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MINIREVIEWS

Hepatocyte transplantation: Consider infusion before incision

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Abstract

Human hepatocyte transplantation is undergoing study as a bridge, or even alternative, to orthotopic liver transplantation (OLT). This technique has undergone multiple developments over the past thirty years in terms of mode of delivery, source and preparation of cell cultures, monitoring of graft function, and use of immunosuppression. Further refinements and improvements in these techniques will likely allow improved graft survival and function, granting patients higher yield from this technique and potentially significantly delaying need for OLT.

Key words: Hepatocye; Transplantation; Cell therapy; Liver; Graft; Orthotopic

Core tip: Further human studies involving humans are needed, however, the current collectively suggest progress in terms of improved effectiveness of human hepatocyte transplantation (HTx). With improvements in optimizing delivery technique and assessing proper recipients of livers, monitoring graft function, as well as recognizing and treating graft rejection, HTx may be able to be used more widely in metabolic liver disease and potentially delay necessity of orthotopic liver transplantation.

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INTRODUCTION

Human hepatocyte transplantation (HTx) is being studied as a potential future alternative and currently use as a bridge to orthotropic liver transplantation (OLT). Over the last 10 years it has been noted that the number of patients requiring transplant as well as total transplants being performed has been stable (NIHMS). Given the inadequate supply of donor organs in relation to patients who would benefit from transplantation, continued research into alternate therapies for treatment or to prolong time before transplantation becomes necessary is timely. HTx is a technique which has been refined over the past three decades which seeks to improve liver function *via* transplantation of donor hepatocytes directly, rather than transplanting an entire organ. While a number of disorders have been evaluated for efficacy of therapy with this technique, individuals with inborn errors of metabolism appear the greatest benefit[1,2]. Sustained benefits have not been observed, however, refinements in the practice may lead to greater temporal benefits. While this review aims to summarize use of HTx in studies, it also seeks to highlight potential shortcomings of previously utilized technique and focus on areas of future study which may lead to improved yield of HTx.

PREPARATION OF HEPATOCYTE CULTURES

While many consider avoidance and delay of surgery appealing when considering HTx compared to OLT, it should be noted that the source of hepatocytes utilized for HTx generally come from livers deemed unsuitable for OLT[1-4]. The most common reason for rejection of a liver for OLT being steatosis, which is associated with both lower cell viability and yield[5-7]. Ischemic damage to livers is also a common reason for rejection, similarly affecting the yield and viability of extracted hepatocytes[8]. That stated, there is evidence that high quality hepatocytes may be obtained from cardiac death donors with prolonged warm ischemia, though prolonged episodes of ischemia predictably decreases viability[9,10]. While a current argument in favor of expanding research and use of HTx is that one is able to utilize cells from a larger pool of donor organs, one suspects that use of hepatocytes for HTx cultured from livers deemed suitable for OLT would likely result in greater success of this therapy. Beyond simple increased efficacy, multiple recipients could benefit from a single donor liver. Admittedly, there are concerns regarding evaluating the fitness of a recipient to receive donor hepatocytes. For instance, the cytochrome P450 enzyme is involved metabolism of drugs and steroids, bile synthesis, cholesterol synthesis, and vitamin D production. This enzyme system has been noted to have different levels of expression and function within humans, however, and this variability may be partially responsible for variant viability of HTx[11-13]. Not every person may be fit to receive any donor hepatocyte culture due to pre-existing chronic condition or associated medication they take, however, increasing the donor pool would still likely increase overall access to HTx. Furthermore, cell cultures can be cryopreserved and stored until needed, whereas there is a finite amount of time a whole liver can be stored before it is no longer viable for OLT[14].

CLINICAL INDICATIONS FOR HEPATOCYTE TRANSPLANTATION

Further discussion of refinement in technique warrants first discussing potential clinical indications for its use. As previously noted, congenital metabolic disorders appear to hold the greatest promise for use of HTx as metabolism of substrates in questions occur almost exclusively in hepatocytes. The cases reviewed below demonstrate HTx as a successful bridge to OLT.

Crigler-Najjar syndrome (CN) Type Ⅰ is an autosomal recessive condition with complete absence of a uridine diphosphate glucuronosyltransferase (UDPGT) enzymes, resulting in life threatening unconjugated hyperbilirubinemia with long term risk of kernicterus. While phototherapy can be an effective treatment, its effectiveness has been observed to decrease with increased age[15]. The first hepatocyte transplantation was performed in a rat model deficient in UDPGT enzymes[16-18]. A minimal percentage of liver mass comprised of engrafted cells (0.2%), resulted in a 40% decrease in unconjugated bilirubin levels[18]. Humans with CN Type Ⅰ have subsequently undergone HTx with marked improvement in unconjugated bilirubinemia, however, all patients subsequently required OLT anywhere from 4 to 20 mo after HTx due to either loss of graft or insufficient improvement in symptoms[19-23].

Urea cycle disorders, comprising a group of disorder due to deficiencies in one of six different enzymes in the urea cycle, are another group seemingly optimally situated to benefit from HTx. These deficiencies collectively result in hyperammonemia with significant neurologic sequelae. Most patients present as neonates, with current therapy involving protein restriction, hemodialysis, or hemofiltration. Hyperammonemia is still noted despite these treatments, however, with OLT being the only current definitive treatment. Humans have successfully undergone HTx as a bridge to whole organ transplantation, with stabilization of ammonia metabolism noted between 4-13 mo before OLT became necessary[24,25].

Familial hypercholesterolemia (FH) is caused by absence of the low density lipoprotein receptor (LDLR) resulting in early onset severe coronary artery disease. Low density lipoprotein (LDL) apheresis or OLT are the only current treatments, however, a rabbit model of FH undergoing HTx was noted to have decreased levels of serum cholesterol by 30%-60% for 100 d[26-28]. In 1995, 5 patients between the ages of 7 and 41 underwent HTx, demonstrating up to a 20% reduction in LDL in three of the patients, the other 2 not responding to therapy[29].

Glycogen storage disease Type Ⅰ (GSD-I) is an

Table 1 Summary of hepatocyte transplantation reports in human patients

Ref.	Indication	No. of patients	Infusion site	Outcome
Ambrosino *et al*[21]	Criggler-Najjar Type I	A 9-year-old boy	Portal vein	Decreased bilirubin approximately 4 mo, underwent OLT
Lysy *et al*[22]	Criggler-Najjar Type I	A 9-year-old girl	Jejunal vein	Decreased bilirubin approximately 6 mo, underwent OLT
Lysy *et al*[22]	Criggler-Najjar Type I	A 1-year-old girl	Splenic vein	Decreased bilirubin approximately 4 mo, underwent OLT
Zhou *et al*[53]	Criggler-Najjar Type I	2 (4-mo-old boy and newborn boy)	Portal vein	Decreased bilirubin approximately 3-4 mo with subsequent OLT
Meyburg *et al*[24]	Urea cycle disorders	4 (1-d to 3-year-old)	Portal vein	Stable 4-13 mo before OLT, 1 death at 4-mo
Grossman *et al*[29]	Familial hyper-cholesterolemia	5 (7-year-old to 41-year-old)	Portal vein	Three patients with approximately 40% reduction in LDL lasting 4 mo
Lee *et al*[31]	Glycogen storage disorders	A 8-year-old kid	Portal vein	Followed for 7 mo, on tacrolimus and able to fast for 7 h without hypoglycemia
Muraca *et al*[1]	Glycogen storage disorders	47-year-old, female	Portal vein	Followed for 9 mo, on tacrolimus and able to fast for 7 h without hypoglycemia
Sokal *et al*[33]	Refsum disease	4-year-old girl	Portal vein	16 mo improvement
Dhawan *et al*[36]	Hemophilia A	2 (3-mo-old and 35-mo-old)	Portal vein	6 mo with 70% reduction in Factor VII requirements
Hansel *et al*[42]	A1AT deficiency	A 52-year-old	Portal vein	A1AT levels did increase before OLT available 2 d later
Soltys *et al*[52]	Phenyl-ketonuria	A 27-year-old female	Portal vein	7 mo of unrestricted diet

A1AT: Alpha 1 antitrypsin; OLT: Orthotopic liver transplantation.

autosomal recessive metabolic disorder resulting from deficiency of the hepatic enzymes glucose-6-phosphatase (Ia) or glucose-6-phosphate transporter (Ib), resulting in deficiency in glucose production with noted severe hypoglycemia, lactic acidosis, hyperlipidemia, growth retardation, hyperuricemia, and renal dysfunction. While many patients can be treated with consumption of starch, some are unresponsive to dietary therapy and require OLT to correct the underlying defect[30]. Two patients, 18 and 47 years old, underwent HTx with subsequent ability to maintain unaltered diet for up to 7-9 mo[1,31].

Infantile Refsum disease is an autosomal recessive disorder characterized by impaired peroxisome function, resulting in accumulation of very long chain fatty acids and branched chain fatty acids which are normally degraded in peroxisomes. Patients present with severe neurologic defects and rarely survive beyond age 10, with treatment generally centering around supportive care[32]. One 4 years old female patient underwent HTx, demonstrating significant biochemical improvement for more than 16 mo[33].

HTx has been suggested as a treatment for Hemophilia A and B; with murine models demonstrating in 5%-10% increase in factor Ⅷ and 1%-2% increase in factor Ⅸ[34,35]. These increases do result in decreased bleeding time and do provide a therapeutic benefit. In one 2004 study, a 3 mo and 35 mo old patients underwent HTx with 70% reduction in factor Ⅶ requirements noted after 6 mo, however, both patients eventually underwent OLT[36].

Progressive familial intrahepatic cholestasis (PFIC) encompasses a group of autosomal recessive liver diseases presenting in infancy and childhood with progressive cholestasis of hepatocellular origin, with three subtypes noted involving different components of bile metabolism[37]. Murine models of this disease process demonstrated improved bile metabolism using intrasplenic HTx[38]. Two children have been treated with HTx, however, both required OLT after 5 and 14 mo. Biopsies of the livers demonstrated extensive fibrosis and no donor cells on pathology before transplantation, the conclusion made that existing fibrosis likely impaired engraftment[39].

Phenylketonuria (PKU) is one of the most common inborn errors of metabolism, a deficiency of the enzyme phenylalanine hydroxyls (PAH) resulting in toxic concentrations of phenylalanine, the only current treatment involving phenylalanine restricted diet[40]. Murine models demonstrate significant improvement in PAH levels[41].

Alpha 1 antitrypsin (A1AT) deficiency - in 1997, a 52 years old patient underwent HTx as a bridge to transplant, with wild type A1AT levels were noted to increase in the interval between OLT, which occurred 2 d later[42].

This list is not exhaustive, however, it serves to illustrate the potential for this route of therapy in a large number of disorders mediated by hepatocyte dysfunction and subsequent metabolic derangements. While temporary improvements have been noted, others suspect the temporal benefits of HTx could be extended with transplantation of adequate cell mass, improved stock and implantation of transplanted hepatocytes, evaluating the ideal route of delivery, and improved and more accurate monitoring of graft function with emphasis on timely detection of rejection (Table 1).

METHODS OF DELIVERY

Regarding adequate transplantation, two issues warrant discussion. One, culturing of hepatocytes from livers deemed unsuitable for OLT, has been previously discussed. Another issue regarding viability deals with transplantation of "fresh"

vs cryopreserved hepatocytes. Fresh hepatocytes do demonstrate higher viability, with cryopreserved hepatocytes observed to have mitochondrial respiratory chain alterations and decreased ATP production[43]. Furthermore, protein synthesis has been noted to be impaired in cryopreserved cells relative to fresh hepatocytes[44,45]. A 2013 cohort study compared viability of freshly isolated hepatocytes against cryopreserved hepatocytes at 24, 48, and 72 h[46]. Freshly isolated hepatocytes demonstrated mean viability of approximately 81%, while means viability was approximately 61% at 24 h, 52% at 48 h, and 48% at 72 h. There was no noted increased caspase activity, an enzyme involved in apoptosis, though there did appear to some mild derangement in Cytochrome activities, previously noted above to be involved in hepatic metabolism of many different substrates.

Hepatocytes have been transplanted into the liver, spleen, and peritoneal cavity, with intraportal injection being the preferred and most physiological site for clinical transplantation[14,42]. This site may be accessed *via* percutaneous trans-hepatic puncture, cannulation of the umbilical vein, or open cannulation of a mesenteric vein[14]. Shear stress from catheterization can have an effect on viability, however, it has been demonstrated that catheters as small as 4.2 F are associated with acceptable viability[47]. Portal hypertension and any thrombosis are associated with lower engraftment levels, however, use of heparin infusion has been proposed as a potential mechanism to improve engraftment[48]. In cases of known portal hypertension, the spleen may be used as an alternate engraftment site, however, there are cases of splenic necrosis after injection into the splenic artery[8,49]. The peritoneal cavity is another alternate site, however, engraftment levels and long term viability of the graft have been observed to be significantly lower than portal vein infusion[50,51]. There are studies comparing efficacy of any method of delivery against another, and proper determination of the relative efficacy of each would be invaluable toward design of future studies evaluating HTx.

MONITORING GRAFT FUNCTION

Beyond just the method of delivery, appropriate pre-treatment of the recipient has been evaluated to improve efficacy of HTx. A 2017 case series details use of pre-operative liver-directed radiation[52]. Preoperative liver-directed irradiation has been noted to demonstrate complete correction of the bilirubin conjugation defect noted in rat models of Criger-Najjar syndrome Type I following HTx[53]. This case series demonstrated improved function of HTx from porcine hepatocytes comparing primates receiving hepatic pre-irradiation *vs* those who did not. Function was assessed by measuring levels of porcine albumin after HTx; pre-irradiated subjects demonstrated significantly higher levels of this protein than control subjects. Using immunohistochemical staining, spatial analysis of stained recipient liver tissue post HTx demonstrated level of engraftment to be approximately 11.8% in experimental subjects *vs* approximately 5% in control subjects. Survival of the graft appears improved in the pre-treated group appears improved as well, with no evidence of infiltrating T cells or macrophages noted in cells of the experimental group. Given the promising nature of the above results, two children with urea cycle defects were subsequently infused after undergoing the irradiation preconditioning protocol. One child was 4 mo of the age, the other underwent HTx shortly after birth. Regarding the patient receiving HTx shortly after birth, at 26 h, cell viability was noted to be approximately 63% with ammonia metabolism noted at normal levels[52]. One patient was noted to have intermittent episodes of hyperammonemia, however, it was noted that goal tacrolimus levels post-transplant were not sustained. This patient did eventually undergo OLT at 3.5 mo of age. The other patient maintained normal levels of ammonia for approximately 40 d, however, was not to have intermittent episodes of hyperammonemia after this point. On day 84 acutely increased levels of ammonia, glutamine, and urinary orotic acid suggested graft failure.

This same case series included a 27 years old female patient with PKU also undergoing HTx after irradiation pretreatment, doing well for 7 mo on an unrestricted diet before demonstrating evidence of rejection. Tacrolimus levels were again noted to be below goal level, and the patient was treated with corticosteroids and augmented immunosuppression protocol with phenylalanine tolerance returning. Phenylalanine levels remained normal for over one year, however, the patient's follow became inconsistent and adequate monitoring of immunosuppression was not performed. Her brother, also afflicted with PKU, was used a control agent. At this point in the study, the graft was assumed to be rejected and immunosuppression discontinued without any adverse effects noted. All three cases demonstrated improved length of graft function after HTx has taken place, and suggests pre-operative irradiation may serve as standard pretreatment to improve HTx efficacy.

Also evident in the above case series, however, is the issue of recognizing and treating graft rejection. The case series did detail how rejection was diagnosed, however, there remains no consensus on pretreatment to reduce risk of rejection, graft monitoring, and treatment once rejection is recognized or suspected. This case series chose to utilize monitoring for CD154+ T-cytotoxic memory cells, previously demonstrated to be sensitive for acute rejection in pediatric liver or intestinal implants[53-56]. Increasing concentration of this T cell was noted to generally correlate with suspected decreased function of the hepatocytes, however, the authors do note that significant daily variance of measured total bilirubin in the CN Type I patients and phenylalanine levels in the PKU patient[52]. Reviewing the aforementioned cases and use of immunosuppression, it

appears tacrolimus is an acceptable immunosuppressive agent, however, that closer monitoring of drug levels may be necessary to ensure continued appropriate function of the transplanted hepatocytes[1,31,52]. Further prospective cohort studies utilizing different monitoring intervals or alternate immunosuppressive therapy is likely necessary to ensure sustained and optimized graft function.

CONCLUSION

Further human studies involving humans are needed, however, the above collectively suggest progress in terms of improved effectiveness of HTx. With improvements in optimizing delivery technique and assessing proper recipients of livers, monitoring graft function, as well as recognizing and treating graft rejection, HTx may be able to be used more widely in metabolic liver disease and potentially delay necessity of OLT.

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