

Research Article

The Impact of the Analgesic Agents Administered in Recipients of Liver Transplants on Graft Results

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Received: 15 February 2022; **Accepted:** 22 February 2022; **Published:** 11 March 2022

Citation: Gamze Cabakli. Department of Anesthesiology and Intensive Care, Marmara University, Pendik Training and Research Hospital, Istanbul, Turkey. Anesthesia and Critical Care 4 (2022): 43-51.

Abstract

Introduction and Objective

The ischemia-reperfusion injury that occurs in both the donor and the recipient during liver transplantation and the hemodynamic changes that may occur in graft afterward significantly affect the graft, sometimes triggering graft failure by causing hepatocyte damage. It is known that inhalation anesthetics provide ischemic preconditioning that prevents ischemia-reperfusion injury, but their effect on graft dysfunction caused by post-reperfusion syndrome has not yet been clarified. Our study aimed

to reveal the effects of desflurane and sevoflurane used during liver transplantation on graft survival.

Material and Method

This retrospective study was conducted following the ethics committee approval (protocol no: 09.2021.1004/03.09.2021) and included 60 donors and recipients of liver transplantation procedures performed between 2015 and 2021. The patients were divided into two groups depending on the agent administered for anesthesia maintenance after

standard anesthesia induction: desflurane group (Group 1, n=30) and sevoflurane group (Group 2, n=30).

Recorded patient data included age, gender, body mass index, smoking status, comorbidities, presence of renal disease, total liver volume, graft volume, remaining liver volume, total ischemic time, and duration of anesthesia and surgery, graft survival, hospital stay, diastolic blood pressure measured at the beginning and the end of the procedure, systolic blood pressure; and the values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), albumin, total bilirubin, blood urea nitrogen, creatinine, platelet count, and hemoglobin at the postoperative 1, 7, and 30 days.

Results

Demographic data and length of hospital stay of the recipients were similar ($p > 0.05$). Intraoperative urine output of the recipient patients in the desflurane group (Group 1: 1909.52 ± 1269.90 , Group 2: 918.75 ± 618.14), ALT level at postoperative 7th day, and total bilirubin value at the 6th month were found to be significantly higher compared to the sevoflurane group ($p < 0.01$).

Discussion and Conclusion

Our study revealed that preconditioning with sevoflurane during liver transplantation may have greater positive effects on early hepatic and renal functions as compared to desflurane. However, we think that it is necessary to carry out further prospective randomized studies.

Keywords: Liver; Transplantation; Volatile agent; Ischemia-reperfusion

1. Introduction

During the removal of the organ to be transplanted during transplantation, the graft undergoes a process characterized by hot and warm ischemia followed by warm reperfusion, and the patient is under general anesthesia during this process. Both inhalation anesthetics and intravenous anesthetics are used for this procedure. However, our knowledge of the agents used and the effects of these agents on graft survival is limited. It is known that inhalation anesthetics used achieve ischemic preconditioning that protects organs from subsequent ischemia-reperfusion injury (IRI) [1]. Due to the technique of the operation, ischemia-reperfusion injury occurs in both the donor and the recipient. Later, hemodynamic changes lead to partial ischemia and seriously affect the survival of the graft. Hepatocyte damage caused by these ischemic periods determines the function of the graft. Primary dysfunction determines the early prognosis and the need for retransplantation for both the graft and the patient. Preventive approaches to IRI are generally divided into two categories as surgical and pharmacological interventions. These interventions are aimed at preconditioning the ischemic event or preventing events that lead to cellular damage during reperfusion [2]. There are conflicting results from studies regarding the superiority of pharmacological agents over each other in this regard, and the common view is that most of the hepatocyte damage seen in the post-transplantation period is caused by IRI. In their study comparing desflurane with isoflurane, Redel et al.

concluded that desflurane is more effective in preconditioning. It has been shown that preconditioning with desflurane limits NF- κ B activation induced by TNF- α and leads to a protective effect on cells [3]. On the other hand, volatile anesthetic agents can cause a decrease in hepatic blood flow. The effect of volatile anesthetics on the incidence of post-reperfusion syndrome has not yet been clarified. High doses of volatile anesthetics cause hypotension, and as a result, can increase inflammation and cellular adhesion with transient hypoxia. Sevoflurane inhibits the intracellular signaling cascade and plays a role in inflammation as a transcription factor [4]. However, as desflurane is a fluorinated methyl ethyl ether and highly stable in soda-lime, it is hardly metabolized even when it is administered at a minimum alveolar concentration (MAC) of 7 [5]. Pharmacological post-conditioning has been shown to reduce organ damage and postoperative complications and is recommended to be used in patients that have continuous inflow occlusion for a long time [10].

However, it is still controversial whether there is a difference between volatile agents regarding the pharmacological clinical protective effects on ischemia-reperfusion injury in donors of liver transplants. For this reason, there is still a lack of consensus on the choice of an ideal inhalation agent for anesthesia application during liver transplantation. The primary purpose of this study was to determine the most ideal anesthetic agent that can maintain graft perfusion. The secondary purpose was to reveal the effects of anesthetic agents on other organ systems.

2. Material and Methods

Following the approval (protocol no: 09.2021.1004/03.09.2021) of our hospital's local Ethics Committee, donors and recipients of liver transplantation procedures performed between January 2015 and January 2021 were recruited in this retrospective study. When the patients were admitted to the operating room, vascular access was established with a 16G intravenous (IV) catheter, and IV fluid infusion with 0.9% normal saline was started. The patients were monitored using ECG, non-invasive blood pressure measurements, peripheral oxygen saturation, and body temperature measurements. For the induction of anesthesia, the patients were intravenously administered propofol 2-3 mg/kg, fentanyl 1-2 mcg/kg, and rocuronium 0.6 mg/kg. Maintenance of anesthesia was achieved with IV remifentanyl infusion given at a dose of 0.2 mcg/kg/min. Concomitantly, desflurane 6% or sevoflurane 2% was given as inhalation anesthesia in a mixture of air and oxygen. Donors and recipients were evaluated in separate groups depending on whether they received sevoflurane or desflurane. Patients' age, gender, body mass index, smoking status, comorbidities, renal diseases (if present), total liver volume, graft volume, remaining liver volume, total ischemic time, and duration of anesthesia and surgery, graft survival, hospital stay, diastolic blood pressure at the beginning and the end of the procedure and systolic blood pressure were recorded. Additionally, the recorded data included the values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), albumin, total bilirubin, blood urea nitrogen, creatinine, platelet count, and hemoglobin

at the postoperative 1, 7, and 30 days. Patients who underwent cadaveric liver transplantation, whose data could not be reached, and who developed intraoperative complications were excluded from the study.

Statistical Analysis

The IBM SPSS 21 statistical package program was used in the analysis of the study data. The Student's test and the Mann Whitney U test were used to compare quantitative values, and the Chi-square and the Fisher exact tests were used to evaluate categorical data. $p < 0.05$ was considered statistically significant.

3. Results

A total of 60 patients consisting of donors and recipients were enrolled in the study. As a patient received a transplant from a cadaver, that patient was excluded from the study. Data belonging to a total of 29 recipient patients were analyzed. The mean age of the recipients was 31.75 ± 24.347 years in the sevoflurane group and 37.62 ± 15.705 years in the desflurane group ($p = 0.542$). The mean body mass index (BMI) was 20.75 ± 4.496 in patients receiving sevoflurane. In the desflurane group, the mean BMI was 22.38 ± 3.442 ($p = 0.375$). The recipients of liver transplantation that received sevoflurane and desflurane did not differ in terms of gender distribution, smoking status, dialysis treatment, and 3-month mortality rate ($p > 0.05$, Table 1). Total ischemic time, duration of anesthesia and surgery, and length of hospital stay did not differ significantly between liver transplant recipients that were given sevoflurane or desflurane ($p > 0.05$, Table 2). There

was no significant difference between the desflurane and sevoflurane groups in terms of intraoperative fluid requirement, blood loss volume, and the need for blood and blood products ($p > 0.05$, Table 3). Intraoperative urinary output levels were found to be significantly higher in the desflurane group than in the sevoflurane group ($p = 0.01$). The ALT value on the 1st postoperative day was similar in desflurane and sevoflurane groups. On the other hand, the ALT level on the 7th postoperative day significantly increased in the desflurane group as compared to the sevoflurane group ($p = 0.018$, Table 4). But the groups were found to be similar in the ALT levels measured on the 30th day and 6th month in the postoperative period ($p > 0.05$). Postoperative 6th month total bilirubin values were found to be significantly higher in patients given desflurane than in patients in the sevoflurane group ($p = 0.049$). Total bilirubin values on the postoperative 1st day, 7th day, and 30th day were similar between the groups ($p > 0.05$, Table 5). When compared in terms of other hepatorenal functions and coagulation parameters, no significant difference was found in the recipients of liver transplantation ($p > 0.05$, Table 6).

4. Discussion

This retrospective study investigated the impact of desflurane and sevoflurane on postoperative patient outcomes in both donors and recipients of liver transplantation. The two agents were found to be similar in effects on length of hospital stay, 3-month mortality rate, blood loss, and need for blood transfusion. Total intraoperative urine output, ALT level on the postoperative 7th day, and total bilirubin values at the 6th month were higher in the desflurane

group. Since desflurane and sevoflurane have low blood-gas partition coefficients [11], rapid induction and quick recovery are possible. They also have similar features for creating hemodynamic stability [12]. Moreover, the fact that these agents are not metabolized by the liver is the reason for preference in liver transplant recipients. However, there is a limited number of studies comparing these two volatile anesthetics in liver transplantation. In a study comparing the rates of the post-reperfusion syndrome, the post-reperfusion syndrome was observed at a lower rate in living donor liver transplantation patients that received sevoflurane [13]. The authors emphasized that the arteriolar resistance-reducing effect of desflurane may have contributed to this result because of the reduction in systemic vascular resistance. In that study, there was greater bleeding in patients given desflurane. However, there was inconsistency in the results. Because although there was a significant increase in bleeding, no significant difference was found between the groups in terms of hemodynamic data. According to the data we obtained in the present study, the volume of bleeding, the rate of blood and blood product transfusion, and accordingly hemodynamic parameters were found to be similar in patients receiving desflurane and sevoflurane. Volatile anesthetic agents were historically believed to reduce cardiac output as a result of peripheral vasodilation they created, resulting in a decrease in hepatic blood flow and in this way, some changes may occur in liver functions hepatic blood flow [12,14]. However, in recent years an increasing number of studies have shown that volatile agents do not reduce hepatic blood flow more than iv anesthetics [13]. It was demonstrated that volatile

agents given to transplant patients provide better blood glucose hemostasis, require less inotropes and can be extubated earlier [14]. Today, the hepatic protective effects of volatile anesthetics are more frequently mentioned. It has been reported that administration of sevoflurane 30 minutes before inflow hepatic occlusion may reduce hepatocyte damage [15]. In addition, it has been reported that volatile agents have anti-oxidant and anti-inflammatory properties and do not cause oxidative stress and DNA damage and it is also known that they have potentiating effects on nitric oxide production [16,17]. All of them are the mechanisms that explain the hepatoprotective properties of volatile anesthetic agents. Thus, they have become pharmacological agents that can be applied for hepatic preconditioning, such as adenosine agonists or protease inhibitors. Many studies have emphasized that low postoperative ALT and total bilirubin levels are associated with the degree of ischemia-reperfusion injury, indicating less hepatocyte damage and better liver function. Pharmacological preconditioning has been shown to reduce organ damage and postoperative complications and is recommended for use in patients with long-term continuous inflow occlusion [18]. In a study investigating the effects of volatile agents on liver regeneration, 1629 patients with right hepatectomy were evaluated retrospectively [7]. The patients were divided into two groups depending on whether they received sevoflurane (n=1206) or desflurane (n=423). In that study, no difference was found between early liver injury scores, and thus, it was concluded that both sevoflurane and desflurane can be used safely without affecting liver regeneration and delaying liver function recovery. In our study, hepatic

functions were evaluated both in the early and late postoperative period after preconditioning with desflurane and sevoflurane, and an increment was detected in both ALT and total bilirubin levels in the late period in desflurane group. Although many factors affecting graft functions associated with drugs, viruses or ischemic events in the late postoperative period are effective, the fact that these levels were found to be normal in patients receiving sevoflurane suggested that sevoflurane may have a positive effect as a volatile agent in hepatic transplant recipients [19]. It has been demonstrated that preconditioning with sevoflurane during hepatic transplantation improves graft function by reducing the incidence of early allograft dysfunction in the recipients of steatotic liver grafts [8]. The patients with primary graft dysfunction were found to have longer hospital stays and intensive care unit stays due to increased complications such as infection and renal dysfunction [9]. In our study, patients given sevoflurane and desflurane were also compared in terms of hospital stay, duration of surgery and anesthesia, and amount of fluid and blood transfusion. However, no significant difference was found between the groups. In addition to all these, in our study in which renal functions were evaluated, it was found that patients given desflurane had a higher volume of urine output in the intraoperative period. This increase in urine output may have developed secondary to the increase of vasopressin secretion by desflurane in this stress environment triggered by ischemia-reperfusion injury [23,24]. Although this situation can be interpreted as in favor of renal functions, it can be evaluated as an early sign of kidney damage as revealed in previous studies. Because the increase in total renal blood flow

increases the glomerular filtration rate, the tubular sodium load increases, and this may lead to further deterioration of kidney functions with worsening medullary oxygenation [25]. An example of this contradiction is increased urine output despite a decrease in GFR due to tubular aquaporin-2 dysfunction that develops after endotoxemia. Therefore, tubulopathy developing secondary to ischemia may also have caused this situation. As can be seen, urine output is therefore both a non-specific and a weak parameter in the prediction of kidney damage in critically ill patients. In our study, creatinine values were found to be normal in the postoperative period. However, with only creatinine values in the postoperative period and this limited sample size, it is clear that this needs to be proven, and we think that it can be a source of ideas for researchers. Considering their pharmacological structures, these two agents are among the halogenated anesthetic agents [26]. However, it has been argued that the metabolization of sevoflurane to form trifluoroacetic acid may be hepatotoxic, and on the contrary, since desflurane is not metabolized to trifluoroacetic acid, its hepatotoxicity potential is low. For this reason, desflurane has been described as an ideal agent in major hepatic surgery or hepatic transplantation surgery in some sources [27]. However, studies published in recent years have reported that sevoflurane is protective against IRI [28,29]. The results of our study also explain the mechanism and evidence presented in these current publications.

Limitations

Our study has some limitations that should be noted. The main limitation is that only blood parameters that

are frequently used as indicators of hepatic and renal functions were studied. However, no other more specific markers revealing hepatic or renal damage were investigated. Due to the nature of the study, hepatic histopathological examination could not be performed in the patients. For this reason, additional biochemical and histopathological studies supporting the hepatic enzymatic changes and showing this is related only to volatile anesthetic could not be performed. Another limitation is that the study was designed as a retrospective study and a small sample size could be obtained. We need prospective randomized comparative studies to be conducted with larger series.

5. Conclusion

Our study indicated that preconditioning with sevoflurane during liver transplantation may have greater positive effects on early hepatic and renal functions as compared to desflurane. However, further studies are needed to prove the clinical significance of these findings.

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