dl eingeschätzt wurden, und die Einschlusskriterien soll-
ten eine Sicherheitsgrenze von 22,3 mg/dl umfassen. Es gibt verschiedene mögliche Mechanismen, wie die Apherese die Leberfunktion während Lebertransplantation verbessern kann. Einer besteht darin, dass die essentiellen Proteine zur Verfügung gestellt werden, die den Gesamtzustand des Patienten verbessern können. Der zweite Mechanismus ist die Entfernung der vielen toxischen Substanzen, wie Bilirubin, Ammonium, zytotoxische Substanzen, Entzündungszytokine und Antikörper. Artifizielle und bioartifizielle Leberunterstützungsgeräte wurden entwickelt. Im klinischen Einsatz dieser Geräte können die gleichen Einschlusskriterien - um 20 mg/dl Bilirubin - angewendet werden.

Schlüsselwörter: Plasmaaustausch, Apherese, Lebertransplantat von einem verwandten Lebendspender, progressives Leberversagen, Bilirubin

1. Therapeutic Apheresis in ABO-incompatible Liver Transplantation

Apheresis before Transplantation

Recently, ABO incompatible organ transplantation has been developing not only in kidney transplantation, but also in liver transplantation. Basically, liver transplant recipients are selected based on ABO histo-blood group type, so ABO-incompatible liver transplantation is performed in the case of emergency, resulting in an unsatisfactory prognosis (1,2). Severe hyper-acute rejection due to anti-donor ABO antibodies during early post operative period had caused this poor prognosis of ABO-incompatible liver transplantation. To reduce anti-donor ABO antibodies, there are several methods. One is apheresis to remove anti-donor ABO antibodies, and second is splenectomy. These two procedures are usually combined for the recipient patients before solid organ transplantation, especially in kidney or liver transplantation. In the case of emergency liver transplantation, therapeutic apheresis is used both for removal of anti-donor ABO antibodies and for the liver support therapy, and the splenectomy is performed during liver transplantation. One session of apheresis leads to half or quarter titer of anti A or B antibody (3). Usually several times of apheresis can reduce the anti A or B antibody to the safe level where the organ transplantation can be performed. Third way to reduce anti-donor ABO antibody is immunosuppressive therapy. Rituximab has been used for the kidney transplantation (4). This drug is adopted into liver transplantation (5,6). In addition to these therapies, the operation procedure itself has made great improvements by portal vein or hepatic artery infusion therapy. Using these kinds of therapies, the prognosis of ABO-incompatible therapy has been improved as shown in Figure 1 (7).

Apheresis after Transplantation

After the transplantation, accommodation usually comes to existence in solid organ transplantation, such as liver transplantation and kidney transplantation (8). After liver transplantation, anti-donor ABO antibodies usually did not raise a lot (3). Therefore, after liver transplantation, apheresis therapy is not usually required. But, the titer of anti-donor ABO antibodies should be strictly monitored and if the titer was going up, plasma apheresis should be performed. Apheresis therapy for post-operative liver failure in the case of ABO incompatible liver transplantation is the same as in the case of ABO compatible liver transplantation described in the next section.

2. Therapeutic Apheresis in Postoperative Liver Failure during Liver Transplantation

How to Recognise Postoperative Liver Failure

Traditionally, bilirubin international normalized ratio of prothrombin time (PT-INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and ammonia are used for the diagnosis of liver failure. Our group assessed the

Fig. 1: Patients' survival curve for ABO incompatible living donor liver transplantation patients over 16 years old (Naoki Kawagishi and Susumu Satomi Transplantation 2008;85: 1523–1525). Several methods to reduce anti-donor ABO antibodies including apheresis and the improvements of the operation procedures such as portal vein or hepatic artery infusion therapy ameliorated the prognosis of the ABO incompatible living donor liver transplantation patients. The prognosis of the patients after 2005, January was much better than that of the patients before 1999 December.
maximum levels of AST, ALT, total bilirubin, PT-INR, and creatinine between postoperative day (POD) 4 and 28 (a short-term follow-up period) as potential predictors of short-term prognosis; good prognosis (length of hospital stay ≤ 100 days) and poor prognosis (length of hospital stay > 100 days, retransplant, or death) (9). Statistically significant predictors of a short-term prognosis were compared by receiver operating characteristics (ROC) curve analyses (Figure 2). According to this analysis, Bilirubin is the best predictor of the liver failure. Unfortunately, ammonia could not be testified because of lack of data. Ammonia may be also useful for the diagnosis of liver failure, but as we know, the ammonia levels are very liable to variation, so the diagnosis only from ammonia level requires caution. The clinical features of liver failure are also helpful, but they are not quantitative.

When Apheresis should be Considered

Our group assessed the effectiveness of plasma exchange, that is, a change in liver functions after the session of plasma exchanges, mainly by bilirubin metabolism, indicated by an incremental rate of total bilirubin and a bilirubin conjugation rate:

\[ TB_N: \text{total bilirubin on day } N \text{ (mg/dL)} \]

An incremental rate of total bilirubin on day \( N \):

\[ RN = \frac{TB_{N+1}}{TB_N} \]

A geometric mean of incremental rates of total bilirubin:

\[ R_{\text{MEAN}} = \sqrt[N]{R_1 \times R_2 \times \ldots \times R_N} \]

Bilirubin on the day after the session was excluded in the present analyses because of a significantly rapid increase of total bilirubin probably due to “rebound phenomenon” which was caused by diffusion of bilirubin from the extravascular space into the blood. Consequently, bilirubin metabolism before the session was based on the data for three days before the session (day -3 to -1) and on the day of the session (day 0) and metabolism after the session was based on the data between day +2 and day +5. Besides bilirubin metabolism, mean ammonia levels before and after the session (day -3 to 0 and day +1 to +4, respectively) were also assessed as a rapid turnover substance chiefly metabolized in the liver. TB3 had a significant positive correlation with \( R_{\text{MEAN}} \) after plasma exchanges (\( r = 0.536, p = 0.048 \)). All recipients with TB0 below 22.3 mg/dL resulted in less than 1.0 of \( R_{\text{MEAN}} \) after the session, indicating that a stepwise increase of total bilirubin was remarkably suppressed.


*Adjusted for multiple testing using the method of Holm. AUROC = area under the receiver operating curve; PT-INR = international normalized ratio of prothrombin time; AST = aspartate aminotransferase; ALT = alanine aminotransferase; MELD = model for end-stage liver disease

Fig. 3: Total bilirubin level before plasma exchange (TB0) and bilirubin metabolism after plasma exchange (Original Figure for this review, based on Yamamoto R, Nagasawa Y, Marubashi S. Blood Purif. 2009;28(1):40-6. Epub 2009 Mar 27.).

\[ TB_N: \text{total bilirubin on day } N \text{ (mg/dL)} \]

An incremental rate of total bilirubin on day \( N \):

\[ RN = \frac{TB_{N+1}}{TB_N} \]

A geometric mean of incremental rates of total bilirubin:

\[ R_{\text{MEAN}} = \sqrt[N]{R_1 \times R_2 \times \ldots \times R_N} \]

All recipients with TB0 below 22.3 mg/dL resulted in less than 1.0 of \( R_{\text{MEAN}} \) after the session, indicating that a stepwise increase of total bilirubin was remarkably suppressed.
According to this analysis, a bilirubin level before apheresis of below 20 mg/dL is considered to be favorable for liver function. Bilirubin may be a common indicator for various liver support therapies. In the trial of the Molecular Adsorbents Recirculating System (MARS™, Gambro, Lund, Sweden), the inclusion criteria in the patients with acute-on-chronic liver failure awaiting liver transplantation were reported to be bilirubin >15mg/dl besides MELD >15, PT-INR>2.1 (10). If the bilirubin level in patients with liver transplantation increased up to around 20 mg/dl, some liver support therapies such as apheresis, artificial liver support therapies as listed below, and re-transplantation should be considered.

Tab. 1: Considered substances removed by apheresis in liver failure

<table>
<thead>
<tr>
<th>No.</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>2</td>
<td>Ammonia</td>
</tr>
<tr>
<td>3</td>
<td>Cytotoxic substances</td>
</tr>
<tr>
<td>4</td>
<td>Inflammatory cytokines</td>
</tr>
<tr>
<td>5</td>
<td>Antibody</td>
</tr>
</tbody>
</table>

Tab. 2: Artificial and bioartificial liver support devices

<table>
<thead>
<tr>
<th></th>
<th>Non-cell based Liver Support device</th>
<th>Cell-based liver Support device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Name</td>
<td>MARS™</td>
<td>Prometheus™</td>
</tr>
<tr>
<td>Official Name</td>
<td>Molecular Adsorbents Recirculating System</td>
<td>Prometheus™ Liver Assist Device</td>
</tr>
<tr>
<td>Country</td>
<td>Sweden</td>
<td>Germany</td>
</tr>
<tr>
<td>Company</td>
<td>Gambro</td>
<td>Fresenius Medical Care</td>
</tr>
<tr>
<td>Cells</td>
<td>NA</td>
<td>7 billion Procine hepatocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C3A human hepato blastsoma cell line</td>
</tr>
<tr>
<td>Status</td>
<td>Phase I/II</td>
<td>Phase I/III</td>
</tr>
</tbody>
</table>

Why Apheresis is Effective for Liver Transplantation

Apheresis is considered to be effective for liver failure both because of removal of harmful substances and because of supply of useful substances. As for the supplied substances by apheresis, there are many proteins generated by the liver, such as coagulation factors, albumin, and so on. These proteins usually improve the condition of patients including bleeding tendency and malnutrition. The molecules, which are considered to be removed by apheresis, are summarized in Table 1. A detailed investigation of an effect of plasma exchange on the bilirubin metabolism in patients with postoperative liver failure by high-performance liquid chromatography revealed that the bilirubin metabolism was improved by apheresis in patients with better prognosis (11). In an animal model of postoperative liver failure, apheresis did not only improve bilirubin metabolism but also mitochondrial function, suggesting metabolic improvement of the hepatocytes (12). The hepatocytes, metabolically improved by apheresis, may also detoxify a small molecular toxin; ammonia. A study of ammonia, urea, and amino acids in the artery and the hepatic vein before and after apheresis (13), suggested that decreased arterial ammonia concentration after apheresis should be attributed mainly to enhanced hepatic urea synthesis. Our results and all these reports implied that plasma exchange can not only directly remove protein-bound or large molecular weight substances, including bilirubin, bile acids, aromatic amino acids, mercaptans, and phenols. A few reports disclosed antibody-mediated rejection in ABO-compatible liver transplant recipients (16-18), which might explain conflicting graft outcomes using ABO-compatible livers in the setting of a positive HLA cross-match (16). Besides the removal of various kinds of cytotoxic substances, the effectiveness of the plasma exchange might be partially due to the removal of the antibodies specific for the graft liver in some recipients (19,20).

3. Future Therapy in Liver Failure

Recently, artificial and bioartificial liver support systems have been developed instead of apheresis therapy (21,22). There are two categories in these kinds of liver support system. One is the pure mechanical devices including albumin dialysis. This system can basically support the liver function to remove the toxins from patients. Second is the devices with cellular components such as primary hepatocytes or hepatic cell line. These systems can potentially support the liver function both to remove the toxin and to supply the essential proteins. These artificial and bioartificial liver support systems are summarized in Table 2. MARS™ was clinically used for human therapy in 1999 (23). To date, MARS™ was used for approximately 7500 patients (22). In the study using MARS™, the inclusion criteria were bilirubin >15, MELD >20, PT-INR>2.1.
INR>2.1 with clinical features (10). This criteria is similar to our criteria of bilirubin described above. Therefore, the devices will be used just the same as therapeutic apheresis. Unfortunately these devices cannot be used in Japan at this point.

References


Yasuyuki Nagasawa
Department of Nephrology
Osaka University
Graduate School of Medicine
2-2 Yamadaoka, Suita
Osaka 565-0871
Japan
nagasawa@kid.med.osaka-u.ac.jp

2010, 22. Jahrg., S. 343