The Effect of Intraoperative Magnesium-Sulfate Supplementation on the Reperfusion Injury in Living Donor Liver Transplantation

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by

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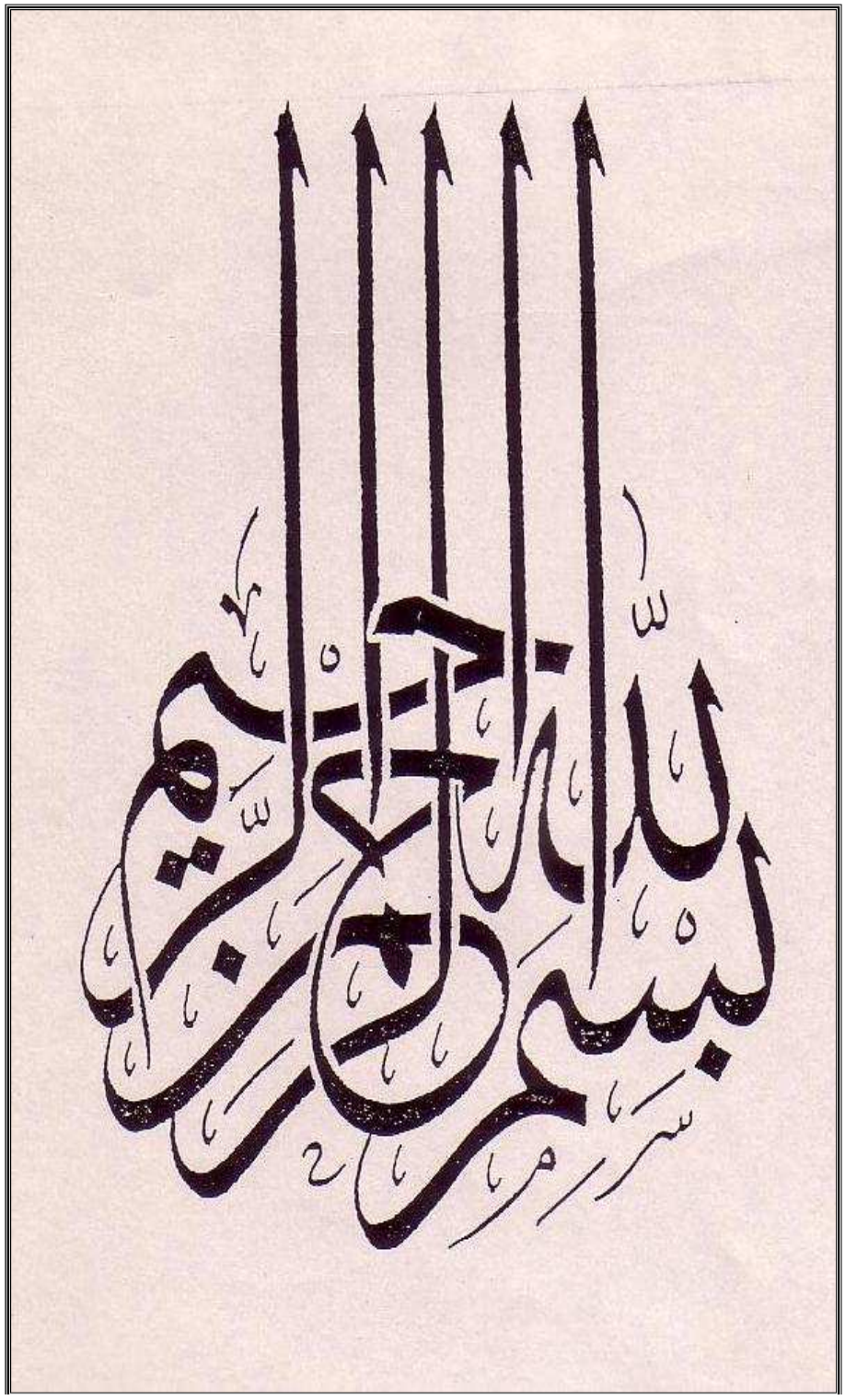
بسم الله الرحمن الرحيم

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Contents

List of abbreviations

AIH	:Auto immune hepatitis
ALD	:Alcoholic Liver Disease
ALF	:Acute Liver Failure
ALT	:alanine aminotransferase
ASA	**:**American Society of Anesthesiologists
AST	:aspartate aminotransferase
ATP	:adenosine triphosphate
AV	:Atrioventricular
BMI	:Body mass index
BP	:Blood pressure
Ca	:Calcium
CTP	:Child-Turcotte-Pugh Classification of Liver Disease
DDLT	:Deceased donor liver transplant
DNA	:deoxyribonucleic acid
ECG	:Electrocardiogram
ELTR	**:**European Liver Transplant Registry
ESLD	:End stage liver disease
HAT	:Hepatic artery thrombosis

HBIG :hepatitis B immunoglobulin

HCC :Hepatocellular carcinoma

HCV :Hepatitis c virus

HIV :Human immunodeficiency virus

I/R :ischemia-reperfusion

IL :Interleukin

INF :Interferon gamma

INR :International Normalized Ratio

K :Potassium

LDLT :Living donor liver transplantation

MELD :Model for End-Stage Liver Disease

Mg :Magnesium

MHC :Major histocompatibility complex

MMF :mycofenolate mofetil

mTOR :Mammalian target of rapamycin

NMDA :N-Methyl-D-aspartic acid

NO :Nitric oxide

ºC :Degree Celsius

PAF :Platelet activating factor

PaO_2 :Partial pressure of oxygen

PAP :pulmonary arterial pressure

PBC :primary biliary cirrhosis

PDF :primary dysfunction

PNF :primary non-function

POD :Postoperative day

PRS :Post reperfusion syndrome

PSC :primary sclerosing cholangitis

RHA :Right hepatic artery

RPV :Right portal vein

TDP :torsades de pointes

TF :tissue factor

TNF :Tumor necrosis factor alpha

UK :United kingdom

UNOS :The United Network for Organ Sharing

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Introduction

Magnesium (Mg^{2+}) is an important electrolyte that plays a key role in numerous physiological processes. ATP must be bound to a magnesium ion in order to be biologically active and nucleic acids have an important range of interactions with Mg^{2+}. The binding of Mg^{2+} to DNA and RNA stabilizes its structure. Both Mg^{2+} and Ca^{2+} regularly stabilize membranes by the cross-linking of carboxylated and phosphorylated head groups of lipids (**Barrera, *et al.,* 2000**).The ionized fraction is the physiologically active form, and less than 1% of total body magnesium is present in circulating blood. Serum magnesium exists in ionized form (62%), protein-bound (33%) and anion-complexed (5%) forms (**Fawcett, *et al.,* 1999**).

Hypomagnesemia is common in surgical, and critically ill patients; with the prevalence as high as 20% (**Barrera, *et al.,* 2000).** It causes cardiovascular, neuromuscular and coagulation dysfunctions, also associated with increased inflammatory response and mortality. Moreover; hypomagnesemia is a common finding following cardiac, major gastrointestinal and liver transplant surgery (**Lanzinger, *et al.,* 2003).** Total Hypomagnesemia invariably occurs during Living donor liver transplantation (LDLT) mostly because of transfusion-related citrate toxicity and chelation of magnesium during the anhepatic phase (**De Wolf, *et al.,* 1996**).

Patients with end-stage liver disease (ESLD) are prone to Hypomagnesaemia as a result of malnutrition, malabsorption, diarrhea, secondary hyperaldosteronism and diuretic treatment (**Diaz, *et al.,* 1996).**

Significant hemodynamic derangement usually occurs immediately after declamping of the portal vein due to reperfusion of the grafted liver. Profound hypotension, systemic vasodilatation, and a decrease in cardiac output have been reported, this is called postreperfusion syndrome (PRS). This hemodynamic instability usually requires adequate and aggressive cardiovascular pharmacologic intervention and fluid support. It takes over a period of 30 to 60 minutes to recover. *Since the severity of PRS correlates with the patient and allograft outcome, prevention of its occurrence or attenuation of the hemodynamic changes may improve the outcome. However, not much knowledge is known about how to protect against this reperfusion injury* (**Andreas, *et al.,* 2010**).

Magnesium supplementation is indicated during OLT to prevent the deleterious effects of hypomagnesemia and to produce many beneficial effects of magnesium such as coronary vasodilatation, reduced dysrhythmias, reduced afterload, sympatholysis, reduced reperfusion injury, improved coagulation, neuromodulation, bronchodilation, reduced inflammatory response, and efficient energy metabolism (**Bussiere, *et al.,* 2002).**

Aim of the Work

The aim of the study is to assess the efficacy and safety of intraoperative magnesium supplementation in the prevention of perioperative hypomagnesemia and its effect(s) on the graft function and to minimize the reperfusion derangement usually occurs after declamping and its effect on early graft function.

Liver transplantation

Liver transplantation or hepatic transplantation is the replacement of a diseased liver with a healthy liver allograft. The most commonly used technique is orthotropic transplantation, in which the native liver is removed and replaced by the donor organ in the same anatomic location as the original liver. The first human liver transplantation was performed in 1963 in Denver, USA, by Thomas Starzl ***(Starzl et al. 1963).*** During the past 40 years, liver transplantation has been evolved from a highly experimental procedure into the treatment of choice for acute liver failure (ALF), end-stage liver disease, and liver tumors of limited size and number. In Europe it was pioneered by Sir Roy Calne, who in 1968 performed the first liver transplantation in Cambridge, UK ***(Busuttil RW, and Tanaka K 2003)***.

Living donor liver transplantation (LDLT) has emerged in recent decades as a critical surgical option for patients with end stage liver disease, such as cirrhosis and/or hepatocellular carcinoma often attributable to one or more of the following: long-term alcohol abuse, long-term untreated hepatitis C infection, long-term untreated hepatitis B infection. The concept of LDLT is based on the remarkable regenerative capacities of the human liver and the widespread shortage of cadaveric livers for patients awaiting transplant and its prohibition in our country. In LDLT, a piece of healthy liver is surgically removed from a living person and transplanted into a recipient, immediately after the recipient's diseased liver has been entirely removed***(Cameron et al.2006).***

In a typical adult recipient LDLT, 55 to 70% of the liver (the right lobe) is removed from a healthy living donor. The donor's liver will regenerate approaching 100% function within 4–6 weeks, and will almost reach full volumetric size with recapitulation of the normal structure soon thereafter. It may be possible to remove up to 70% of the liver from a healthy living donor without harm in most cases. The transplanted portion will reach full function and the appropriate size in the recipient as well, although it will take longer than for the donor ***(Koffron and* Stein. *2008)***,.

Patient outcome has improved along with advances in patient selection, organ preservation, surgical techniques, perioperative anesthetic and intensive care, infection control, and immunosuppression. Currently in Europe, the overall 1-year survival is 82% and 10-year survival 61%, with the best outcome in recipients with chronic liver disease. During the first postoperative year, recipients who had ALF have the worst outcome, whereas long-term survival is unfavorable for those who had malignancy ***(Eghtesad et al. 2005)***.

As the survival has improved, emphasis has shifted to detection and treatment of long-term complications, such as late allograft dysfunction, and medical problems related to immunosuppression. However, graft function early after transplantation still continues to influence significantly the long-term outcome ***(Farmer et al. 2000).***

Several events at the time of transplantation can influence initial graft function and thereby the outcome. The liver may suffer damage already in the donor by prepreservation injury and the following period of intensive care induces

alterations in hemodynamic and metabolic regulation, and also inflammatory responses. These factors contribute to liver viability ***(Neuhaus et al. 2004)***. Cold preservation of the graft leads to impaired cellular metabolism, non-parenchymal cell injury, and disturbances in microcirculation. During implantation into the recipient, the graft is exposed to rewarming ischemia, a period deleterious to hepatocytes. When the liver blood flow is restored, the graft sustains ischemia-reperfusion (I/R) injury, characterized by the activation of the Kupffer cells, neutrophil recruitment into the liver, tissue destruction by reactive oxygen species (ROS) and proteases, and also the amplification of the inflammatory response by cytokines ***(Clavien et al. 2005)***.

Indications for Liver Transplantation

The list of indications for liver transplantation includes all the causes of end stage liver disease which are irreversible and curable by the procedure. In 1997 the American Society of Transplant Physicians and the American Association for the Study of the Liver Disease put forward the minimal listing criteria for patients with end stage liver disease. To qualify for the listing, the patient's expected survival should be ≤90% within 1 year without transplantation. Liver transplantation should lead to prolonged survival and an improved quality of life ***(Navascues et al. 2003).***

Acute Liver Failure (ALF)

Fulminant hepatic failure (ALF and subfulminant hepatic failure) is characterized by encephalopathy, jaundice, and coagulopathy. It accounts for 5-6% of all patients