Safe and effective use of Hyperbaric Oxygen Therapy for late hepatic artery thrombosis in split liver transplantation: a case report

* O.T.I.P Center, Torino, Italy - ** Liver Transplantation Center, Torino, Italy

Abstract
Hepatic artery thrombosis (HAT) occurring after liver transplantation (LT) is a significant complication with a reported incidence of 5% in adults and 9% to 18% in children (1, 2); it can lead to septic complications related to bile leak, bilioma, abscess or cholangitis, forcing an immediate or delayed retransplantation. Clinical reports demonstrated the safety and the efficacy of HBO therapy to reduce hepatocytes necrosis and to carry patients with early HAT after LT to a delayed retransplantation or even to restore graft arterial flow, probably because of the development of collateral vessels (3-5).

We describe the use of HBO therapy in a particular case of late HAT after split liver transplantation.
Keywords: Hepatic artery thrombosis, liver transplantation, hyperbaric oxygenation

Case report
A 64-year-old woman underwent liver transplantation in may 2005 because of HCV related cirrhosis. She received a left split graft from a 22-years-old donor. The weight of the left graft (segments I-II-III-IV) was 480 gr and the Graft-to-Recipient Body Weight (GRBW) ratio was 0.9. The common hepatic artery of the donor was end-to-end anastomosed to the common hepatic artery of the recipient. Primary immunosuppressive therapy was represented by Cyclosporine, Steroids and Azathioprine. The first postoperative course turned out without complications and the patient was discharged on postoperative day 11. Routine controls, biochemical tests and hepatic Doppler Ultrasonography was carried out following the protocol of our Center. Two months after LT, the patient had a biopsy-proven hepatitis C recurrence (Ishak score: Grading 5/18, Staging 2/6); antiviral therapy (Ribavirine + PEG-Interferon) was administered throughout 6 months and subsequent hepatic biopsy proved a resolution of the hepatitis damages, but showed an aspecific initial cholangitis. Cholangio-MR evidenced the presence of biliary sludge in extrahepatic biliary tract that was medically treated. Because of a new increase of cholestatic indexes associated to a dilatation of intrahepatic biliary ducts, 20 months after transplantation the patient was submitted to a Percutaneous Transhepatic Cholangiography (PTC) with dilatation of an anastomotical stricture. The procedure had not efficacy because of an early stricture recurrence after two consecutive procedures. An internal-external biliary drainage was maintained and 23 months after LT the patient underwent a surgical conversion of the biliary anastomosis in a Roux-en-Y hepatico-jejunoanastomosis. An intra-operative accidental hepatic artery injury occurred: the damaged tract was removed and an end-to-end anastomosis with interposition of an iliac arterial graft was performed.

Indirizzo per la richiesta di estratti:
Lidio Maffi
c/o OTIP s.r.l.
Via Pola, 37
10135 Torino

Questo articolo è stato pubblicato in forma definitiva dai medesimi autori su Transplant Int. 2009 Oct 6 con il titolo “Hyperbaric oxygen therapy in liver transplantation; is its use limited to the management of hepatic artery thrombosis?".
Ossigenoterapia iperbarica adiuvante nella fascite necrotizzante estesa: caso clinico

Autori vari

Safe and effective use of Hyperbaric Oxygen Therapy
Maffi, Franchello, Ricchiuti, Romagnoli, Salizzoni

Figure 1. Doppler US showing the absence of intrahepatic arterial blood flow.

Figure 2. A CT-scan performed on POD 6 confirmed the absence of intrahepatic arterial blood flow.

Figure 3. A CT-scan performed on POD 6 showed the presence of ischemic areas in the contest of segments II-III.
Ultrasound flowmeter at the end of surgery showed a regular patency of intrahepatic arterial blood flow. Patient was started on systemic heparin. On post-operative day (POD) 1, a Doppler US showed the absence of intrahepatic arterial flow (Fig. 1); a CT-scan achieved on POD 6 confirmed the absence of blood flow inside the graft and evidenced the presence of ischemic areas in the contest of segments II-III (Fig. 2, 3). Bilirubin and the indexes of citolisis and cholestasis were normal, as the other biochemical assays, except a mild leukocitosis (9.65 x 10⁹/L).

HBO therapy was proposed with the purpose of to reduce the graft ischemic damages. In the absence of absolute or relative contraindications (6), the patient underwent 20 HBO therapy sessions, performed once a day in a multiplaces chamber (Drass s.p.a. Type 1502.6+2 places) considering the following protocol: 12 minutes for compression time, 30 minutes for breathing O₂ at 2.5 ATA, 3 minutes for breathing in environmental air, 30 minutes for breathing O₂ at 2.5 ATA and 15 minutes for decompression time.

During HBO therapy arterial O₂ saturation was assessed; biochemical tests and Doppler US was performed throughout HBO therapy.

At the end of HBO sessions biochemical tests and white blood cells count were normal. Doppler US showed the presence of intrahepatic arterial blood flow, since the 4th day after beginning of HBO application. A CT-scan performed at the end of HBO sessions (fig. 4) showed a significant decrease of ischemic areas and the presence of intrahepatic arterial vessels revascularization, confirmed by hepatic Doppler.

Five months later, the patient underwent a percutaneous transhepatic biliary anastomosis dilatation and stone removal; two sessions of PTC restored a regular bile flow. A Doppler US performed 18 months after HBO showed the presence of arterial flow inside the graft; ischemic areas completely disappeared and intrahepatic biliary tree was not enlarged.

Actually (20 months after HAT) the patient is asymptomatic and the biochemical tests are normal.

**Discussion**

HAT after LT is a severe complication that occurs more frequently in pediatric patients or when a partial livers (split, living donor graft) are used (7).

Current management of HAT after LT involves the attempt of urgent revascularization when possible, the use of anticoagulant or fibrinolitic therapy, an appropriate antibiotic coverage, the drainage of intrahepatic collections or bile duct strictures, and a retransplantation in the occurrence of irreversible liver failure or septic complications localized in the liver.

Hyperbaric oxygen therapy has been described to have a therapeutic effect in several conditions such as wound healing, carbon monoxide poisoning, acute necrotizing infections, ischemic disease, and a useful effect on liver diseases and liver regeneration after hepeatectomy (3, 8-17).

Recently, it has been observed that HBO is also effective on hepatic artery thrombosis after liver transplantation (3, 4, 15): in that condition, HBO treatment can improve hepatocellular necrosis (5) and, when retransplantation is required, the procedure can be performed in a more stable clinical condition (3).

HAT after LT produces an hypoxic injury on the liver that can cause hepatic gangrene and liver failure or, conversely, ischemia-reperfusion injury if the flow in the hepatic artery is restored.

The ischemic damages cause a depletion of L-arginine, precursor of the nitric oxide (N.O.), and an elevation of Endothelin 1 (ET-1) that induces an increase of congestion and flow disorders, promoting worsening of hypoxic injury with activation of Kupfer cells and release of proinflamatory cytokines (TNF, IL-1, IL-2, IL-8) associated to an increased expression of adhesion molecules (18).

Three enzyme isoforms account for N.O. synthesis: neuronal N.O. syntase (nNOS), inducible N.O. syntase (iNOS), endothelial N.O. syntase (eNOS); nNOS and eNOS are controlled by intracellular levels of calcium-calmodulin and phosphorylation, and require also O₂ and L-arginine (19).

Hyperbaric hyperoxia increases eNOS and nNOS activities in systemic vascular bed, by modulation of intracellular Ca++ levels (20) and by production of superoxide H₂O₂, that enhances the conversion of N-hydroxy-L-arginine to citrulline and N.O. (21); HBO modulates also
iNOS activation and its greater production of superoxide radicals (18).

Many studies showed that HBO therapy may produce an increase by 125% on blood oxygen content, and the oxygen tension is highly increased in plasma and other tissue fluids (22-24); it may reduce the effects of interruption of arterial blood flow when HAT occurs by increasing portal blood oxygen content and enhancing the development of hepatic artery collateral vessels (3, 15, 25). When tissue oxygen tension falls below 30 mmHg, in fact, fibroblasts fail to function and neovascularization is stopped (26, 27).

We described the application of HBO therapy in a particular case of HAT occurred in a late period post-transplantation, but strictly related to a iatrogenic hepatic artery lesion occurred performing an hepatico-jejunoanastomosis for anamotomical biliary stricture. The graft was a left split liver with an immediate and a long term good function; intercurrent hepatic artery thrombosis was immediately life-threatening for the patient because of the development of hepatic abscess with the risk of its septic consequences. The immediate arterial recanalization failed, such as medical anticoagulation and antiaggregation; the long term prospective for the patient was to lose the graft for intrahepatic biliary complications if early infective complications were overcome (28). HBO therapy avoided a very technically complex late retransplantation: abscess was totally cleared and intrahepatic arterial flow was restored. Five months after HBO an intrahepatic biliary stricture occurred, but it was successfully treated by a percutaneous approach.

There is actually an experimental evidence that HBO may attenuate hepatic reperfusion injury (29). Ischemia-Reperfusion Injury is one of the main causes of liver dysfunction, such as Primary Non Function (PNF) or Delayed Non Function (DNF) and it is responsible of increased morbidity and risk of death (1, 2). Each graft is subjected to IRI, but partial and marginal grafts are more susceptible to that particular type of damage. The shortage of donation forced to extend selection criteria, and to utilize partial or poor quality grafts (1), and consequently early non function became a relevant clinical problem.

Protective strategies against Ischemia/Reperfusion injury are different, varying from medical to surgical techniques; HBO treatment may be effective in ameliorating the function of neutrophils in oxidatively bacteria killing, improving their ability to generate oxygen-derivated toxic radicals (30); HBO stimulates down-regulation of cell surface adhesion molecules like ICAM-1(31) leading to a reduction of neutrophil adhesion, and it also improves, in endothelial cell model, the synthesis of fibrinolytic enzymes with stimulation of tissue plasminogen activator(t-PA), urokinase plasminogen activator and plasminogen activator inhibitor type 1[PAI-1] (32). Finally, HBO up-regulates the synthesis of VEGF-A, the most specific growth factor for neovascularization (33).

All these properties may lead to hypothesize that the use of HBO treatment could reduce a possible malfunction of poor quality grafts (considering macrovascular steatosis or donor age).

Furthermore, many in vitro and in vivo studies confirmed the ability of HBO treatment to stimulate hepatocyte regeneration (9, 10, 34, 35), and these data may suggest a possible role in improving the initial disfunction of the partial grafts. In conclusion, our experience suggested that HBO therapy is a safe technique and it is effective in reducing the risk of hepatic necrosis after HAT even in a particular case like a late thrombosis in split liver transplantation.

Given its useful effects on liver regeneration and on IRI, further studies are needed to evaluate if HBO therapy may also be useful in the postoperative course of malfunctioning partial and marginal grafts.

---

**Riassunto**

La Trombosi dell’arteria epatica è una frequente complicazione ché si verifica dopo il trapianto di fegato (LT), con una incidenza del 5% segnalata negli adulti e dal 9% al 18% nei bambini (1, 2), ma si riscontrano anche complicanze settiche connesse alla perdita di bile, bilioma, accessi o di colangite, che costringono a un nuovo trapianto immediato o differito.

Studi clinici hanno dimostrato la sicurezza e l’efficacia della ossigenoterapia iperbarica per ridurre la necrosi degli epatociti, per posticipare un nuovo trapianto epatico in pazienti con Trombosi dell’arteria epatica subito dopo l’attuazione di un LT o infine per ripristinare un flusso arterioso epatico, probabilmente per lo sviluppo di circoli collaterali (3-5). Si riporta l’uso del cosiddetto termofluido per ridurre la necrosi degli epatociti, per posticipare un nuovo trapianto epatico in pazienti con Trombosi dell’arteria epatica subito dopo l’attuazione di un LT o infine per ripristinare un flusso arterioso epatico, probabilmente per lo sviluppo di circoli collaterali (3-5). Si riporta l’uso del cosiddetto termofluido per ridurre la necrosi degli epatociti, per posticipare un nuovo trapianto epatico in pazienti con Trombosi dell’arteria epatica subito dopo l’attuazione di un LT o infine per ripristinare un flusso arterioso epatico, probabilmente per lo sviluppo di circoli collaterali (3-5).

Parole chiave: Trombosi dell’arteria epatica, Trapianto di fegato, ossigenoterapia iperbarica.

---

**References**


