Long-Term Outcome of Patients Undergoing Liver Transplantation at Rajavithi Hospital, Thailand

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Objective: *Examine long-term outcome and survival of patients with liver transplantation at Rajavithi Hospital, a small-volume transplant center in Bangkok, Thailand.*
Material and Method: *Between May 1996 and December 2010, 21 liver transplantations were performed. Piggyback technique and portal vein flushing with one liter of cold normal saline was used to prevent reperfusion injury. Color Doppler ultrasound was performed routinely. Data collection included demographic data, complications, operation time, ischemic time, duration of stay in intensive care unit (ICU), hospitalization period, and survival.*
Results: *There were two cases withdrawn from immunosuppressant drugs due to loss of follow-up and recidivism. Late death in three patients was from bleeding after hemiarthroplasty, chronic rejection, and lymphoma. Overall, 5-year and 10-year survival were 62% and 42% respectively. Biliary complication rate was 9.5%. Two cases were under early reoperation due to bleeding from hepatic artery and retrohepatic vein. Hepatic vein occlusion was found in one case that had underlying Budd Chiari. One case with hepatocellular carcinoma, 10 nodules in both lobes of liver had survived more than three years after transplantation.*
Conclusion: *Liver transplantation is a high-cost procedure. Good long-term results depend on expensive drugs, skilled surgeons, state-of-the-art equipment, and good team work. Policy and support from the government play an important role for successful transplantation, especially in developing countries.*

Keywords: *Liver transplantation, Long-term survival, Immunosuppression, Hepatocellular carcinoma*

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After the first liver transplantation (OLT) by Professor Starlz in 1963, this procedure has become a standard therapeutic modality for end stage liver disease in Western countries[1]. There have been considerable advances in both medical and surgical management, resulting in more than 90% of one-year survival rate. After OLT, the time associating to highest risk of mortality is within the first year, particularly within the first three months[2]. The common causes of death, include graft dysfunction, technical problem, and infection[3]. The main factors responsible for increased survival include good surgical technique, anesthetic management, and intensive care unit (ICU). This combination has been well established in large transplantation centers. Thailand has six liver transplantation centers, in which four centers are located in the capital city Bangkok, whereas two other centers are located at northern and eastern regions. The present study aimed to examine long-term outcomes and survival rate of patients with liver transplantation in Rajavithi Hospital, the small-volume transplantation center in Bangkok.

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Material and Method

The study was approved by the ethics committee of the Rajavithi Hospital. All data were obtained retrospectively from the database of Rajavithi Hospital. Between May 1996 and December 2010, 21 liver transplantations were performed. Liver grafts were obtained from cadaveric donors. All patients underwent a standard reverse L incision. No temporary veno-venous bypass was used. Piggyback technique and portal vein flushing with one liter of cold normal saline was applied to prevent reperfusion injury. Bile duct anastomosis was done by choledocho-choledochostomy with plastic tube via cystic duct in the first five cases but no tube insertion in the last 16 cases. Hepatic artery anastomosis was done

with prolene 7-0 and no vascular graft was used. Cyclosporine, steroid, and azathioprine were the choices of our immunosuppressant. Later, tacrolimus was substituted for cyclosporine and mycophenolate mofetil had replaced azathioprine as alternative regimens. Color Doppler ultrasound was performed routinely at 24 hours, 72 hours, and 168 hours after operation. Liver biopsy was not performed routinely. Consideration for biopsy depended on clinical and abnormal liver function test. Preoperative assessment for hepatitis B cirrhosis for transplantation included checking level of HBV-DNA. Lamivudine without combining with hepatitis B immune globulin (HBIG) was given post transplantation. In the case of hepatocellular carcinoma (HCC), bridging treatment with chemoembolization or radiofrequency ablation was performed during waiting for transplantation. Detection of recurrent or progressive HCC was performed by computer scan every three months. In the case that HCC progression was beyond the criteria for transplantation, active waiting list for transplantation was stopped and excluded. Data collection included demographic data, complications, operation time, ischemic time, ICU stay, hospital stay, and survival. Data analysis was reported by frequency and percentage, mean and standard deviation (mean ± SD). Kaplan-Meier was used for survival rate.

Results

Baseline demographic data are demonstrated in Table 1. The results and complications are shown in Table 2. Indications for liver transplantation were hepatitis B cirrhosis six cases (28.6%), hepatitis C cirrhosis three cases (14.3%), hepatocellular carcinoma (HCC) three cases (14.3%), alcoholic cirrhosis two cases (9.5%), biliary atresia four cases (19%), cryptogenic cirrhosis three cases (14.3%). Perioperative death within 30 days occurred in six cases, intraoperative cardiac arrest after reperfusion one case, abdominal compartment one case, massive bleeding one case, and sepsis with renal failure was found in three cases. Two cases were withdrawn from immunosuppressant drugs due to loss of follow-up and recidivism, one of them had chronic rejection. Late death in three patients was from bleeding after hemiarthroplasty, chronic rejection, and lymphoma. Overall survival rate is shown in Fig. 1. Five-year and ten-year survival rate were 62% and 42%, respectively. No tumor recurrence was found in these three cases of HCC. Biliary complication was 9.5%, the authors found one case of anastomosis stricture and one case of bile leakage. Both

Table 1. Demographic data of patients with liver transplantation

Total patients	21
Sex (F/M)	6/15
Age (years)*	44.3 ± 19.1
Waiting time (days)*	252.7 ± 267.6
Operation time (hours)*	9.9 ± 2.8
Cold ischemic time (hours)*	12.4 ± 2.3
Blood loss (cc)*	2,294.7 ± 1,617.7
Blood transfusion (unit)*	10.3 ± 10.9
ICU stay (days)*	5.0 ± 2.0
Hospital stay (days)*	18.1 ± 14.1
Return to work (months)*	4.1 ± 1.9

* Mean ± SD

Table 2. Results & complication post liver transplantation

Results	n (%)
Acute rejection	8 (38.0)
Chronic rejection	1 (4.8)
Bile complication	2 (9.5)
Hepatic artery thrombosis	1 (4.8)
Lymphoma	1 (4.8)
Hypertension	4 (19.0)
Recidivism	1 (4.8)
Renal insufficiency	2 (9.5)

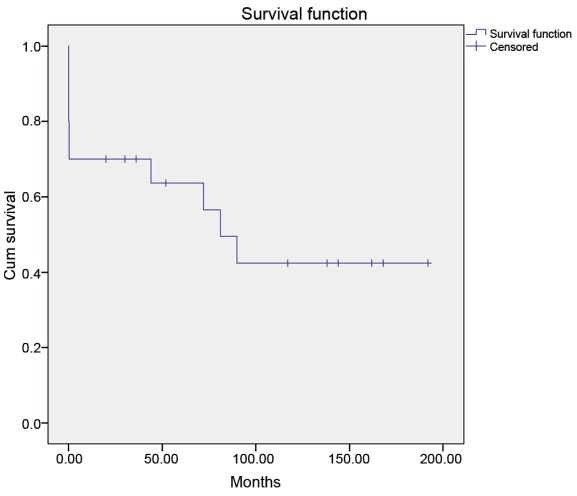

Fig. 1 Survival rate of post liver transplantation patients 5 year survival rate 62%,10 year survival rate 42%

of them underwent endoscopic biliary stent with uneventful recovery. Two cases had to be under early reoperation to stop bleeding, from hepatic artery anastomosis and retro hepatic vein. Hepatic vein occlusion was found in one case with underlying Budd Chiari and was successfully managed with radiologic intervention and anticoagulant drug. Three cases of recurrent hepatitis B post transplantation were treated with adefovir dipivoxil added to ongoing lamivudine. Acute rejection was reported to be 38% and all of them were treated with a high dose of methylprednisolone for three days with continuing regular protocol of immunosuppressive drugs. They recovered from rejection without any complication.

Discussion

OLT is a life-saving procedure for end stage liver failure with 5- and 10- year survival rates of over 70 and 65% respectively[4]. These figures were higher than the rates in our center that had small-volume cases. Liver transplantation is well recognized treatment for selected patients with HCC based on Milan criteria[5]. More recently, many centers expanded this criterion for more advanced HCC[6]. Good results with disease-free survival for more than three years were achieved in one recipient under unknown condition beyond those criteria before transplantation. This patient had three nodules suspected to be HCC on CT scan but explanted liver revealed 10 nodules of HCC.

Six liver transplantation centers have been established in Thailand and only three centers are able to perform more than 20 liver transplantations per year. Our results were similar to one of these centers[7] in terms of indication for transplant, blood loss, and length of hospital stay. However, more blood transfusion, operation time, and higher morbidity was found in our center probably due to small-volume cases. Most of morbidity and mortality occurred between 1996 and 2002. Before 1991, the incidence of chronic rejection was 8 to 17%, but with new immunosuppressant agents and early diagnosis since 1992, the incidence declined to 3 to 8%[8]. One case in the present study had chronic rejection due to poor compliance, which is the most common cause of late rejection and died while waiting for retransplantation. Acute rejection was reported to be 38%, which was comparable to other studies reporting at 25 to 70%[9,10]. Drug withdrawn and recidism are still a problem in many transplantation centers. This circumstance could be ameliorated with careful evaluation and strictly follow protocol management in this group of patients. De novo malignancy affected more than one-fifth of transplanted patients and the probability of invasive malignancy after liver transplantation is twice of general population. The present study was found to demonstrate this trait as well. Therefore, rigorous protocols for malignancy detection are warranted[11]. Hypertension and renal dysfunction were found to be 19% and 9.5% after transplantation, respectively. All these adverse effect including risk of de novo malignancy could be reduced by adjustment of immunosuppressant regimens[12]. A 9.5% biliary complication in the present study was comparable to other studies[13,14]. During the operation, tube insertion during bile duct anastomosis was commonly performed to prevent bile duct stricture[15]. However, randomized studies comparing transplantation outcomes with and without tube insertion found no difference in stricture[16]. The authors therefore used no tube insertion during bile duct anastomosis in the last 16 cases. Initial reports with a daily administration of lamivudine before OLT and continued thereafter were promising to prevent hepatitis B reinfection[17,18]. Unfortunately, long-term follow up data revealed a disappointingly high rate of reinfections[19]. This reinfection of hepatitis B was also demonstrated in the presented patients. Zheng et al also reported the use of lamivudine and low-dose intramuscular HBIG in 114 patients and compared them with 51 patients on lamivudine monotherapy in the post liver transplantation period. Sixteen out of the 114 (14%) patients showed hepatitis B recurrence post-LT in the combined therapy group compared with 21/51 (41%) in the monotherapy group. The conclusion of this author is that combining lamivudine with low-dose intramuscular HBIG demonstrates better results in preventing hepatitis B recurrence than HBIG alone[20].

Conclusion

OLT is a high-cost procedure. Good long-term results depend on expensive drugs, skilled surgeons, high technology equipment, and good teamwork. Policy and support from the government play an important role for successful transplantation, especially in developing countries.

Potential conflicts of interest

None.

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ผลลัพท์รยะยาวในผู้ป่วยได้รับการเปลี่ยนตับในโรงพยาบาลราชวิถี

สมบูรณ์ ทรัพย์วงศ์เจริญ, สอาด ตรีพงษ์กรุณา, กวิญ ลีละวัฒน์, กาญจนา รักษากุล

วัตถุประสงค์: *การศึกษานี้มีจุดประสงค์เพื่อศึกษาผลลัพท์และอัตราการอยู่รอดของผู้ป่วยที่ได้รับการเปลี่ยนตับในโรงพยาบาลวิถี*

วัสดุและวิธีการ: *ข้อมูลผู้ป่วยตั้งแต่ พศ. 2539-2553 จำนวน 21 ราย ที่เข้ารับการผ่าตัดเปลี่ยนตับมีอายุเฉลี่ย 44.3 ± 19.1 ปี โดยการใช้เทคนิคพิกกี้แบคและใส่น้ำเกลือเย็น 1 ลิตร เข้าหลอดเลือดดำพอร์ทัล เพื่อลดอุบัติการณ์บาดเจ็บจากการที่เลือดไหลกลับระบบ ร่วมกับการตรวจหลอดเลือดดำและแดงโดยใช้อัลตราซาวด์ เพื่อประเมินการอุดตันของหลอดเลือดแดงเฮปาติก และหลอดเลือดดำพอร์ทัล รวบรวมข้อมูลพื้นฐานภาวะแทรกซ้อน, เวลาขาดเลือด, ระยะเวลานอนในห้องวิกฤตและในโรงพยาบาล รวมทั้งอัตราการอยู่รอดของผู้ป่วย*

ผลการศึกษา: *มีผู้ป่วย 2 ราย ที่หยุดยากดภูมิคุ้มกัน เนื่องจากไม่มาติดตามการรักษาและกลับไปดื่มเหล้า สาเหตุการตายในผู้ป่วย 3 ราย หลังผ่าตัดเปลี่ยนตับไปนานมากกว่า 2 ปี เนื่องจากเสียเลือดมากในขณะเปลี่ยนข้อสะโพก, ภาวะการต้านตับชนิดเรื้อรัง และมะเร็งต่อมน้ำเหลือง อัตราอยู่รอด 5 ปี และ 10 ปี เท่ากับร้อยละ 62 และ 42 ตามลำดับ มีภาวะของท่อน้ำดีตีบ 1 ราย อีก 1 ราย มีรอยรั่วจากรอยต่อ ผู้ป่วย 2 ราย ต้องเข้ารับการผ่าตัดห้ามเลือดฉุกเฉิน เนื่องจากเลือดออกจากหลอดเลือดแดงเฮปาติก และหลอดเลือดดำรีโทรเฮปาติก ผู้ป่วย 1 ราย พบหลอดเลือดดำเฮปาติกอุดตันจากโรคเดิม Budd Chiari ผู้ป่วยมะเร็งที่มีจำนวนมะเร็ง 10 ก้อน กระจายในตับ 2 กลีบ ยังมีชีวิตมากกว่า 3 ปี หลังเปลี่ยนตับ โดยยังไม่พบการกลับมาเป็นใหม่ของมะเร็งตับ*

สรุป: *การผ่าตัดเปลี่ยนตับเป็นวิธีการรักษาที่ค่าใช้จ่ายสูง ผลที่ดีระยะยาวขึ้นกับยาราคาแพง เครื่องมือ และทีมงานที่ดี นโยบายและการสนับสนุนจากรัฐบาลมีผลต่อความสำเร็จ โดยเฉพาะประเทศที่กำลังพัฒนา*