HEPATOCYTES TRANSPLANTATION IN CHRONIC LIVER DISEASES.

Essay
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GENERAL SURGERY

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List of Abbreviations

Abbreviation	Meaning
ABO:	ABO system for blood grouping
ALF:	Acute Liver Failure
ALT:	Auxiliary Liver Transplantation
AOCLF:	Acute on Chronic Liver Failure
BAL:	Bio-Artificial Liver
CFSE:	Carboxyl Fluorescin Diacetate Succinimidyl Ester
D-gal:	D-Galactosamine.
D-MEM:	Dubleco's Modified Eagle Medium
EGF:	Epidermal Growth Factor
ESLD:	End Stage Liver Disease
FHF:	Fulminant Hepatic Failure
HCCs:	Hepatocellular Carcinoma
HGF:	Hepatocyte Growth Factor
HSCs:	Haemopoietic Stem Cells
HSS:	Hepatic Stimulatory Substance
HT:	Hepatocytes Transplantation
HtRT:	Human Telomerase Reverse Transcriptase
IDA:	Imino Diacetic Acid
LDL:	Low Density Lipoprotein
MARS:	Molecular Adsorbent Recirculating System
MEM:	Minimum Essential Medium
MHC:	Major Histocompatability Complex
NAR:	Analbuminemic Rat
OLT:	Orthotopic Liver Transplantation
OTC:	Ornithine Tramacarbamylase
RT-PCR:	Reverse Transcription Polymerase Chain Reaction
TNF:	Tumor Necrosis Factor

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زراعة الخلايا الكبدية فى حالات أمراض الكبد المزمنة.

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Introduction

The liver is an important organ which performs complex functions including metabolism, synthesis and detoxification. As a central metabolic organ the liver regulates the body's energy supply, secretes a diverse group of essential compounds and detoxifies the toxic waste by inactivation, recycling and excretion ***(Jamal et al., ٢٠٠٠)***.

Fulminant hepatic failure (FHF) is a multi-factorial process leading to instability and derangement of essential functions such as acid base balance, energy supply and thermoregulation. If not rapidly reversed, complications will lead to hepatic coma by affecting the brain and kidneys. With additional organ failure, recovery becomes irreversible and leads to a high patient mortality. The catastrophic failure of a previous normal liver is one of the most challenging emergencies in clinical medicine ***(Jamal et al., ٢٠٠٠)***.

Liver cell transplantation is a procedure that shows great promise for the treatment of many

diseases now treated definitively only, with whole organ transplantation. Organ transplantation involves major surgery, requires the use of scarce donor organs, is expensive and requires life-long immuno-suppression. Potential advantages of cell transplantation include a simpler, safer, less costly procedure that takes advantage of currently discarded liver segments, and could use stem or in-vitro expanded cells ***(Gupta and Chowdhury, ١٩٩٢)***.

Candidate diseases for liver cell therapy include acute liver failure, liver based metabolic diseases and end-stage chronic liver disease. There are much animal data on the effectiveness of this treatment for these conditions. There are mounting data on the safety and potential effectiveness of liver cell transplantation in humans. It is now widely accepted that liver cells have great regenerative capacity in vivo. This proliferative capacity enables transplanted cells to reconstitute injured, or metabolically defective, liver tissue ***(Mito and Kusano, ١٩٩٣)***.

Despite the spectacular success of whole or partial liver transplantation in the treatment of acute and chronic liver failure, and inherited metabolic diseases, the technique remains complex, expensive and associated with significant morbidity and mortality. Furthermore, the supply of cadaver donor organs has remained constant for a decade, while demand for transplantable livers is increasing progressively, outpacing the availability of donated cadaver organs ***(Jamal et al., ٢٠٠٠)***.

Although the use of adult living donors may abate the organ shortage to some extent, this procedure is not without significant risk to the donor and the recipient. In view of this, many investigators have evaluated transplantation of isolated liver cells as a less invasive alternative to whole organ transplantation or as a “bridge” while awaiting the availability of a donor liver ***(Goldstein et al., ٢٠٠٣)***.

In contrast to intact livers, hepatocytes could be cryo-preserved for immediate availability in emergencies. Since the recipient liver remains

intact, the metabolic risk of transplant rejection is minimized and the possibility of subsequent orthotopic liver transplantation or liver directed gene therapy remains open. This minimally invasive procedure requires minimal or no hospitalization, which should lower the cost of the procedure and permit earlier treatment of inherited or acquired liver disorders, thereby reducing complications of the diseases ***(Moshage et al., ١٩٨٨)***.

It is anticipated, therefore, that in the coming years, investigators will focus on identifying alternatives to adult primary hepatocytes for transplantation and methods for inducing selective proliferation of the transplanted cells. A brief discussion of the current issues in liver cell transplantation follows.

However, more extensive clinical studies and routine clinical application are hampered by the shortage of good quality of donor cells. To overcome these hurdles, current research has focused on the search for alternatives to adult primary hepatocytes, such as liver cell progenitors,

fetal hepatoblasts, embryonic, bone marrow or umbilical cord blood stem cells and conditionally immortalized hepatocytes.

Cross-species hepatocyte transplantation is also being explored. It is hoped that ongoing research will permit the application of hepatocyte transplantation to the treatment of a wide array of liver diseases.

Several approaches are actively investigated to offer a potential solution to the limited availability of hepatocytes including the development of stem cells, use of bone marrow, in-vitro expansion of primary hepatocytes and use of conditionally immortalized hepatocytes. ***(Schumacher et al., ١٩٩٦)***.

Aim Of The Work

The aim of this essay is studying of hepatocytes transplantation in chronic liver disease

Historical review of hepatocyte transplantation

- **How the concept of whole liver transplantation has been progressed to hepatocyte transplantation:**

Hepatocyte transplantation and the technology associated with it were not ideas that just came out of the blue. Immortality has been humankind's oldest dream and produced the chimera of legend. The chimera has come true in the latter half of the ٢٠th century through the development of advanced surgical techniques and investigation of the rejection reaction and the means to prevent it. Organ transplantation is now an established therapeutic modality which enables a damaged organ to be replaced with a functioning new one. In ١٩٥٦, the first experimental trials of liver transplantation as a treatment of irreversible hepatic failure involved auxiliary liver transplantation and OLT in dogs as reported by Cannon et al., at the same year ***(Goodrich et al.,*** ١٩٥٦***)***.

The first clinical liver transplant was performed at ١٩٦٣, but long-term survival was not achievable due to the status of medicine at that time

and lack of effective immunosuppressive techniques. After the introduction of immuno-suppressants such as azathioprine and prednisone, and technical advances in transplant surgery, liver transplantation was no longer an experimental therapeutic technique and by ١٩٨٣ had become an established method for treatment of hepatic failure. Organ donation from brain-dead donors, the introduction of new immuno-suppressants such as cyclosporin and FK-٥٠٦, and the development of the Bio-pump have resulted in a marked improvement in the outcome of liver transplantation. The indications for liver transplantation have expanded from end-stage liver disease to metabolic disorders and acute hepatic failure and shortage of donor organs is now a serious problem in transplantation medicine ***(Wiesner,*** ١٩٩٦***)***.

☛ **Partial liver transplantation:**

While only one liver is available from each donor, the idea of partial liver transplantation came from the fact that the liver has an excellent regenerative capacity. A large number of animal experiments conducted in the ١٩٦٠s confirmed that partial liver transplantation was technically possible

and that transplanted partial liver grafts regenerate to an appropriate volume in proportion to the size of the recipient ***(van der Heyde et al.,*** ١٩٦٦***)***. It took approximately ٢٠ years before partial liver transplantation was first applied clinically. In ١٩٨٤, a reduced-size adult partial liver graft was successfully transplanted into a pediatric patient. Split liver transplantation, which enables the transplantation of two partial liver grafts from one donor liver into two recipients, was first attempted in ١٩٨٨, and living-related partial liver transplantation was performed successfully in the following year. The road from whole liver transplantation to partial liver transplantation was thus completed ***(Bismuth & Hussien,*** ١٩٨٤***)***.

In Japan, where organ donation from brain-dead donors is not permitted, more than ٣٠٠ living-related liver transplants have been performed and have produced better results than whole liver transplantation. It has already been confirmed that the volume of transplanted partial liver grafts increases in proportion to the growth of pediatric recipients. The concept of partial liver transplantation utilizing liver segments or lobes has