Influence of anesthesia type on post-reperfusion syndrome during liver transplantation: a single-center retrospective study

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Background: Post-reperfusion syndrome (PRS) results in sudden hemodynamic instability following graft reperfusion. Although PRS is known to influence outcomes following liver transplantation, little is known regarding the effects of anesthetics on PRS. This study investigated the association between the type of anesthetic agent and PRS in liver transplantation.

Methods: This single-center retrospective cohort study included patients who underwent liver transplantation between June 2016 and December 2019. Patients were divided into sevoflurane and propofol groups according to the anesthetic agent used. Stabilized inverse probability of treatment weighting (IPTW) analysis was performed to investigate the association between PRS identified based on blood pressure recordings and the type of anesthesia. Associations between the anesthetic agent and the duration of hypotension as well as early postoperative outcomes were also investigated.

Results: Data were analyzed for 398 patients, 304 (76.4%) and 94 (23.6%) of whom were anesthetized with propofol and sevoflurane, respectively. PRS developed in 40.7% of the 398 patients. Following stabilized IPTW analysis, the association with PRS was lower in the sevoflurane group than in the propofol group (odds ratio, 0.47; P = 0.018). However, there was no association between the type of anesthetic used and early postoperative outcomes.

Conclusions: The association of PRS was lower in the sevoflurane group than in the propofol group. However, there was no association between the type of anesthetic and the early postoperative outcomes. Further studies are required to determine the optimal anesthetic for liver transplantation.

Keywords: Liver transplantation; Propofol; Reperfusion; Sevoflurane.

INTRODUCTION

Hemodynamic instability, which occurs frequently during liver transplantation, is most severe, especially following graft reperfusion [1]. The reported incidence of the post-reperfusion syndrome (PRS), which results in sudden cardiovascular depression following de-clamping of the portal vein, ranges from 12–77% [2]. PRS is known to increase intraoperative transfusion requirements as well as the length of stay in the intensive care unit and overall hospital stay, and
several studies have demonstrated the major clinical impact of PRS on morbidity and mortality in the recipient [3,4].

Known recipient-, donor-, and organ-related risk factors for PRS include donor age, degree of macrovesicular steatosis, organ size mismatch, prolonged cold ischemic time, recipient age, Model for End-Stage Liver Disease (MELD) score, and high potassium levels [1]. Anesthetic agents may also influence the risk of PRS given their cardiovascular effects [5]. Previous studies have reported the effects of anesthetic agents on intraoperative hemodynamics and postoperative outcomes in patients undergoing liver transplantation [6-9]; however, these reports mainly focused on deceased donor liver transplantation (DDLT) [8] and compared desflurane [6,7] or isoflurane [9] with other agents. In contrast, the effects of sevoflurane and propofol on PRS following liver transplantation remain unclear. Therefore, the present study aimed to investigate the association between the most widely used anesthetic agents (sevoflurane and propofol) [10,11] and the occurrence of PRS.

**MATERIALS AND METHODS**

This retrospective observational study was approved by the Institutional Review Board of our hospital (no. 2107-182-1236), which waived the requirement for informed consent due to its retrospective design. We reviewed the electronic medical records, laboratory results, and anesthetic records of all recipients who underwent living donor liver transplantation (LDLT) or DDLT at our hospital from June 2016 to December 2019. Patients aged < 18 years, those with missing data for vital recordings, those anesthetized with agents other than sevoflurane and propofol, those who had undergone simultaneous transplantation, and those who had died before reperfusion during liver transplantation were excluded.

Anesthesia was administered in accordance with our hospital’s anesthesia protocol for liver transplantation: The anesthetic agent was selected according to the preference of the attending anesthesiologist. In the sevoflurane group, anesthesia was induced with 1–2 mg/kg of propofol and maintained using sevoflurane and continuous infusion of remifentanil. In the propofol group, propofol and remifentanil were infused for both the induction and maintenance of anesthesia using a target-controlled infusion device (Injektomat™ total intravenous anesthesia [TIVA] Agilia, Fresenius Kabi, Germany). In both groups, the anesthetic depth was controlled to maintain a bispectral index (BIS) under 60. Rocuronium was used for neuromuscular blockade. Fluid resuscitation; transfusion targeting a hemoglobin level of 8 g/dl, platelet count of 50 k/μl and a prothrombin time international normalized ratio (PT-INR) of 2.0; and vasopressor (ephedrine, epinephrine, norepinephrine) treatment were performed at the discretion of the anesthesiologist to ensure hemodynamic stability during the surgery.

The vital data automatically recorded from various anesthesia instruments from all patients, which included blood pressure recorded at 2-s intervals by the Vital Recorder [12] during the operation, were obtained and analyzed to define PRS.

**Data collection**

We reviewed electronic medical records, demographic characteristics, laboratory values, surgical data, anesthetic data, and postoperative outcomes for each patient. Demographic data analyzed for recipients included age, sex, weight, height, body mass index (BMI), and etiology of the liver disease (chronic hepatitis, non-viral related liver cirrhosis, hepatocellular carcinoma, cholestatic disease, fulminant liver failure, metabolic disease). Clinical and laboratory data analyzed for recipients included ABO incompatibility and baseline medical status (preoperative hemodialysis, preoperative beta blocker use, preoperative insulin use, preoperative diuretic use, MELD score). Clinical factors analyzed for donors included age, graft weight to recipient body weight ratio (GRWR, %), and the degree of macrovesicular steatosis. The following surgical and anesthetic data were also obtained: type of general anesthetic agent (propofol-based TIVA vs. sevoflurane), anesthesia time (min), operation time (min), estimated blood loss (ml/kg), cold ischemic time (min), warm ischemic time (min), anhepatic time (min), potassium (mM/L) level at the time of portal vein anastomosis, calcium (mM/L) level at the time of portal vein anastomosis, and transfusion amount (red blood cell count, fresh frozen plasma [FFP], platelet concentration). Cold ischemic time was defined as the interval from initiation of donor in vivo cold organ preservation to removal of the graft from 4°C cold storage. Warm ischemic time was defined as the interval from removal from cold storage to reperfusion of the liver graft. Anhepatic time was defined as the interval from the recipient’s hepatectomy to reperfusion of the liver graft.

Laboratory values for total bilirubin, PT-INR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum creatinine (sCr) levels until postoperative day (POD) 7 were also collected.

The primary outcome of our study was the occurrence of
PRS. PRS was defined as a decrease in the mean arterial pressure greater than 30% below the anhepatic level at the time of reperfusion, lasting for at least 1 min during the first 5 min following graft reperfusion [2]. The analysis was performed based on the femoral artery pressure, which is expected to better reflect the central pressure owing to the extreme vasodilation that occurs after reperfusion in the distal vessels [1]. Secondary outcomes included the occurrence of acute kidney injury (AKI), the occurrence of primary graft dysfunction (PGD), length of stay in the intensive care unit (ICU), and length of hospital stay. AKI was defined as an sCr increase ≥ 0.3 mg/dl within 48 h postoperatively or a percentage increase in sCr ≥ 50% from baseline, which is known or presumed to have occurred within the previous 7 days [13]. PGD was defined as (1) bilirubin ≥ 10 mg/dl on POD 7, (2) PT-INR ≥ 1.6 on POD 7, or (3) AST or ALT > 2,000 IU/L within the first 7 days postoperatively [14].

**Statistical analysis**

Stabilized inverse probability of treatment weighting (IPTW) analysis was performed using a propensity score [15] using logistic regression with logit link to determine the association between PRS and the type of anesthesia in the R package “survey” [16]. The following covariates were used for propensity score matching: whether LDLT or DDLT was performed, ABO compatibility, the recipient factors, such as age, sex, BMI, etiology of liver disease, MELD score, baseline medical status, and donor and graft factors, such as donor age, GRWR, steatosis, cold ischemic time, and warm ischemic time and intraoperative factors, such as anhepatic time, inferior vena cava (IVC) clamping time, estimated blood loss, packed red blood cell units transfused, FFP units transfused, and potassium and calcium levels before reperfusion. Before and after stabilized IPTW analysis, the balance of the two groups was compared using the standardized mean difference (SMD), and an SMD greater than 0.1 was considered as an imbalance. Primary and secondary outcomes were compared before and after stabilized IPTW analysis. The Shapiro–Wilk test was used to evaluate data normality. Univariate logistic regression and the Mann–Whitney U test were used to analyze categorical and continuous variables, respectively.

Categorical variables are reported as numbers (%), while continuous variables are reported as medians (IQR, 3Q). R software (version 4.1.1 with R packages, R development Core Team, Austria) was used for all the statistical analyses, and a two-sided P value of less than 0.05 was considered statistically significant.

**RESULTS**

During the study period, 471 patients underwent liver transplantation. Among them, we analyzed 398 eligible patients after excluding patients aged < 18 years (n = 23), those with missing data for vital recordings (n = 38), simultaneous transplantation of another organ (n = 4), patients anesthetized with desflurane (n = 7), and those who died before reperfusion (n = 1). Among the 398 patients, 304 (76.4%) were anesthetized with propofol, while 94 (23.6%) patients were anesthetized with sevoflurane during the operation (Fig. 1); PRS developed in 40.7% of the 398 patients.

Table 1 shows the baseline characteristics and perioperative parameters of the two groups before and after stabilized IPTW analysis. Prior to stabilized IPTW analysis, the groups exhibited differences in living donors, recipient age, MELD score, preoperative hemodialysis, preoperative diuretic use, donor age, GRWR, cold ischemic time, IVC clamping time, level of potassium before reperfusion, level of calcium before reperfusion, and level of sodium before reperfusion. Before and after stabilized IPTW analysis, the balance of the two groups was compared using the standardization mean difference (SMD), and an SMD greater than 0.1 was considered as an imbalance. Primary and secondary outcomes were compared before and after stabilized IPTW analysis. The Shapiro–Wilk test was used to evaluate data normality. Univariate logistic regression and the Mann–Whitney U test were used to analyze categorical and continuous variables, respectively.

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fore reperfusion, packed red blood cell units transfused, and FFP units transfused (SMD > 0.1). However, these differences disappeared following stabilized IPTW analysis.

Table 2 and Fig. 2 present a comparison of the primary and secondary outcomes. Before and after stabilized IPTW analysis, the association with PRS was lower in the sevoflurane group than in the propofol group (before: odds ratio [OR]: 0.57, 95% confidence interval [CI]: 0.35–0.93; P = 0.035; after: OR: 0.47, 95% CI: 0.28–0.80, P = 0.018). The duration of hypotension was also higher in the propofol group than in the sevoflurane group. However, there were no differences in the association with PGD, AKI, ICU stay, or hospital stay between the groups either before or after stabilized IPTW analysis.

**DISCUSSION**

In this study, we investigated the association between the type of anesthesia and PRS in patients undergoing liver transplantation, as well as early postoperative outcomes following liver transplantation. Our findings indicated that, following graft reperfusion, propofol exhibited a greater association with PRS than sevoflurane; however, the type of anesthesia was not associated with early postoperative outcomes.

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Table 2. Between-group Comparison of Primary and Secondary Outcomes Before and After Stabilized IPTW

| Outcomes                        | Before stabilized IPTW | After stabilized IPTW | Odds ratio* (95% CI) | Odds ratio* (95% CI) |
|---------------------------------|------------------------|-----------------------|----------------------|----------------------|
|                                | Propofol (n = 304)     | Sevoflurane (n = 94)  | P value              | Propofol (n = 303)   | Sevoflurane (n = 92)  | P value              |                         |
| PRS                             | 133 (43.8)             | 29 (30.9)             | 0.035                | 127.6 (42.8)          | 24.7 (27.2)           | 0.018                | 0.47 (0.28–0.80)        |
| Duration of hypotension after reperfusion (s) | 50.0 (0.0, 102.0)      | 7.0 (0.0, 81.5)       | 0.013                | 48.0 (0.0, 102.0)     | 1.8 (0.0, 76.6)       | 0.007                |                          |
| PGD                             | 23 (7.6)               | 9 (9.6)               | 0.068                | 22.5 (7.5)            | 5.3 (5.9)             | 0.565                | 0.73 (0.26–2.02)        |
| AKI                             | 91 (29.9)              | 30 (31.9)             | 0.813                | 85.7 (28.7)           | 29.8 (32.7)           | 0.533                | 1.26 (0.75–2.13)        |
| ICU stay (d)                    | 7.2 (14.4)             | 6.1 (4.8)             | 0.469                | 8.0 (16.1)            | 6.0 (5.4)             | 0.138                |                          |
| Hospital stay (d)               | 22 (16, 35)            | 25 (19, 41.5)         | 0.008                | 23 (16, 37.0)         | 22 (17.0, 31.0)       | 0.924                |                          |
| Postoperative day discharge (d) | 17 (13, 26)            | 18 (14, 26.8)         | 0.088                | 17 (13.0, 27.0)       | 17.7 (14.0, 24.0)     | 0.656                |                          |

Data are presented as number (%) or median (1Q, 3Q). IPTW: inverse probability of treatment weighting, CI: confidence interval, PRS: postreperfusion syndrome, PGD: primary graft dysfunction, AKI: acute kidney injury, ICU: intensive care unit, N/V: nausea/vomiting, DGE: delayed gastric emptying, * The Propofol group used as the reference.

![Odds ratios between the groups for primary and secondary outcomes. CI: confidence interval. *P value of less than 0.05.](www.anesth-pain-med.org)
To our knowledge, this study is the first to evaluate the association between PRS and the use of sevoflurane and propofol based on high-resolution data.

Previous studies have analyzed changes in blood pressure following reperfusion according to the anesthetic agent used during liver transplantation, especially for inhaled agents versus propofol. While some studies reported a greater degree of hypotension in the propofol group than in the isoflurane or sevoflurane group [17,18], they only compared blood pressure at two timepoints (i.e., 5- and 10-min following reperfusion). In our study, we evaluated blood pressure recorded at 2-second intervals, allowing us to examine both individual measurements and trends in blood pressure following reperfusion. Shin et al. [19] reported no difference in the incidence of PRS between the propofol and desflurane groups (desflurane, 15.6%; propofol 20.0%, P = 0.452) in their study; however, patients in the propofol group were anesthetized with desflurane at the dissection phase. In another retrospective study, the rate of norepinephrine administration at reperfusion was lower in the propofol-based TIVA group than in the desflurane group (desflurane, 42.2%; propofol, 21.2%; P = 0.020); however, the study included a small number of patients (TIVA, 66; desflurane, 45), and the authors did not evaluate donor or graft characteristics that may have affected PRS [20]. In contrast, we evaluated several factors that may have influenced PRS in a relatively large number of patients while correcting for baseline differences using stabilized IPTW analysis.

Our study demonstrated that propofol-based TIVA was more strongly associated with PRS than sevoflurane anesthesia. This may be explained by the hemodynamic differences between sevoflurane and propofol anesthesia. Propofol inhibits sympathetic vasoconstrictor activity and chronotropy in a dose-dependent manner [21,22]. Sevoflurane inhibits sympathetic nervous activity but has little effect on parasympathetic nervous activity [23]; as such, its use has been associated with relatively low heart rate variability as well as cardioprotective effects [8]. During the anhepatic phase, the rate of propofol clearance decreases to approximately 42% [24], resulting in increased accumulation of propofol in the body, which in turn leads to an increase in the depth of anesthesia. Subsequently, this overdose of propofol causes a decrease in heart rate and vasodilation-induced systemic vascular resistance following sympathetic inhibition [22]. Conversely, sevoflurane has been shown to exert a pre-conditioning effect on skeletal muscles during reperfusion [25], with one previous report stating that sevoflurane maintains cardiac function in the early reperfusion phase [26]. In previous animal studies, recovery of cardiovascular function was faster in the sevoflurane group than in the propofol group [27]. In addition, tumor necrosis factor alpha (TNF-α) is the main cytokine associated with the hemodynamic instability following reperfusion [2]. In one study comparing the use of sevoflurane and propofol in pediatric patients undergoing liver transplantation [18], the concentration of TNF-α was higher in the propofol than in the sevoflurane group following reperfusion. These findings may explain the stronger association between propofol and PRS than between sevoflurane and PRS.

Several studies have demonstrated that PRS is associated with poor postoperative outcomes [3,4,17]. However, we observed no significant differences in postoperative outcomes between the two groups in our study. There are several possible explanations for this result. (1) It is possible that the transplantation procedure itself [28] affects early postoperative outcomes to a greater extent than PRS. Further, (2) as the median MELD score in both groups following stabilized IPTW analysis was 13.8 owing to the large proportion of LDLT; ischemic reperfusion injury may not have been severe in our patients. (3) Despite the development of PRS, recovery from hypotension occurred within 5 min in all patients because the attending anesthesiologist was a liver transplantation specialist with substantial experience. Previous reports have demonstrated that the poor outcomes associated with PRS are concomitant with severe PRS lasting for more than 5 min [29]. In our study, the degree of hypotension following reperfusion may not have been severe enough to induce clinical damage. In a previous study comparing sevoflurane and propofol use among patients undergoing LDLT [8], the authors observed no difference in early liver function between the groups. Together, these results suggest that there is no association between PRS and early postoperative outcomes.

This study had several limitations. First, owing to the retrospective design of the study, unmeasured covariates may have impacted our results; however, stabilized IPTW analysis was used to balance the differences between the groups while preserving sample size [30]. Second, this analysis was performed in a single center in Korea; thus, our results cannot be generalized to patients in different centers and of different races. Third, no information regarding cytokines, which are known to affect PRS, was available for this analysis. Fourth, although the depth of anesthesia may have influenced vital signs, we did not analyze BIS data in this study.
However, the anesthetic level was controlled by the attending anesthesiologist to maintain a BIS level of 40–60.

In conclusion, our findings indicated that propofol use was more strongly associated with PRS than sevoflurane use in patients undergoing LDLT, although there was no association between the type of anesthetic used and early postoperative outcomes. Further prospective trials are warranted to determine the association between the anesthetic agent and intraoperative PRS/postoperative outcomes to identify the optimal anesthetic for liver transplantation.

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**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**DATA AVAILABILITY STATEMENT**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**AUTHOR CONTRIBUTIONS**

Conceptualization: Hye-Yeon Cho, Seong-Mi Yang. Data curation: Hye-Yeon Cho, Hyung-Chul Lee, Suk Kyun Hong. Formal analysis: Hye-Yeon Cho, Ho-Jin Lee, Seong-Mi Yang. Funding acquisition: Seong-Mi Yang. Methodology: Ho-Jin Lee, Seong-Mi Yang. Writing - original draft: Hye-Yeon Cho, Seong-Mi Yang. Writing - review & editing: Hye-Yeon Cho, Ho-Jin Lee, Won Ho Kim, Hyung-Chul Lee, Chul-Woo Jung, Seong-Mi Yang. Supervision: Chul-Woo Jung, Seong-Mi Yang.

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