

Liver Transplantation: Mesenchymal Stem Cell (MSC) Therapy as Alternative to Liver Transplantation

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Abstract– Liver transplantation was stated as the best solution for treating the end-stage liver disease patients but as there are some serious problems such as immune rejection, patients had to take immunosuppressive drugs for a long time after their transplantation process and this often leads to many dangerous side effects. So, an urgent alternative method was needed. Mesenchymal stem cell therapy (MSCT) after research become one of the very efficient methods to replace transplantation and its complicated consequences due to its immunomodulation property. This research mainly aims to show the effectiveness of Mesenchymal stem cell therapy (MSCT) through overviewing the current research and clinical trials which proved the safety of using the Mesenchymal stem cell therapy (MSCT) as alternative to transplantation with a high percentage. As a result, to the complications that might make someone lose his life or a vital part of his body, a new method in this paper would be identified to replace liver transplantation using python programming language and prop ability percentage to prove its essential need.

I. INTRODUCTION (HEADING 1)

YOUR GOAL IS TO SIMULATE THE APPEARANCE OF PAPERS LIVER FAILURE HAPPENS WHEN A LARGE AND IMPORTANT PARTS OF THE LIVER ARE DAMAGED WITHOUT HAVING THE ABILITY TO REGENERATE OR FIX THEMSELVES, SO LIVER TEND TO STOP FUNCTIONING NORMALLY. THERE ARE TWO TYPES OF LIVER FAILURE, ACUTE LIVER FAILURE (ALF) WHICH OCCURS WITHIN A MATTER OF DAYS OR WEEKS ACCOMPANIED WITH SEVERAL COMPLICATIONS AND MOST PEOPLE WHO GET THIS TYPE OF FAILURE DO NOT HAVE ALREADY EXISTING LIVER

DISEASE THROUGHOUT THEIR LIVES. FOR THE SECOND TYPE, CHRONIC LIVER FAILURE (CLF) WHICH OCCURS WHEN A DAMAGED TISSUE REPLACES THE HEALTHY TISSUE AND OVERTIME IT CAUSES LIVER TO STOP WORKING LEADING TO A CHRONIC LIVER DISEASE. LIVER TRANSPLANTATION IS ONE OF THE METHODS WHICH SOMETIMES TREAT LIVER DISEASES EFFICIENTLY, BUT AS MOST OF THE PEOPLE RECEIVING THE TRANSPLANTS MIGHT FACE SOME HARD COMPLICATIONS SUCH AS ORGAN REJECTION DUE TO IMMUNOSUPPRESSION, STEM CELLS HAVE BEEN TESTED TO SOLVE THIS PROBLEM THROUGH MESENCHYMAL STEM CELLS (MSC).

LIVER TRANSPLANT IS A SURGICAL PROCEDURE THAT ELIMINATES A LIVER WHICH IS NO MORE OPERATING NORMALLY AND NEEDS TO REPLACE IT WITH A NORMAL WORKING LIVER OF A DECEASED INDIVIDUAL OR PART OF A LIVING DONOR'S HEALTHY LIVER. THE LIVER IS THE PRIMARY INTERNAL ORGAN THAT HAS MANY IMPORTANT ROLES, INCLUDING THE ABSORPTION OF FOODS, DRUGS AND HORMONES, THE PRODUCTION OF BILE THAT LETS THE BODY DIGEST FATS,

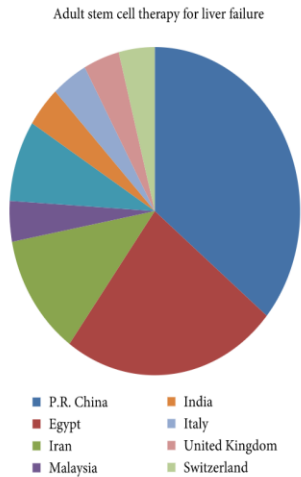
CHOLESTEROL AND FAT-SOLUBLE VITAMINS, PROTEINS THAT AID BLOOD CLOTTING, THE CLEARANCE OF BLOOD BACTERIA AND CONTAMINANTS, THE PREVENTION OF INFECTION AND THE REGULATION OF IMMUNE RESPONSES.

LIVER FAILURE IS DESCRIBED AS DECOMPENSATION COMPLICATIONS OF SOME DEGREE OF ASCITES, ENCEPHALOPATHY, AND COAGULOPATHY, AND OTHER LIVER PHYSIOLOGICAL FUNCTION IS AFFECTED. LIVER FAILURE MAY BE DIVIDED INTO THREE FORMS IN THE GIVEN DISEASE COURSES, PATHOLOGICAL MODIFICATIONS, AND CLINICAL PRESENTATIONS, AS: ACUTE LIVER FAILURE (ALF) HAS BEEN LINKED WITH MANY COMPLICATIONS WITHIN 48 HOURS TO MANY DAYS. ADDITIONAL JAUNDICES AND ASCITES ARE SHOWN AS ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) WITH UNDERLYING CHRONIC LIVER DISEASE THAT LEADS TO THE ACCELERATED PROGRESSION OF LIVER DAMAGE AND CHRONIC LIVER FAILURE (CLF) TENDS TO OCCUR FOR SEVERAL MONTHS OR YEARS WITH CHRONIC LIVER DISEASES. THEREFORE, ACLF AND CLF OFTEN OCCUR. ALSO, THEIR MORTALITY RATE VARIES FROM 40 TO 80 PERCENT. BOTH PHYSICIANS AND SURGEONS, WHICH INCLUDED MOSTLY NUCLEOSIDE ANALOGS, USED INTEGRATED THERAPY FOR INPATIENT TREATMENT WITH ALF, ACLF AND CLFF. IN ADDITION TO THE DIFFICULT-TO-ACQUIRE COMPLICATIONS OF POSTOPERATIVE IMMUNOSUPPRESSION WITH LIVER TRANSPLANTATION, ONLY AROUND 5,000 PATIENTS UNDERWENT HEAVY LIVER TRANSPLANTATION LAST YEAR. LIVER RESTORATION IS STILL CONSIDERED IN CLINICAL PRACTICE TO BE AN IDEAL ALTERNATIVE THERAPEUTIC

APPROACH TO LF BY ACTIVATING MATURE HEPATOCYTES, ENDOGENOUS STEM CELLS AND CIRCULATING STEM CELLS FOR LIVER CELL REGENERATION.

MESENCHYMAL STEM CELLS (MSC) WHICH ARE TESTED TO BE AN EFFECTIVE ALTERNATIVE TO TRANSPLANTATION, HAVE MANY CHARACTERISTICS SUCH AS DIFFERENTIATION, ANTI-INFLAMMATION AND IMMUNOMODULATION AND THEY ARE MAINLY EXTRACTED FROM THE BONE MARROW, ADIPOSE TISSUE, AND UMBILICAL CORD. AFTER THE CLINICAL TRIALS AND EXPERIMENTS ON THE EFFECT OF MESENCHYMAL STEM CELLS, IT WAS STATED THAT IT COULD HELP IN TWO WAYS WHICH REGENERATING THE TISSUE CELLS IN A DIRECT WAY OR INDIRECTLY ENHANCE AND ACTIVATE THE IMMUNE CELLS. IT WAS FOUND THAT WITHIN 3 MONTHS AFTER USING THE MESENCHYMAL STEM CELLS, THERE IS AN OBVIOUS IMPROVEMENT IN LIVER DISEASE. THERE IS MORE THAN ONE TYPE OF MESENCHYMAL STEM CELL THERAPY WHICH ARE ENDOGENOUS STEM CELL ACTIVATION, PARACRINE EFFECT, ANGIOGENESIS, AND CELL FUSION, IN ADDITION TO ACTUAL TRANS DIFFERENTIATION. AND ACCORDING TO THE STUDIES AND TRIALS, THIS RESEARCH AIMS TO PROVIDE AN OVERVIEW AND EVIDENCE ABOUT THE EFFICIENCY OF MESENCHYMAL STEM CELL THERAPY IN TREATING LIVER FAILURE PATIENTS

A. Figures and Tables



Fig(1). Country distribution of adult stem cell therapy for liver failure [8]

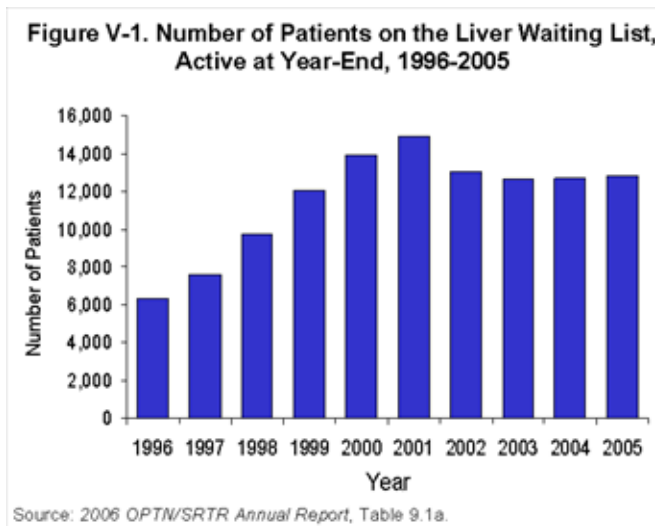


Fig (2). Number of Patients on the Liver Waiting List Active [31]

TABLE I: Transplant team detail [5]

Team member	Role
Transplant physician(ICU practitioner)	He is doctor who is expert in the field of medicine (e.g. specialist of heart, kidney or liver). Supervision and complete care is taken by this physician.
Transplant Surgeon	They are well trained surgeons in field of surgery(e.g. heart surgery, liver surgery,

	abdominal surgery, etc.)
Transplant Pharmacist	They will dispense medications and guide patients in taking them.
Transplant Social Worker	Emotional and family support and practical suggestions is given by this social worker to help patient to obtain proper care and benefits. They also suggest social, psychological and financial resources available.
Transplant Dietitian	As diet is important part of this transplant, they are having expertise in nutrition and right meals suitable for patients. They supervise, plant and suggest diet to patient.
Financial Counselor	They people help to arrange various funds from govt. organizations. They also help for billing, advance, settlement of accounts.
Anesthetics	To induce, manage anesthesia during surgery.
Osteologist, cardiologist, endocrinologist, pulmonologist, vascular surgeon, nephrologist	For suggestion in surgery in their respective fields.
The psychologist or psychiatrist	They assist in keeping normal mental state. They suggest some medication and help to keep good state of mind.

TABLE II: History of liver transplant [30]

1958	Research programs on liver replacement at Northwestern and Harvard
1963	First liver transplant (Univ. of CO)
1967	First long survival
1979	Cyclosporine
1987	Univ. of WI solution for improved organ preservation
1989	FK 506
1999	Living Donor liver transplantation

B. Abbreviations and Acronyms

(ALF): Acute liver failure

(CLF): Chronic liver failure

(MSCT): Mesenchymal stem cell therapy

C. Equations

$$\text{MELD} = 3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$$

(1)

II. METHODOLOGY

COMPREHENSIVE ANALYSIS OF LITERATURE WAS CONDUCTED IN MAJOR MEDICAL JOURNALS AND SEVERAL PRIMARY SOURCES WERE CHOSEN TO BE USED IN THIS PAPER. 103 PATIENTS WERE RECRUITED TO PARTICIPATE IN THE STUDIES; 50 WERE IN THE TRANSPLANT GROUP, AND THE OTHER PATIENTS WERE IN THE CONTROL GROUP. CONTROLLED TRIALS WITH LARGER COHORTS OF PATIENTS HAVE FURTHER CONFIRMED THE FEASIBILITY OF MSC TRANSPLANTATION THERAPY FOR VIRUS-RELATED CIRRHOSIS. COMPARED TO THE CONTROL GROUP, THE PATIENTS TRANSPLANTED WITH MSCS SHOWED SIGNIFICANTLY IMPROVED LIVER FUNCTION, AS INDICATED BY THE ELEVATION OF SERUM ALBUMIN LEVELS, A DECREASE IN TOTAL SERUM BILIRUBIN LEVELS, AND A DECREASE IN THE SODIUM MODEL FOR ENDSTAGE LIVER DISEASE SCORE (MELD SCORE) OF THE 14

PATIENTS WHO RECEIVED THE TRANSFUSIONS, 8 SUFFERED FROM CHB-RELATED DECOMPENSATED LIVER CIRRHOSIS, 3 CHB-RELATED HCC, 2 FROM ALCOHOLIC LIVER CIRRHOSIS AND 1 FROM CHB+ ALCOHOLIC LIVER CIRRHOSIS. BOTH GROUPS RECEIVED THE TYPICAL IMMUNOSUPPRESSION REGIMENTS ASSOCIATED WITH LIVER TRANSPLANT AND WERE FOLLOWED FOR 12 WEEKS.

USING THE UNITED STATES ORGAN TRANSPLANT DIRECTORY, DATA WAS COLLECTED ON 12,000 PATIENTS AND A SIMULATION WAS BUILT TO COMPARE WAITING TIMES OF PATIENTS RECEIVING TRANSPLANTS WITH THOSE WHO CAN HYPOTHETICALLY RECEIVE ALTERNATIVE TREATMENTS SUCH AS STEM CELL INFUSIONS. THE MEAN WAIT TIME FOR A PATIENT ON THE TRANSPLANT WAITLIST WAS 179 DAYS (MEDIAN 246). ALTERNATIVE METHODS OFFER FAR SHORTER WAIT TIMES AND CAN POTENTIALLY SAVE THOUSANDS OF DEATHS EACH YEAR.

THE DATA WE HAVE USED:

[HTTPS://DOCS.GOOGLE.COM/SPREADSHEETS/D/17Ah4e1dBTFkJwQEPZLwTLb0BUxoRYG-955P8hCuPoMM/EDIT?USP=SHARING](https://docs.google.com/spreadsheets/d/17Ah4e1dBTFkJwQEPZLwTLb0BUxoRYG-955P8hCuPoMM/edit?usp=sharing)

III. ANALYSIS

THE IMPROVEMENT OF LIVER FUNCTION WAS FOUND AFTER MSC TREATMENT IN A SHORT TIME OF LESS THAN 3 MONTHS, ESPECIALLY ALT (IN HALF A MONTH), WHICH MIGHT BE CLOSELY LINKED WITH THE MECHANISMS OF MSCS IN THE TREATMENT OF PATIENTS WITH LF. WANG ET AL. HYPOTHESIZED THAT MSCS COULD PROMOTE HEPATOCYTE

PROLIFERATION TO STIMULATE LIVER REGENERATION; ON THE OTHER HAND, IT DIFFERENTIATED INTO THE PARENCHYMAL HEPATOCYTES TO IMPROVE THE LIVER FUNCTION. HOWEVER, OTHER PREVIOUS STUDIES REVEALED THAT IT WAS VIA SECRETING PROTECTIVE FACTORS (HEPATOCYTE GROWTH FACTOR (HGF) AND EPIDERMAL GROWTH FACTOR (EGF)) THAT STRUCTURED A WELL-DONE MICROENVIRONMENT TO PREVENT AGGRESSIVE DAMAGE. MOREOVER, IMMUNOMODULATION AND ANTIFIBROSIS OF MSCs MAY PLAY AN IMPORTANT ROLE IN LIVER REGENERATION AND DELAYING THE LIVER CELL PROGRESSIVE DAMAGE BY DOWNREGULATION OF THE LEVEL OF LIVER FIBROSIS MARKER IN LIVER CELL FAILURE. OUR RESULTS SHOWED THAT IN 0.5 TO 3 MONTHS AFTER MSCT, THE EFFICACY OF MESENCHYMAL STEM CELLS WAS PERFORMED. TERAJ ET AL. SHOWED THAT LIVER CELLS REPOPULATED 25% OF THE RECIPIENT'S DAMAGED LIVER BY ONE MONTH AFTER MSCT AT THE MODEL OF MICE WITH LF, WHICH WAS SUPPLEMENTARY OF OUR RESULTS. THEN, OUR OTHER NEW FINDING WAS THAT MSCT HAD A MORE DOMINANT ADVANTAGE ON ACLF THAN ON CLF. FIRSTLY, THE HEPATOCYTES HAVE LIVELY REVERSE-DIFFERENTIATE INTO STEM CELL TO TAKE PARTICIPATION IN THE REGENERATION OF LIVER CELLS, WHILE THE HEPATOCYTES OF CLF PATIENTS ALMOST LOST THEIR SECRETORY AND DIFFERENTIATION CAPACITY (E.G., HEME OXYGENASE-1). IN ADDITION, MANY INFLAMMATORY CELLS OF T-LYMPHOCYTE AND B-LYMPHOCYTE WERE INVOLVED IN THE ACUTE INFLAMMATION ACTIVITY OF ACLF, WHICH COULD BE REPRESSED BY MSCs

CHARACTERIZED BY ITS ANTI-INFLAMMATORY ABILITY. THEREFORE, IN THE ABOVEMENTIONED STATEMENTS, THE MESENCHYMAL STEM CELLS HAD THE ABILITY OF IMPROVING LIVER FUNCTION AND PROMOTING LIVER REGENERATION.

IV. RESULTS

OUR STUDY ANALYZED THE IMPROVEMENT OF LIVER CAPACITY (ALT, TIBL, ALB, AND PT) AFTER MSCT AND THE EFFECT OF MSCT ON THE VISUAL MODERATION OF THE IMMUNE FLEXIBILITY OF UNDEVELOPED CELLS. ALL OF THEM CAN PROVIDE ACCURATE SURVEY OF MSC APPLICATION IN PATIENTS. THESE NEW TREATMENT ALTERNATIVES CAN EFFECTIVELY SUPPRESS LIVER CELLS, AND THE RESULTS WILL ALSO PROVIDE AN EXTRAORDINARY BENEFIT TO PHYSICIANS AND CLINICIANS IN THE FUTURE. MSCs ARE A PROMISING AND TESTING METHODOLOGY PREPARING TO TREAT LIVER DISAPPOINTMENT. HOWEVER, MORE EFFORTS NEED TO BE MADE TO OVERCOME THE PROBLEMS BEFORE THIS NEW METHODOLOGY CAN BE APPLIED SAFELY AND APPROPRIATELY TO PEOPLE. DUE TO THEIR ABILITY TO DIFFERENTIATE IN THE LIVER IN ADDITION TO ITS IMMUNOLOGICAL PROPERTIES, STEM CELLS ARE THERAPEUTIC AGENTS THAT PREDISPOSE TO THE TREATMENT OF ACUTE LIVER AND CIRRHOSIS. HOWEVER, MANY PROBLEMS REMAIN, INCLUDING CONFLICTING DATA REGARDING THE INTERFERENCE OF MESENCHYMAL STEM CELLS IN THE BODY AND THEIR LONG-TERM EFFICACY, POTENTIAL RISKS OF MALIGNANT TRANSFORMATION, AND UNWANTED CHANGES IN VIVO, LIMITING THEIR ABILITY TO BE USED AS THE MAIN DOMINANT TREATMENT. AN APPROACH TO LIVER

REGENERATION. THE MAIN FACTOR DETERMINING NUMBER OF TRANSPLANTS PER YEAR ARE DONORS. SINCE STEM CELL THERAPY DOES NOT REQUIRE A DONOR, AVERAGE WAIT TIMES CAN BE REDUCED TO UNDER 30 DAYS. ACCORDING TO SIMULATION, STEM CELLS ARE PRIMITIVE, NON-SPECIALIZED CELLS THAT ARE ABLE TO DIVIDE AND PRODUCE NEW CELLS OF DIFFERENT TYPES DUE TO THEIR ABILITY TO DIFFERENTIATE INTO LIVER CELLS IN ADDITION TO THEIR IMMUNE PROPERTIES AND THE ABILITY TO SECRETE NUTRITIONAL FACTORS. THUS, THE ORGAN IS ABLE TO GROW AND REGENERATE DAMAGED TISSUE TO TREAT LIVER FAILURE WITHOUT THE NEED FOR A LIVER TRANSPLANT.

V.CONCLUSION

LIVER FAILURE HAS MANY CAUSES; THEREFORE, PEOPLE NEED TRANSPLANTATION THAT STARTS FROM THE WAITING LISTS THAT THE COMMITTEES IN EACH CITY ARE RESPONSIBLE FOR. THE DONATION PROCESS IS AN INTEGRAL PART OF TRANSPLANTATION PROCESS, THERE ARE TYPES OF DONATION SUCH AS CADAVER DONATION AND BRAIN DEATH. THE ORGAN IS SELECTED FOR WHO ARE MATCHED WITH BLOOD GROUP'S DONOR AND AFTER APPLYING SOME TESTS, THE PATIENT UNDERGOES THE OPERATION BUT THERE IS ALWAYS A RISK OF ORGAN REJECTION OR SUCH INFECTION. SO, IT SHOULD BE AN ALTERNATIVE METHOD TO AVOID THESE RISKS THAT MAY HAPPEN AFTER TRANSPLANTATION WHICH IS STEM-CELL THERAPY. AS STEM CELLS VARIOUS FUNCTIONS SUCH AS IMMUNOMODULATION, ANTI-INFLAMMATION, PROMOTION OF TISSUE REPAIR AND PRODUCTION OF GROWTH FACTORS.

ESPECIALLY MESENCHYMAL STEM CELLS COULD PUT DOWN THE PROGRESSION OF END-STAGE LIVER DISEASE.

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