"The Efficacy of Orthotopic Liver Transplantation in Patients with Different Liver Diseases"

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In General Surgery

By

Hussein Kalahy Ossman, M.S.

Supervisors

Prof. Dr. Abdallah Said Draz, FRCS, FROSE
Prof. of General and Pediatric Surgery
Faculty of Medicine- Ain Shams University

Prof. Dr. Madbouli Emam, M.D.
Prof. of General Surgery
Faculty of Medicine- Ain Shams University

John J. Fung, M.D., Ph.D.
Associate Professor of Surgery
Chief of Transplant Division
University of Pittsburgh

Kareem M. Abu-Elmagd, M.D., Ph.D.
Assistant Professor of Surgery
Transplant Division
University of Pittsburgh
USA

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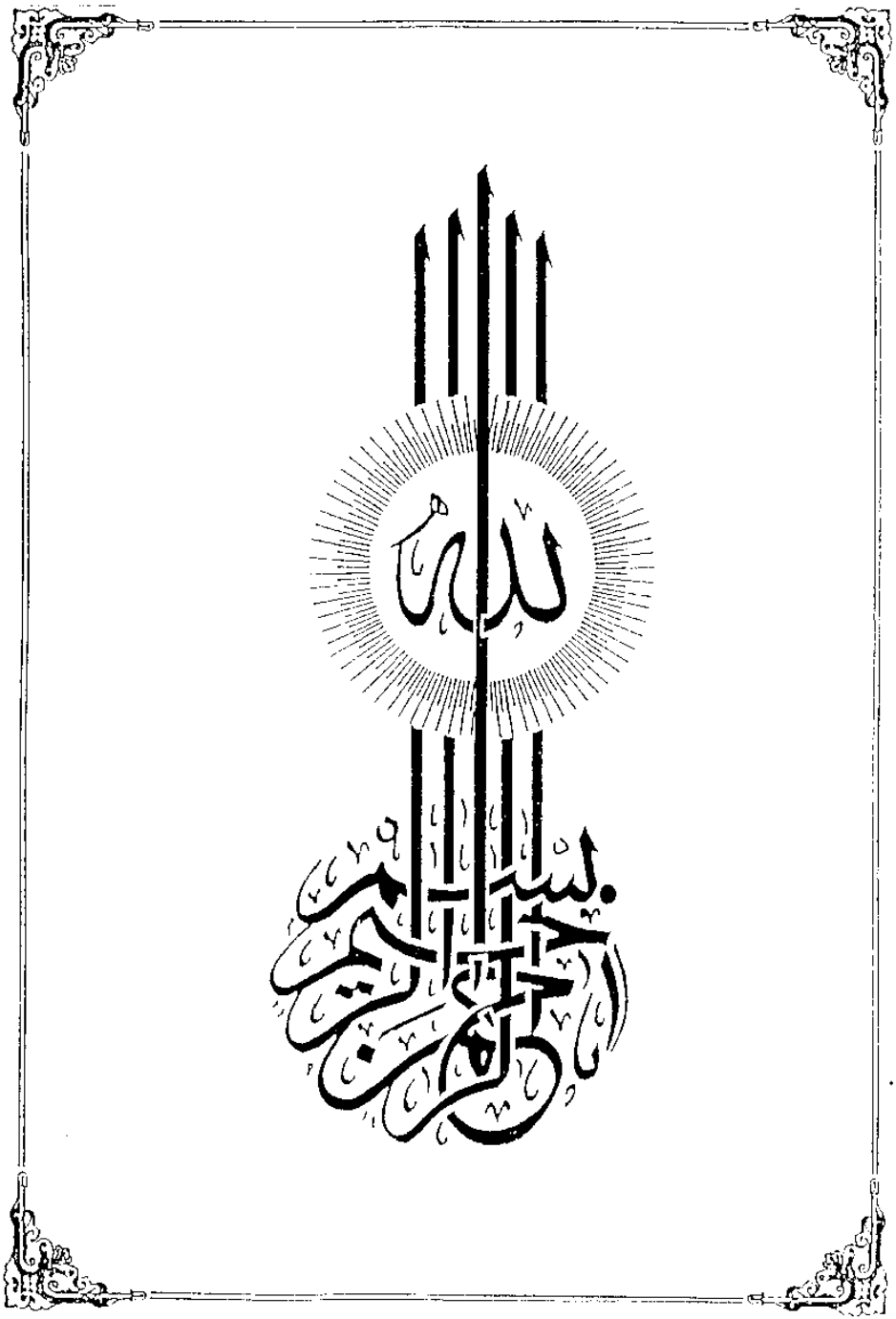

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INTRODUCTION

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Liver transplantation (fig.1) is the treatment of choice for patients with irreversible acute and chronic hepatic diseases (Starzl TE et al, 1989). The concept of transplanting the entire liver was first mentioned in medical literature in 1955 (Welch CS, 1955). The first human liver transplantation was performed on March 1, 1963 by Dr. Thomas Starzl in Denver, Colorado (Starzl et al, 1963). Since that time, the idea of transplanting a liver became a practical reality and thereby helped the specialty of hepatology and changed its aspects over the past 30 years to the extent that it is no longer possible to have a liver disease center without hepatic transplant capability (Starzl TE et al, 1990).

Liver transplantation has advanced remarkably over the past three decades due to parallel advances in organ procurement, operative technique, immunosuppression and infection control. Among the most important advances are use of the University of Wisconsin (UW) organ preservation solution, the employment of venovenous bypass and/or "piggyback" operative technique, the development of cyclosporine A (CyA) and FK 506 and the emergence of acyclovir, ganciclovir, foscarnet, and alpha interferon to combat life-threatening viral infections.

Still, one of the major obstacles for performing this life saving operation is the current organ shortage. In addition, liver transplantation from a brain death donor has not yet been accepted by some countries such as Japan and Egypt. These issues

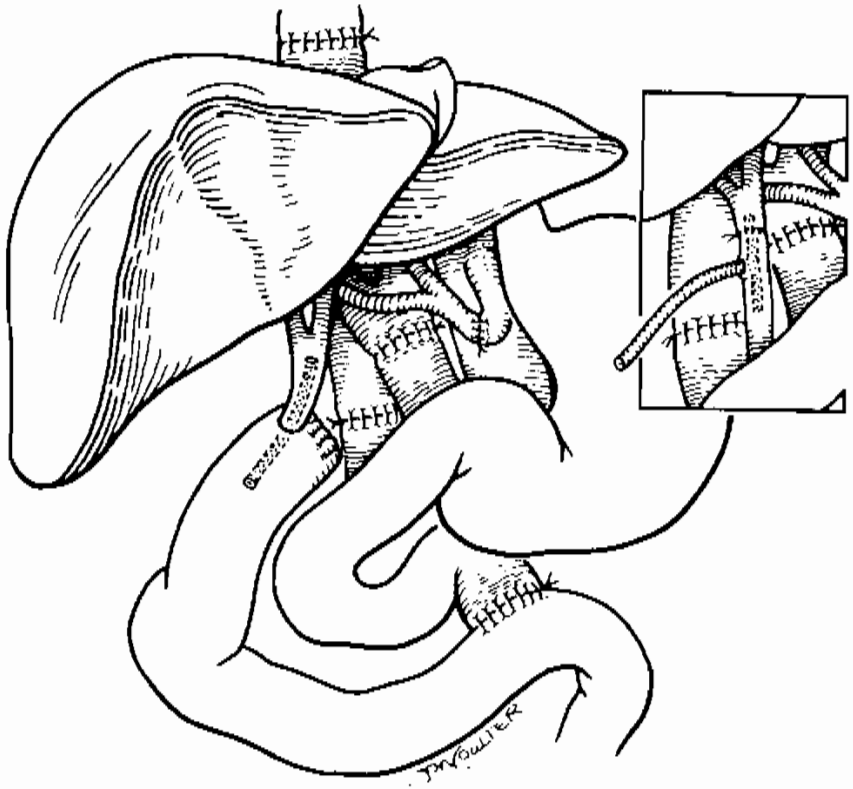

Fig. (1) : The various vascular and biliary anastomosis in a transplanted whole human liver. From starzl TE et al, 1991.

are being partially addressed by cutdown liver transplantation, "split liver" transplantation (Emond JC et al, 1990), and living related donations (Emond JC et al, 1993).

Disease recurrence is a major risk factor that affects long term graft and patient survival while short term survival after liver transplantation is related to the pre-operative status of the patient. Good pre-operative assessment and intensive care, better case selection and the current investigation of some antiviral therapy may help improvement of both short and long term graft/patient survival. The next decade is likely to see more progress in multivisceral transplantation, augmentation of chimerism by simultaneous bone marrow and solid organ transplantation, more availability of donor organs via more acceptance of organ donation and brain death criteria, and finally, the performance of cross-species xenografting.

The primary goal of this study is to evaluate the effect of the recipient original liver disease on the outcome after liver transplantation. Subsequently, this study will estimate the patient and graft survival,the quality of life after the transplant operation and the incidence of disease recurrence in the liver graft particularly in patients with pretransplant chronic viral, autoimmune and malignant liver diseases. Such informations may be helpful to determine patient candidacy with successful long term outcome particularly in countries such as Egypt where graft availability and socioeconomic circumstances are major limiting factors for cadaveric liver transplantation.

REVIEW OF LITERATURE

Indication for liver transplantation

INDICATIONS FOR LIVER TRANSPLANTATION

New immunosuppressive agents, better knowledge of anesthesiology and postoperative reanimations as well as refinement in surgical techniques modified the indications for and results of orthotopic liver transplantation (OLTx). At the beginning of the OLTx era, liver tumors that could only be removed by total hepatectomy were one of the most frequent indications. Nowadays, this indication is mostly abandoned in view of a high rate of recurrence and poor long-term results (Mentho G, et al, 1992). In contrast, the prognosis of fulminant hepatic failure has been dramatically improved by OLTx, once efficient organization system allowed adequate organ supply in addition to overall monitoring of patients' neurological status and emergency transplantation within a few hours.

The indications for liver replacement include the following:

A. Indications for primary liver transplantation

1) Viral hepatitis
   - viral A
   - viral B
   - viral B & D
   - viral C
   - Non A, Non B, Non C (herpes, CMV, others)

2) Alcoholic cirrhosis (inactive)

3) Autoimmune disorders
   - autoimmune hepatitis
   - primary biliary cirrhosis (PBC)
   - primary sclerosing cholangitis (PSC)

4) Metabolic disorders
   - alpha-1- antitrypsin deficiency
   - Wilson's disease
   - Glycogen storage disease
   - Hemochromatosis

- Tyrosinemia

5) Biliary atresia

6) Primary hepatic neoplasm

7) Hepatic veno-occlusive disease

8) Polycystic disease

9) Fulminant/sub-fulminant hepatic necrosis

B. Indications for retransplantation include failed prior graft:

1) Primary non-function (PNF)

2) Vascular complications

3) Biliary complications

4) Rejection

5) Recurrence of primary disease

6) Infection

The disease indications in pediatric patient (individuals under 18 years of age) are different from those in adults. In children, biliary atresia is the leading indication; in adults, it is post-necrotic cirrhosis. Other common indications in adults included primary biliary cirrhosis, sclerosing cholangitis and a large number of metabolic liver diseases (Van Thiel DH, et al 1988).

Lake and associates, 1993, divided the indications for liver transplantation generally into two groups (Lake JR, 1993):

A. Indications for liver transplantation according to the severity of disease:

* chronic liver disease with one or more of the following:
  - hepatorenal syndrome
  - recurrent spontaneous bacterial peritonitis

- serum albumin < 2.5 g/dl
- prothrombin time > 5 seconds prolonged
- serum bilirubin > 5.0 mg/dl

* cholestatic liver disease with serum bilirubin > 10 mg/dl

B. Indications for liver transplantation according to the severity of symptoms:

* cholestatic liver disease with one or more of the following:
  - intractable pruritis
  - metabolic bone disease
  - recurrent episodes of biliary sepsis
  - xanthomatous neuropathy
* chronic liver disease with one or more of the following:
  - intractable ascites
  - encephalopathy
  - bleeding from esophageal and/or gastric varices
  - fatigue
* metabolic disease of the liver with non-hepatic manifestations

I- *CHRONIC ACTIVE HEPATITIS AND CIRRHOSIS*:

Chronic active hepatitis encompasses a variety of progressive cirrhotic states caused by viral agents, toxins or autoimmune disorders. Biopsy samples typically exhibited inflammation, necrosis and fibrosis of the liver parenchyma with progression to frank cirrhosis over a variable time interval. Multiple etiologic agents have been identified including the

hepatitis B virus, C virus, D virus, non A non B non C (herpes, CMV, adenovirus and others) and several pharmacological agents (Jenkins, 1989).

Worldwide, chronic viral hepatitis leading to decompensated cirrhosis is due either to type B or C hepatitis and is the single most frequent indication for liver transplantation. Most of the patients with chronic type B hepatitis are in their fourth decade and should therefore have the potential for a long life following successful liver transplantation. The major impediment to achieving this goal has been the high rate of disease recurrence (Van Thiel et al, 1991).

* HEPATITIS B VIRUS:

Worldwide, it has been estimated that over 250,000 people die annually from HBV associated with acute and chronic liver disease (Margolis et al, 1991). The prevalence of hepatitis B virus (HBV) infection is highest in developing countries in North America, Western Europe and Australia. In areas of high HBV incidence, transmission is usually vertical from infected mother to child or horizontal within families. In intermediate areas of prevalence, HBV is spread horizontally, with the highest rate of infection occurring among older children, adolescents and adults. In areas of lower prevalence, HBV is primarily a disease of adolescents and young adults and is transmitted sexually or parenterally (Perrillo, 1993).

Hepatitis B, has been considered a relative contraindication to transplantation because of the high risk of viral reactivation in the donor organs. It is well known now that there is a much lower rate of HBV recurrence after the transplantation when there is no evidence of HBV replication (i.e. HBeAg and HBV DNA seronegative) at the time of transplantation. The severity of the recurrence is extremely variable, ranging from an asymptomatic deviation of the transaminase to cirrhosis.

Hepatitis B hyperimmune globulin (HBIG), hepatitis B vaccine (HBVx), and α-interferon (α-IFN) have been administered in some combination to such patients to prevent HBV infection in the new liver (Todo et al, 1991). The effectiveness of such therapies at clearing either the infection or the antigenemia is not established.

*** HEPATITIS C VIRUS:**

It is not known until 1989, with the application of newly available molecular techniques, that the virus responsible for the majority of transfusion-related hepatitis is HCV (Wright TL, 1993).

End-stage cirrhosis of hepatitis C virus, is now successfully treated by OLTx (Maddrey WC et al, 1988). In the present investigation, the diagnosis of HCV reactivity and recurrence can be easily diagnosed by second generation anti-HCV