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MINIREVIEWS

Elderly donor graft for liver transplantation: Never too late

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Abstract

The definitive treatment for end stage liver disease remains a liver transplant and hence livers are needed for these patients along with cases of acute fulminant liver failure. Hence livers are a scarce and highly valuable commodity in the current time. By extending the pool of donors to include the elderly livers, it allows for increased availability of donors and reduces the mortality that is associated with the waiting list itself. There is an increasing prevalence of end stage liver disease due to conditions like chronic hepatitis B and C, non-alcoholic steatohepatitis, alcoholic liver disease. Many studies show non-inferior outcomes when elderly livers are used as a vigorous selection process is implemented. The process takes into account the characteristics of the donor, graft and recipient allowing for appropriate donor-recipient coupling. To meet the increasing demands of livers, elderly donors should be utilized for liver transplantation. The aim of this review article is to describe the aging process of the liver and the outcomes associated with use of elderly livers for transplantation.

Key words: Liver transplantation; Donor age; Elderly; Age; Outcome; Success

Core tip: There is an increasing demand of livers for transplantation. Several studies showed successful results with elderly donors. We reviewed the aging process of the liver and the transplant outcomes of elderly donors. We highlight that elderly donors can be utilized given the extensive screening process allowing for risk factor analysis and appropriate allocation. Hence they should be used to allow for treatment of

liver disease globally and help mitigate the shortage of hepatic grafts.

Chela H, Yousef MH, Albarrak AA, Romana BS, Hudhud DN, Tahan V. Elderly donor graft for liver transplantation: Never too late. *World J Transplant* 2017; 7(6): 324-328 Available from: URL: http://www.wjgnet.com/2220-3230/full/v7/i6/324.htm DOI: http://dx.doi.org/10.5500/wjt.v7.i6.324

INTRODUCTION

Orthotropic liver transplantation is an area of hepatology that is under continuous evolution. It is the definitive treatment for end stage liver disease as well as cases of acute fulminant liver failure. The fact that livers are a paucity and in high demand all over the world has forced the medical community to evaluate livers from marginal or extended criteria donors thus allowing the pool of donors to enlarge. The term marginal donors or extended criteria donors encompasses a group of criteria that allows for the enlargement of the donor pool. These comprise of elderly donors (aged > 60 years), steatosis > 30%, grafts with cold ischemia time > 12 h, hypernatremia, hepatitis B and C viral infections, split-liver grafts, donors who are living relatives, donors from cardiac arrest patients[1]. The need for livers greatly exceeds the supply and hence leads to prolonged waiting time and the associated subsequent mortality while awaiting transplant. The availability of younger donors is decreasing given the advances in medicine overall less motor vehicle accidents. The purpose of this review is to evaluate the impact of age on the liver and the implications that it carries on the outcome of the transplantation. Genetic and environmental factors also influence the aging process of the liver itself[2]. Multiple series of studies have revealed that the stigma that aging livers carry is not completely viable. The fear associated with elderly donors is that the increased risk of complications due to concern for impaired function and lack of a robust response to external and internal stressors as compared to younger livers[2]. There is a potential of transmission of occult malignancies as well as concern of overall decreased survival of the recipient and the graft itself[1,2]. Numerous variables are taken into account with regards to the donor, the recipient and the graft itself. Balancing these and carefully selecting the correct donor-recipient pair yields good outcomes which are comparable to those obtained from transplanting donor livers.

Impact of age on the liver

Similar to all organs in the human body, the liver undergoes many age related changes. Though as compared to other organs, the liver possesses the capacity to regenerate, abundant vascularity, as well as superior functional reserve[1]. Two of the main changes in the liver include a decrease in the overall hepatic mass and the blood flow[1]. Understanding the changes in the structural, morphological and functional changes that occur as the liver ages can help in making appropriate decisions regarding the use of older livers for transplantation.

Macroscopic and microscopic changes

As the liver ages, it tends to shrink in size and undergoes a process brown atrophy. Grossly, it acquires a brownish colored appearance and is due to the deposition of lipofuscin which are insoluble proteins[1-5]. The Glisson's capsule also acquires a fibrous thickening[1-5]. Microscopically, there is reduction of the number of hepatocytes though the cell volume increases[1-2]. There is increased variation in the cell size and the nuclear size increases as well as the amount of nuclear DNA along with aneuploidy[1]. Similar to the cells themselves, the mitochondria undergo a process of acquiring increased volume but reduction in the overall number of mitochondria[1,2,6]. These alterations reflect that the cells and their organelles are attempting to overcome the reduction in the overall number[1]. The cells are vulnerable to reperfusion injury due to the reduced mitochondrial adenosine-triphosphate content[2]. There is reduction of smooth endoplasmic reticulum and buildup of lysosomes[2]. Hepatic sinusoids exhibit increased thickness of the endothelial lining and reduction in the fenestration in the endothelial cells[2]. There is increased thickness of the hepatic arteriolar walls as well[2]. Reduction in the secretion of bile acids as well as reduced bile flow is also reported[1,2].

Vascular changes

Along with reduction in liver mass there is a substantial reduction in the hepatic blood flow with age especially after the age of 30 years[1,2,4]. This can significantly impact the clearance of medications hence leading to the potential for complications to arise[1]. Age related atherosclerotic changes affect the vascular tree and its branches. The branches of the abdominal aorta is predominantly impacted in the proximal and mid proximal regions, however in cases where there is occlusive pathology of the distal portions there can be involvement of the hepatic artery[1]. This predisposes to vascular complications and can hence impact the graft survival and overall outcome post-transplant.

Functional change

The overall synthetic function of the liver declines with age especially with regards to protein synthesis as well as synthesis of clotting factors[1]. The levels of serum bilirubin, alkaline phosphatase and transaminases are not impacted by age and instead are a measure of liver damage and not to the functional capacity of the liver[1]. It appears that overall age does not have a major effect on function of the liver itself but alters the response to stressors (especially external) including states of increased metabolic need or disease processes[1]. There is also report of diminished phase Ⅰ metabolism of

drugs and increased production of pro-inflammatory cytokines[2]. There is increased predisposition to the development of diseases due to decreased rates of DNA repair, decreased expression of growth regulatory genes and the impact of oxidative stress[2]. Regenerative capacity of the liver is not impaired but the rate of regeneration is decreased as a consequence of aging[1].

Evaluating the aging liver

Diligent and through assessment of the graft as well as the donor is required for selection for transplant. Marginal or extended criteria donors are associated with increased risk of complications including initial poor function and primary non-function[1]. Initial poor function is an aspartate transaminase (AST) value more than 2000 IU/L, ammonia level > 50 μmol/L, prothrombin time > 16 s on post-transplant days 2-6[1]. Primary non-function is defined as graft failure in the first week post-transplant or require a re-transplant for survival[1]. There are many variables associated with the donor that can predict failure of the graft and increased mortality of the recipient[1,2]. By use of Cox regression analysis there are seven major factors that are independently associated with graft failure[1,2,7]. These include donors aged > 40 years (especially > 60 years), prolonged warm ischemia, split/partial grafts, prolonged cold storage > 10 h, length of ICU stay > 5 d, decreased donor height, cerebrovascular accident, black race[1,2]. Scores like the marginal liver score have also been formulated to aid in identifying the higher risk factors associated with poor graft survival and overall outcomes[1]. The factors include donor age > 60 years, cold ischemia time > 13 h, length of intensive care unit (ICU) stay > 4 d, hypotensive episodes < 60 mmHg for > 1 h, alanine transaminase (ALT) > 170 U/L. AST > 140 U/L, dopamine dose > 10 mg/kg, serum sodium > 155 mEq/L, bilirubin > 2.0 mg/dL[1]. Each factor has a score of 2 and an overall score of 3 or above predicts poor survival of the graft[1]. When livers are being prepared for harvesting, caution has to be exercised to ensure adequate circulation to avoid ischemia, hypovolemia, hypoxemia as well as avoiding infection[1]. Dopamine is commonly used in cases of hypotension to augment renal and mesenteric circulation, however doses exceeding 10 mcg/kg per minute can result in acute tubular necrosis and doses beyond 15 mcg/kg per minute have been associated with graft preservation injury[1]. Hence a delicate balance exists and must be maintained to ensure adequate perfusion and oxygenation of the liver.

Increased length of stay in the ICU especially > 4 d can affect the post-transplant function of the liver due to the use of vasopressors and the resultant effect on hormonal status, hemodynamics and nutritional status[1,2,8]. Another factor that is recognized to have a negative impact is hypernatremia which leads to cell swelling and worsens ischemia reperfusion injury and graft dysfunction[1,2]. However increased transaminases in elderly donors were considered as marginal criteria in the past, however these are not commonly elevated in elderly donors that are used in successful transplants and this is indicative of the rigorous selection technique[2,9].

An ultrasound of abdomen is recommended to evaluate the donor liver for steatosis, tumors of the liver and other intra-abdominal malignancy or abscess[1,2]. Many experts also recommend obtaining a liver biopsy as well to assess for fibrosis, steatosis, hepatitis, cholestasis[1,2,9]. Microsteatosis may be linked to early allograft dysfunction, however macrosteatosis > 30% increases the risk of reperfusion injury and is a strong predictor of poor outcome especially when combined with prolonged cold or warm ischemia[1,2]. Some studies have revealed that microsteatosis may not impose any challenges regardless of the severity as opposed to macrosteatosis in which the outcome is negatively influenced with increasing severity of fat infiltration[10]. Prevalence of steatosis does increase with age and is linked to malnutrition, obesity, type Ⅱ diabetes, chronic alcohol intake[2].

Prolonged cold ischemia time leads to ischemia reperfusion injury which is a type of microvascular injury and leads to increased risk of rejection of the graft and morbidity[1,2,11]. There are 4 stages of injury: Pre-preservation, cold preservation, rewarming and reperfusion[1]. The chances of this injury and the severity are affected by various factors which can potentially be controlled hence minimizing the risk of injury and improving the outcome of transplant. Older livers are more vulnerable to this form of injury hence extra caution must be exerted to keep the cold ischemia time to a minimum in them[1,2]. Increased warm ischemia time also has deleterious effects and should also be kept minimized[1,2].

Overall outcome of using elderly donors

Underlying condition of the recipient does influence survival of the graft, however recurrent diseases are a major cause of graft failure[2]. Cirrhosis secondary to hepatitis C is a major cause of liver failure requiring transplantation and has exceedingly high recurrence rates[2]. Graft fibrosis after transplantation was linked to the organ age and hence elderly livers are avoided in such cases, however this may change with the advancements in antiviral therapies or hepatitis C reducing the risk of recurrence[2]. With time post transplantation there is occurrence of chronic hepatitis and eventual fibrosis and hence elderly livers are avoided for transplant in the pediatric population[1,2].

Due to the decreased number of hepatocytes and the alteration in the regenerative capacity of older livers there has been concern to use them for transplant due to fear of early allograft dysfunction and primary non function[2]. Due to the increased prevalence of advanced atherosclerotic disease in the elderly there is increased concern for vascular complications developing post-transplant when elderly donors are used[2]. Though the elderly have increased arteriosclerosis in the celiac axis, it appears that the hepatic arteries are not significantly

impacted by this and more distal portions of the hepatic arterial system is used for transplant[2]. Arteriosclerosis affects the graft by two methods: Decreased blood supply at time of organ harvesting due to stenosis of celiac axis ostium causing poor graft preservation and increasing chances of primary non-function. The second method is effect on the vascular reconstruction process if the donor arteries are diseased by arteriosclerosis leading to early as well as delayed difficulties[2]. Hepatic artery thrombosis is one of the major causes of graft failure and has increased prevalence with increasing age of the donor[1,2,11]. The major causes of mortality in recipients of elderly donors are medical complications, cirrhosis due to hepatitis C recurrence and *de novo* tumors[1]. In a study performed by Zhao *et al*[11], that involved the use of elderly brain-dead donors, it was found that there was no primary non functions or need for re-transplant in the patients receiving the elderly (> 60 years) livers. They also found that early graft function was similar between the elderly and the younger donor group[11]. If careful selection and risk stratification is performed then acceptable and even at times comparable outcomes can be achieved with elderly donors. For example, using high risk donors for low risk recipients so that the risk of the donor is offset by the lower risk of the recipient to achieve more favorable outcomes and to avoid the waiting list mortality[1]. Using marginal or extended criteria donors requires that multiple factors be taken into account to match the appropriate donor with the corresponding recipient. By detailed assessment of the graft characteristics and taking into account factors that will augment each other negatively, appropriate donors can be selected[10]. Evaluating the recipient's ability to accommodate high risk donor grafts allows appropriate matching to occur without yielding a negative outcome[10].

In a retrospective study performed by Zhao *et al*[11] in which they evaluated 106 donor liver transplants which were harvested from cadavers. They were used in total of 98 patients and 7 of these patients were recipients of elderly donor livers (age > 60 years). The patients were divided into two groups. Group Ⅰ received livers from elderly donors > 60 years, and Group Ⅱ received livers from donors < 60 years. They accounted for risk factors like age of the donor, body mass index, the etiology of death, duration of stay in the ICU, gender, blood pressure and the amount of vasopressor used[11]. There were no significant differences overall with regards to parameters like bilirubin levels, transaminases at one week post-operatively[11]. Outcome with regards to recipient and graft survival as well as complications like primary non-function, biliary complications, hepatic artery thrombosis, need for re-transplantation. Zhao *et al*[11] supported the use of elderly donors for liver transplantation.

A study conducted in Birmingham (United Kingdom) revealed that mortality due to primary non function was comparable between the donors less than 70 years (1.3%) and more than 70 years (2.0%)[2]. They noted that recipients of aged livers experienced fewer arterial complications such as hepatic artery thrombosis and though it was not significant at the statistical level but did reflect that elderly livers should not be associated with worse outcomes[2]. Other centers around the world have experienced similar outcomes hence promoting the use of elderly liver donors.

Another study conducted by Rodríguez González *et al*[12] using 100 liver allografts from elderly donors aged > 60 years also supported the use of aged donors > 60 years. They emphasized that elderly donors can be used as long as a comprehensive risk assessment and evaluation is performed. Assessing the pre-transplant conditions like the liver function tests, length of ICU stay, cold ischemia time, hemodynamic status, whether vasopressors were used or not[12]. Factors like cold ischemia time of less than 6 h ideally as well as macrovesicular steatosis < 30% were very important contributors to a favorable outcome when using the elderly donors in their study[12]. Hence their study showed favorable outcomes when elderly donors were used as long as pre-operative risks were assessed and minimized as much as possible[12].

A study conducted by Thorsen *et al*[13] focused on liver from decreased donors aged > 75 years and though they noted an increased rate of biliary complications, they did not see overall worse outcomes with regards to mortality rates in recipients or graft survival.

CONCLUSION

The use of elderly donors is becoming more favorable and helping to reduce the mortality associated with the waiting list itself. The liver is a remarkable organ that possesses several unique qualities though like other organs in the human body it is also subjected to the process of aging. Though advancing age is not an advantage for the process of transplantation, it should not preclude the use of elderly livers for transplant. A careful and meticulous selection process can be carried out allowing to risk stratify the donor, the graft and the recipient. Factors in the graft like the gross as well as microscopic appearance are evaluated to exclude donors with obvious abnormalities like tumors or significant macroscopic steatosis. An ultrasound is recommended along with a liver biopsy to evaluate for occult tumors along with pathologies like fibrosis, steatosis. A thorough evaluation of the donor should be performed including detailed medical history, intra-operative exploration of the abdominal as well as thoracic cavities to exclude malignancies. Recipients should be evaluated as well and accordingly matched to appropriate donors hence achieving optimal outcomes. With this rigorous selection process it has been shown in several studies that elderly donors are comparable to younger donors and have successful outcomes. We would like to emphasize that elderly donors can be utilized given the extensive screening process allowing for risk factor analysis and appropriate allocation. Hence they should be used to allow for treatment of liver disease globally and help

mitigate the shortage of hepatic grafts.

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