Effects of the Hypnotic Agent on Primary Graft Dysfunction After Liver Transplantation

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ABSTRACT

Background. Morbidity and mortality rates in orthotopic liver transplantation have decreased in the past few years. Risk factors related to severe postoperative complications, such as primary graft dysfunction, still need to be analyzed. We evaluated the influence of the hypnotic agent used during anesthesia on primary graft dysfunction.

Methods. We performed a retrospective analysis of 419 consecutive patients who received a liver transplant between 2005 and 2013 in a single center. We analyzed the incidence of primary graft dysfunction (defined as alanine aminotransferase or aspartate aminotransferase levels higher than 1500 IU/L on the first 3 days after surgery) and if the hypnotic agent was associated with this event.

Results. The incidence of primary graft dysfunction was 42.2% (114 patients), similar in both groups (propofol group, 89 patients, 43.2% and sevoflurane group, 25 patients, 39.1%). In the multivariate analysis, we did not find any relationship between the hypnotic agent (propofol or sevoflurane) and early graft dysfunction.

Conclusions. In our patients, we found no differences in the incidence of liver graft dysfunction according to the hypnotic used during transplantation. We can suggest that both drugs (sevoflurane and propofol) are equally safe in orthotopic liver transplantation.

LIVER transplantation remains the only effective treatment for end-stage liver disease and fulminant liver failure. Throughout recent years, due to improved surgical techniques and advances in the field of perioperative management, 12-month survival rates have risen to almost 95% in several specialized centers [1]. Nevertheless, serious complications can still arise both during surgery and in the postoperative period, which contribute to the high morbidity of these patients, entailing increased lengths of stay and related costs.

The degree of severity of ischemia-reperfusion injury determines initial liver graft function, and its primary dysfunction determines the immediate prognosis of both the graft and the patient, especially when initial graft failure leads to urgent retransplantation to avoid fatal consequences. Patients with primary graft dysfunction (PGD) require increased hospitalization and longer intensive care unit stay and therefore present an increased number of associated complications (infections and renal function impairment) leading to reduced survival [2].

According to the United Network for Organ Sharing, primary graft failure is defined as nonrecoverable graft function needing urgent liver replacement during the first 10 days after orthotopic liver transplantation (OLT). The United Network for Organ Sharing characterizes this by an aspartate aminotransferase level (AST) over 5000 IU/L, international normalized ratio (INR) $\geq$ 3, and acidosis (pH $\leq$ 7.3 and/or lactate concentration >2 times normal) [3].

However, there is a lack of standard defining criteria for PGD, which rarely mandates retransplantation to ensure

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survival [4,5]. Among the several definitions found in the literature, that provided by Nanashima et al seems simple, easy to measure, and reproducible (AST and/or alanine-aminotransferase [ALT] over 1500 IU/L during the first 72 hours after OLT) [6].

Certain donor features such as age, the presence of steatosis, the need for high doses of vasopressors, hypernatremia, or increased times of cold ischemia are well-known risk factors of early graft dysfunction [7,8]. Although several strategies have been developed to avoid ischemia-reperfusion injury, rarely, if ever, have they been implemented in daily clinical practice of liver transplantation. Halogenated anesthetics, usually employed in liver transplantation anesthesia, have been hailed as one of the potential strategies to reduce this graft preservation injury. Although the protective effect against ischemia has been associated to its administration before the ischemic event, a potential postconditioning effect after reperfusion has also been proposed. Despite the fact that the potential deleterious effect of volatile anesthetics on hepatic blood flow had been forewarned, several well-designed clinical trials have proven that hepatic blood flow remains unaltered during anesthesia with different halogenated agents [9,10]. Furthermore, they have proven a protective effect against ischemia-reperfusion injury in liver resection surgery [11,12]. These effects, both as preconditioning (before the graft's ischemia by administrating halogenated agents to the donor) and as postconditioning (during transplantation surgery), could somewhat mitigate preservation injury and reduce the complications after transplantation [13].

Nevertheless, propofol, the intravenous hypnotic, has a safe pharmacologic profile in the presence of liver or renal damage, with unaltered clearance due to hepatic dysfunction.

This study studied whether hypnotic agents (propofol vs sevoflurane) used in transplantation anesthesia play any role in the development of PGD following OLT. To confirm such a relationship, we used Nanashima's definition [6].

MATERIALS AND METHODS

A total of 210 OLT procedures were performed at our institution between January 2008 and December 2013. Four patients who died in the operating room and 5 patients with postoperative hepatic artery or portal vein thrombosis were excluded from our study. Therefore, the records of 201 adult liver transplant recipients were retrospectively collected and analyzed. The study was approved by the local ethics committee.

Anesthesia was performed following the liver transplantation anesthesia protocol used at our center. Electrocardiogram, arterial oxygen saturation, radial arterial pressure, and depth of anesthesia (measured by bispectral index) were routinely monitored. Swan-Ganz (Edwards Lifesciences LLC, Irvine, CA, USA) and central venous catheters were used for invasive monitoring. General anesthesia was initiated using a rapid sequence induction, with fentanyl, suxamethonium, and propofol. Anesthesia was maintained either with propofol or sevoflurane depending on the anesthesiologist's preference. Remifentanil infusion to obtain optimal analgesia levels and nondepolarizing neuromuscular blocker agents were administered according to clinical needs. Specialized surgeons, by following a standardized protocol, performed the liver transplant procedure.

Collected donor data included the following: age and gender, ALT and AST levels, bilirubin and sodium serum levels, length of intensive care unit stay before donation, the need for vasoactive drugs, and the cause of brain death. Data from the receptors included gender, age, body mass index, and basal biochemical levels (urea, INR, bilirubin, creatinine, sodium, and albumin). The severity of liver disease was classified by Model for End-stage Liver Disease and Child-Pugh classifications. We assessed recipients' preoperative clinical comorbidities and liver-associated complications prior to liver transplantation. In the operating room, the following variables were recorded: transfusion requirements, length of surgery and anhepatic phase, and presence of reperfusion syndrome. PGD was defined as ALT or AST values over 1500 IU/mL during the first 3 days after surgery.

Univariate analysis of possible factors associated to PGD was conducted by using χ^2 test or Fisher test for categorical variables and t test or Mann-Whitney U test for continuous ones. Data are thus presented as mean values $\pm$ standard deviation or absolute values and percentages. P values $< .05$ were considered statistically significant. All significant variables in the univariate analysis were included in a multivariate logistic regression model that determined the effect of the hypnotic agent on initial graft dysfunction. Statistical analysis was performed using SPSS 15.1 software (Statistical Product and Services Solutions, SPSS Inc, Chicago, Ill, United States) for Windows (Microsoft, Redmond, Wash, United States).

RESULTS

We included 201 liver transplant procedures in our study after excluding those patients who died in the operating room (4 cases), and patients with hepatic artery or portal vein thrombosis (5 cases). Intravenous anesthesia with propofol was used in 143 patients (71.1%), and inhaled anesthesia with sevoflurane in 58 (28.9%).

According to aforementioned criteria, 81 patients presented PGD (40.3%), 60 of whom belonged to the propofol group and 21 to the sevoflurane group. Each group's main features are depicted in Table 1. Raw analysis assessing the influence of different hypnotic agents on the presence of PGD proved no significant difference between groups (odds ratio 0.76, confidence interval 0.42 to 1.47; $P = .45$).

Subsequent univariate analysis performed to determine the uniformity of both groups determined that only the surgical technique used (vena cava preservation vs classical technique) could entail a confounding variable leading to a misinterpretation of final results ($P = .002$). We therefore carried out a logistic regression analysis including the variable surgical technique together with the anesthetic agent used. Once adjusted for this variable, we find no association between the anesthetic agent and the presence of PGD in the postoperative period (odds ratio 0.85; confidence interval 0.45 to 1.63; $P = .63$).

DISCUSSION

Strategies to reduce ischemia-reperfusion injury in transplantation are of high interest as grafts are exposed to a