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ORIGINAL ARTICLE

Vecuronium requirement during liver transplantation under sevoflurane anesthesia

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Abstract
Purpose In liver transplantation patients under intravenous anesthesia, the vecuronium dose is known to be reduced, especially during the anhepatic phase. Volatile anesthetics potentiate a muscle relaxation effect of neuromuscular blocking agents, so the vecuronium dose is supposed to further decrease if sevoflurane is used during liver transplantation. The purpose of this study was to determine the appropriate dose of vecuronium at each phase of liver transplantation under sevoflurane anesthesia.
Methods Thirty-five patients scheduled for living donor liver transplantation because of liver cirrhosis were enrolled in this study. They were anesthetized with 1 MAC of sevoflurane and intermittent administration of fentanyl. Continuous infusion of vecuronium (0.5 mg/ml) was used for muscle relaxation, which was adjusted every 15 min for consistent muscle relaxation aimed at T1/Tc of 0.1 monitored by ulnar nerve stimulation. Vecuronium infusion was stopped after hepatic artery anastomosis was finished. The infusion rate of each operative phase—dissection, anhepatic, and neohepatic—was calculated and analyzed by one-way analysis of variance. The recovery time from train-of-four (TOF) count 1 to TOF ratio 25% was also measured.
Results The vecuronium infusion rate of each operation phase for adequate muscle relaxation was as follows: 0.033 ± 0.009 mg/kg/h during dissection phase, 0.031 ± 0.009 mg/kg/h during anhepatic phase, and 0.026 ± 0.006 mg/kg/h during early neohepatic phase. There was a statistically significant difference between doses at each phase ($P = 0.033$). The recovery time from TOF count 1 to TOF ratio 25% was 103 ± 29 min.
Conclusions The required vecuronium dose in all phases was less than the known dose in the anhepatic phase (0.036 mg/kg/h) under midazolam-fentanyl anesthesia. In addition, the vecuronium infusion dose was not reduced in the anhepatic phase compared to the dissection phases.

Keywords Liver transplantation · Sevoflurane · Vecuronium

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Introduction

Any nondepolarizing neuromuscular blocker can be used in liver transplantation so long as adequate monitoring is performed. However, as some neuromuscular blockers are degraded and cleared in the liver, close attention should be given to prevent an overdose. Vecuronium is eliminated principally by the liver; 30–40% is cleared in bile as the parent compound and 12% is converted to 3-deacetylvecuronium. Although vecuronium has generally been used in liver transplantation at some centers without prolonged paralysis [1, 2], the dose should be carefully adjusted. Under intravenous (IV) anesthesia with midazolam and fentanyl, the vecuronium requirement decreased, particularly during the anhepatic phase [3].

Not only IV anesthetics but some volatile anesthetics are also suitable for liver transplantation anesthesia. If

sevoflurane is used for liver transplantation anesthesia, the vecuronium dose should be reduced because volatile anesthetics potentate the neuromuscular blocking effect of nondepolarizing neuromuscular blockers [4–7]. To prevent an overdose and ensure adequate reversal, it is important to know how much the requirement of vecuronium is to be reduced under sevoflurane and whether additional dose reduction at the anhepatic phase is present. However, the adequate vecuronium dose during liver transplantation under sevoflurane anesthesia is not known.

The purpose of this study was to evaluate the requirement of vecuronium at each phase of liver transplantation when sevoflurane is used as the main anesthetic agent.

Patients and methods

After obtaining Institutional Review Board approval and written informed consent from patients, 35 adult patients undergoing liver transplantation were enrolled in this study. The inclusion criteria were patients undergoing elective living donor-related liver transplantation consequent to liver cirrhosis with hepatic dysfunction including coagulation abnormality (PT INR $>$ 1.7), low serum albumin ($<$2.8 g/dl), and elevated serum bilirubin ($>$2.0 mg/dl). The etiology of liver cirrhosis was hepatitis B in all patients. The exclusion criteria were patients with no evidence of liver dysfunction (e.g., undergoing transplantation because of hepatocellular carcinoma), concomitant cardiac, pulmonary, neurological, or renal disorder, age more than 60 years, transfusion more than 10 U of packed red cells during operation, and any evidence of primary nonfunction of transplanted liver after reperfusion.

Anesthesia was induced using 1–2 mg/kg propofol, 1–2 μg/kg fentanyl, and 0.1 mg/kg vecuronium for facilitating endotracheal intubation. Anesthesia was maintained with sevoflurane [about 1 MAC (minimum alveolar concentration), adjusted for age] with 50% oxygen in air and an intermittent supplement of fentanyl. All the standard monitoring for liver transplantation including pulmonary artery pressure and continuous cardiac output via pulmonary artery catheter was used. Esophageal and pulmonary artery temperature were monitored continuously, and a warming blanket, air warmer, and fluid-warming devices were used. An antibiotic was given every 8 h, and 500 mg methylprednisolone was administered before and after reperfusion as part of the antirejection therapy.

The concentration of vecuronium solution for infusion was 0.5 mg/ml, and the infusion line was directly connected to the patient's IV catheter. To quantify the neuromuscular paralysis, neuromuscular function was monitored by acceleromyography [train-of-four (TOF)-Watch SX Monitor; Organon Teknika, Eppelheim, Germany], which measures the acceleration of the adductor pollicis response to a 50-mA stimulus applied to the ulnar nerve. After calibration of the device, the initial bolus of 0.1 mg/kg vecuronium was given to facilitate endotracheal intubation. During anesthetic maintenance, the first twitch response in relation to the baseline values (T1/Tc) as well as the fourth twitch in relation to the first one of each train (T1/T4) was monitored. When recovery from the initial bolus dose was evident by a single twitch depression (T1/Tc) of more than 0.1, continuous infusion of vecuronium was started. Target neuromuscular relaxation was defined as maintaining T1/Tc of 0.1 during the operation from incision to hepatic artery anastomosis. The infusion rate was started as 0.025 mg/kg/h and manually adjusted every 15 min; the infusion rate was increased by 10% if T1/Tc was more than 0.1, and decreased by 10% if T1/Tc was measured as 0. When hepatic artery anastomosis was completed, the vecuronium infusion was discontinued. From the raw results of the vecuronium infusion rates, the total infused dose during each phase of the individuals was counted and then this calculated dose at each phase was divided by the duration of each phase, respectively; because vecuronium was infused during a part of the dissection phase and the neohepatic phase, the vecuronium dose in these two phase were divided by only the length of infusion period, not the entire period. Throughout this process vecuronium dose at each three phases per each patient was described as the infusion rate of mg/kg/h.

After skin incision was closed and the TOF ratio was more than 25%, 0.2 mg/kg pyridostigmine and 0.05 mg glycopyrrolate per 1 mg pyridostigmine was administered. When consciousness was restored and the TOF ratio was more than 80%, extubation was done on patients of adequate condition: good donor liver function, hemodynamic stability, and alveolar-arterial oxygen gradient $<$200 mmHg.

Statistics

Power analysis was performed by one-way analysis of variance (ANOVA) for the doses of each of the three phases. For a level of significance of 0.05, a sample size of 33 would give an 80% chance of detecting this difference. To compensate for possible dropouts, we decided to include 35 patients. One-way ANOVA and Bonferroni test for post hoc analysis were used to compare the doses of each of the three phases. Power analysis was conducted with PASS 2008, and ANOVA was conducted with SPSS for Windows (version 13; SPSS, Chicago, IL, USA). A P value $<$0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics and the anesthetic durations of each of the three phases are presented in Table 1.

The vecuronium infusion rate at each operation phase for adequate muscle relaxation was as follows: 0.033 ± 0.009 mg/kg/h during the dissection phase, 0.031 ± 0.009 mg/kg/h during the anhepatic phase, and 0.026 ± 0.006 mg/kg/h during the early neohepatic phase from reperfusion to hepatic artery anastomosis. The duration of infusions during the dissection phase and the neohepatic phase are listed in Table 1. There was a statistically significant difference between the doses at each phase ($P = 0.033$), and the dose during the neohepatic phase was significantly less than the dissection phase ($P = 0.039$).

The time required for recovery from the stop of infusion of vecuronium when TOF count was 1 to TOF ratio 25% was 103 ± 22 min.

After administration of the reversal drug, neuromuscular contraction was recovered more than TOF ratio of 80% in all enrolled patients. A total of 33 patients were extubated at the operating room with full recovery from neuromuscular block and restoration of consciousness; 1 patient remained intubated because of a right pleural effusion preoperatively, and another had a tongue injury related to a seizure during the preoperative period.

Discussion

From the results of this study, the vecuronium dose under sevoflurane anesthesia was 0.033 mg/kg/h during the dissection phase, 0.031 mg/kg/h during the anhepatic phase, and 0.026 mg/kg/h during the early stage of the neohepatic phase. No dose reduction was observed in the anhepatic phase but the requirement was slightly reduced in the neohepatic phase.

Table 1 Patient characteristics

Age (years)	52.6 ± 6.2
Sex (M/F)	23/12
Height (cm)	163.2 ± 8.5
Weight (kg)	62.5 ± 8.7
Estimated blood loss (ml)	2,384 ± 1,229
Dissection phase (min)	
Total duration	171 ± 55
Duration of vecuronium infusion	165 ± 52
Anhepatic phase (min)	88 ± 18
Neohepatic phase (min)	
Total duration	235 ± 42
From reperfusion until artery anastomosis	137 ± 34

Dose reduction of vecuronium by volatile anesthetics is reported to be about 70% [8]; from our results, sevoflurane reduced the vecuronium dose by more than half of that resulting under IV anesthesia (0.033 vs. 0.072 mg/kg/h [3]) during dissection phase.

The anhepatic phase is when the hepatic circulation and function are totally excluded; therefore, the vecuronium dose should be adjusted. O'Kelly et al. [3] demonstrated that the vecuronium dose significantly decreases during the anhepatic phase, by a half-dose compared to that of the dissection phase or two-thirds of the neohepatic phase under anesthesia with midazolam and fentanyl. However, our results showed that the vecuronium dose was not significantly reduced in the anhepatic phase compared to the other phases. Several possible causes can be considered for this result. First, the vecuronium dose used during the anhepatic phase could be regarded as the dose that can be used even when the liver hardly functions; from our results, the vecuronium dose reduced by sevoflurane was comparable to the dose in the anhepatic phase studied previously (0.039 mg/kg/h). Therefore, our resultant dose during the dissection phase could be small enough to be unaffected by hepatic function. Second, as the sample size was calculated for presenting the dose difference of the three phases, the number of enrolled patients might be too small to detect the significance of the doses between the dissection phase and the anhepatic phase. Third, the majority of enrolled patients already had severe hepatic dysfunction before transplantation, so the dose during the dissection phase might be already affected by hepatic dysfunction.

Another distinction of our study is that the dose was slightly reduced in the neohepatic phase and recovery took a long time. The potentiation of the neuromuscular blockade by volatile anesthetics is dependent on time course [6], so a long duration of anesthesia might affect vecuronium dose reduction during the neohepatic phase. In addition, augmentation of the neuromuscular blockade effect by volatile anesthetics is known to result not only in dose reduction [7, 9] but also in prolongation of recovery [7]. It is unlikely that unmetabolized or uncleared vecuronium accumulated enough to affect dose reduction during the neohepatic phase because a small amount of vecuronium was infused throughout the dissection and the anhepatic phase. In addition, the duration of vecuronium-induced neuromuscular block was related to liver allograft function [10]. Despite the fact that the transplanted liver functioned well after reperfusion in our enrolled patients, the vecuronium dose was reduced; therefore, if allograft dysfunction is expected, more caution and careful monitoring is needed to prevent vecuronium overdose in the neohepatic phase.

There are some limitations in this study. First, our study did not include the control group that received IV

anesthesia, so the comparison between the results reported by O'Kelly et al. [3] and our study might be a poor fit. This study was primarily planned to evaluate the dose requirement at each phase and recovery profile of the infusion of vecuronium in liver transplantation under sevoflurane anesthesia. The major significance of this study is that there was no vecuronium dose reduction in the anhepatic phase, in contrast to that under IV anesthetics. Second, we monitored the esophageal and pulmonary artery blood temperature, not the direct muscle temperature, so the chance of peripheral hypothermia might influence the effect of vecuronium. Third, the bolus dose of vecuronium infused during induction was excluded. The condition of vecuronium administration was equal in all patients; all patients received 0.1 mg/kg of vecuronium, and continuous infusion began when all patients recovered to the same degree of muscle relaxation. In addition, the effect of bolus administration of vecuronium is diminished mainly by redistribution rather than degradation or clearance. Therefore, the bolus dose may not give a different effect on the results of each patient. Fourth, we used 50-mA stimulation, which is fixed-current stimulation, instead of supramaximal stimulation. Thus, in some cases this stimulation current might not enough to accurately evaluate the degree of neuromuscular blockade.

Vecuronium has now been replaced by rocuronium, which has a more rapid onset and is less readily metabolized in the liver. However, we chose vecuronium because it is a typical neuromuscular blocker with effects that are influenced by hepatic function. We wanted to determine the requirement of vecuronium in a situation in which liver function was entirely impaired and a volatile anesthetic agent was used. Tight dose control under neuromuscular monitoring and well-timed discontinuance of the infusion led to successful extubation in liver transplantation under anesthesia with sevoflurane and vecuronium.

In conclusion, the use of sevoflurane significantly reduces the requirement of vecuronium regardless of the phase of liver transplantation, and the required dose was gradually decreased as the operation proceeded. If vecuronium infusion is stopped about 100 min before the end of surgery, adequate recovery of neuromuscular function is predicted, and extubation even in the operating room can be possible.

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