Use of Dexmedetomidine in Liver Transplant Recipients With Postoperative Agitated Delirium

J.Y. Choi[a], J.M. Kim[a], C.H.D. Kwon[a], J.-W. Joh[a,*], S. Lee[a], J.B. Park[a], J.S. Ko[b], M.S. Gwak[b], G.S. Kim[b], S.J. Kim[a], and S.-K. Lee[a]

[a]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; and [b]Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ABSTRACT

Background and Objective. Agitated delirium has frequently occurred after liver transplantation in the intensive care unit (ICU) and sedative agents are used to treat patients. Recently, dexmedetomidine has been considered to be a promising agent for agitated delirium.

Methods. This study took place between January 2010 and October 2012 and 42 recipients were retrospectively enrolled. Sixteen recipients were enrolled in the dexmedetomidine group and 26 recipients were placed in the haloperidol group. To compare dexmedetomidine and haloperidol, the total ICU length of stay (ICU LOS), the ICU LOS after drug administration, and the supplemental doses of sedative agents used were assessed. The endpoint was discharge from the ICU.

Results. There were no significant drug-related complications in either group. Dexmedetomidine significantly decreased the ICU LOS and ICU LOS after the occurrence of delirium compared to haloperidol (13.7 days vs. 8.3 days, $P = .039$, 10.1 days vs. 3.1 days, $P = .009$). In the dexmedetomidine group, the dose of supplemental midazolam needed was lower than in the haloperidol group (1.5 mg vs. 6.85 mg, $P < .001$).

Conclusion. Dexmedetomidine is a promising agent for the treatment of ICU-associated agitated delirium in liver transplantation recipients.

DELIRIUM is a syndrome with several different etiologies characterized by a disturbance of consciousness with accompanying changes in cognition [1]. Delirium often occurs after liver transplantation (LT), with a reported incidence of 0.5% to 47% [2]. Delirium can be a factor in prolonged mechanical ventilation, longer hospital and intensive care unit (ICU) lengths of stay, and a high rate of after-discharge institutionalization [3]. Particularly in patients with postoperative agitated delirium, rapid and effective pharmacological treatment is often required to ensure the safety of the patients. When agitated delirium occurs in ICU patients, we can use sedative agents such as dexmedetomidine, haloperidol, and chlorpromazine [1].

According to the Society of Critical Care Medicine on the use of medication for the pharmacologic treatment of delirium [4], haloperidol is often chosen despite a lack of evidence of safety and efficacy in liver transplant recipients.

Recently, studies have reported that dexmedetomidine (trade name, Precedex, Hospira, Lake Forest, IL, USA) is safe and as effective as haloperidol, and shortens the total ICU length of stay (ICU LOS) [5]. Dexmedetomidine is an agonist of α_2-adrenergic receptors in certain parts of the brain [6] and compared with haloperidol, dexmedetomidine relieves symptoms without causing excessive sedation, fewer interactions with other drugs, and can be easily titrated. These properties are essential for liver transplant recipients. The most critical side effect of dexmedetomidine is hemodynamic instability, but recent studies have reported on the safety of dexmedetomidine in pediatric or critically ill patients, even transplant recipients [7,8].

*Address correspondence to Jae-Won Joh, MD, PhD, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea. E-mail: jw.joh@samsung.com

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360 Park Avenue South, New York, NY 10010-1710

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We hypothesized that dexmedetomidine would be more effective than haloperidol in the treatment of liver transplant recipients with ICU-associated postoperative delirious agitation. To examine this hypothesis, we compared the ICU LOS, the ICU LOS after the administration of the drug, and the supplemental doses of midazolam or lorazepam needed.

PATIENTS AND METHODS

Patients

This study took place between January 2010 and October 2012, when our institution performed 380 LT procedures. Of these, 42 recipients were retrospectively enrolled in this study. The recipients were identified using records from our pharmacy and the surgery department's database. Recipients were excluded if they had preoperative encephalopathy and included if they had sedation treatment due to delirium during their first ICU admission after LT. All management of liver transplant recipients was performed according to our institution's LT protocol. At our institution, agitation was managed by haloperidol or dexmedetomidine with midazolam for rapid tranquilization (RT) during this study period. Agitated delirium was diagnosed by the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [9] and occurred when the patient needed to be sedated for RT. Recipients were excluded if they had operations or procedures that required sedation. When agitated delirium occurred, ICU doctors chose the sedative agent without guidelines or patients allocation algorithm; according to the our institution's medical records 16 recipients were enrolled in the dexmedetomidine group and the other 26 recipients were included in the haloperidol group retrospectively.

Approval by the institutional review board was not required for this retrospective analysis. Permission was obtained from the hospital to review the patient's medical records including images and data.

Study Intervention

According to our institution's ICU LT protocol, dexmedetomidine was administrated as a continuous intravenous infusion at a rate of 0.3 μg/kg/h without a loading dose, whereas haloperidol was administrated as a bolus intravenous or intramuscular injection by 3 mg to 5 mg. If RT was not achieved, supplemental intravenous midazolam was administrated as a bolus injection. Lorazepam was used for anxiety management as an anxiolytic or sleeping pills.

During ICU management, all recipients routinely had their heart rate, abnormalities in the electrocardiogram, mean arterial pressure, respiratory rate, and systemic oxygen saturation by pulse oximetry recorded every hour.

Endpoints

The primary endpoint was discharge from the ICU. Secondary safety endpoints included the change in the QTc interval, and the duration and rate of vasopressor or inotropic support.

Statistical Analysis

Continuous variables are presented as the median value, the mean ± standard deviation, or both, whereas categorical variables are presented as numbers and percentages. Calculations of *P* values were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. A *P* value of .05 was considered significant for study purposes. All analyses were performed using PASW statistics 21 (IBM, Chicago, IL, USA).

RESULTS

There were no statistically significant differences in the age, gender, original disease, incidence of alcoholism, Model for End-stage Liver Disease score, and deceased donor LT between the two groups (Table 1). Because of the low incidence of preoperative ventilation use, a comparison of preoperative ventilator use was not available. In this study, the incidence of agitated delirium was 11.1% in LT recipients and there were no episodes of hypotension or bradycardia in both groups. There were 15 cases of postoperative complications in agitated delirium and there was no statistically significant difference between the two groups (26.9% vs. 50%, $P = .130$). The postoperative complications were sepsis, bleeding, wound complication, gastric ulcer perforation, and seizure. Five recipients needed an additional operation because of bleeding.

Safety

There were no statistically significant differences in drug-related complications between the two groups. All ICU patients had an electrocardiogram patch applied, and in the haloperidol group, one recipient had transient atrial fibrillation after drug administration. In our data, there were no recipients who required new inotropic infusions while on the study drug. Four recipients needed intubation in the ICU and three recipients maintained their intubation status after their operations. According to our institution's LT protocol, the intubation period in the ICU is 1 day post-LT. In the

Table 1. Clinical Characteristics of 42 Patients Included in the Study

Variable	Haloperidol (n = 26)	Dexmedetomidine (n = 16)	*P*
Age, y (range)	51 (21–69)	55 (35–68)	.747
Males (%)	22 (84.6)	13 (81.2)	.776
Etiology			
Alcoholic LC (%)	5 (19.2)	4 (25)	1.000
HBV-related LC (%)	17 (65.4)	9 (56.3)	.554
HBV with HCC (%)	12 (46.2)	7 (43.8)	.879
HCV with HCC (%)	1 (3.8)	0	N/A
Toxic hepatitis (%)	1 (3.8)	1 (6.3)	N/A
PSC (%)	1 (3.8)	1 (6.3)	N/A
Re-LT due to Graft failure	1 (3.8)	1	N/A
MELD score (range)	23 (6–42)	18 (6–54)	.201
DDLT (%)	5 (19.2)	5 (31.2)	.374
Use of preoperative ventilator (%)	2 (7.7)	1 (6.3)	N/A
Postoperative complication (%)	7 (26.9)	8 (50)	.130
Episodes of hypotension while on study drug	0	0	N/A

NOTE. The *P* values were calculated using the Mann-Whitney U tests for continuous variables and Fisher's exact tests for categorical variables.

Abbreviations: LC, liver cirrhosis; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; PSC, primary sclerosing cholangitis; Re-LT, liver retransplantation; MELD, Model for End-stage Liver Disease score; DDLT, deceased donor liver transplantation; N/A, not available.

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