

Liver transplantation is the well-established method of treatment of patients with liver insufficiency and various tumors located in the liver. However, the number of patients in need for liver transplantation greatly exceeds the number of available donors. In order to decrease this gap, organs at higher risk of poor function after transplantation are commonly used. Over the recent years, hypothermic oxygenated machine perfusion was proposed as a procedure alleviating organ damage during the ischemia-reperfusion period, mainly through a protective effects on mitochondria and endothelium. It is based on a concept of a period continuous flow of oxygen-rich fluid through the procured liver prior to transplantation. In animal studies, hypothermic oxygenated machine perfusion was found to decrease the magnitude of organ injury and improve its function in the postoperative period. In humans, its effects were studied mainly in liver transplantations from donors after cardiac death and predominantly with respect to clinical outcomes. However, vast majority of liver transplantations are performed from donors after brain death and the data on the use of hypothermic oxygenated machine perfusion in this population are extremely limited. The aim of this research proposal is to evaluate the effects of hypothermic oxygenated machine perfusion on reducing the degree of injury of livers procured from donors after brain death for transplantation with subsequent improvement of its function after transplantation.

Patients will be randomly assigned to either end-ischemic hypothermic oxygenated machine perfusion group (at least 2 hours of allograft perfusion at 12 degrees Celsius through hepatic artery and portal vein prior to implantation; n=26) or simple cold storage group (n=78). Circulating levels of proinflammatory cytokines, markers of nuclear damage, serum activity of transaminases, gamma-glutamyl-transpeptidase, bilirubin concentration, and INR will be assessed in the perioperative period. Wedge allograft biopsies will be performed 90 minutes post-reperfusion to evaluate activation of innate immunity, activation of endothelium, hepatocyte necrosis, hepatocyte apoptosis, energy reserves, and oxidative damage. Further, wedge biopsies will be performed at the end of simple cold storage and at the beginning and after two hours of perfusion to determine steatosis and energy reserves. During the perfusion, fluid samples will be periodically tested for lactate, sodium, and potassium concentration, CO₂ partial pressure, and markers of mitochondrial injury. Patients will be closely monitored in the postoperative period for allograft function and secondary end-points: 2-year recipient and graft survival, 2-year incidence of biliary complications, and 90-day complication rate. The impact of hypothermic oxygenated machine perfusion on allograft function and patient clinical course after liver transplantation, inflammatory response and allograft injury will be established.

The results of this study will provide insight both into the potential protective effects of hypothermic oxygenated machine perfusion in patients undergoing liver transplantations from donors after brain death, along with the underlying mechanisms. The study may fill the existing research gap.