

The Effect of Patient-controlled Intravenous Analgesia (PCIA) on Postoperative Delirium in Patients with Liver Transplantation: a Propensity Score Matching Analysis

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Objectives: Postoperative opioid use and pain are related to postoperative delirium. This study aims to compare the incidence of delirium in patients with and without patient-controlled intravenous analgesia (PCIA) among liver transplant recipients.

Methods: The medical records of 253 patients who received liver transplantation (LT) from January 2010 to July 2017 in a single university hospital were retrospectively reviewed. Patients were divided into two groups: the patients who had used PCIA (P group, n = 71) and those who did not use PCIA (C group, n = 182) after LT in intensive care unit (ICU). The patient data were collected, which included demographic data, and details about perioperative management and postoperative complications.

Results: There was no difference in the model for end-stage liver disease (MELD) score between the two groups. Postoperative delirium occurred in 10 / 71 (14.08 %) in the P group and 26 / 182 (14.29 %) in the C group after LT, respectively ($P = 0.97$). After propensity score matching, no differences were observed in the incidence of delirium ($P = 0.359$) and the time from surgery to discharge ($P = 0.26$) between the two groups.

Conclusions: Patients with PCIA after LT exhibited no relationship with postoperative delirium. Therefore, it is necessary to actively control postoperative pain using PCIA.

Key Words: Complication, Liver transplantation, Opioid, Patient-controlled analgesia, Postoperative delirium

In patients undergoing liver transplantation (LT), neurological events are relatively common due to several underlying conditions such as the degree of preoperative hepatic encephalopathy

(HE), metabolic impairments, history of alcoholism, and severe ascites. Impaired liver function due to liver cirrhosis causes frequent electrolyte imbalance, kidney injury, infection,

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Received: Oct. 06, 2020
Revised: Mar. 30, 2021
Accepted: May. 14, 2021



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and HE.^{1,2} In addition, long and complicated surgical procedures with extensive intraoperative blood loss and transfusion, long recovery periods in the intensive care unit (ICU) and postoperative use of narcotic analgesics and immunosuppression may contribute to postoperative neurological complications after LT.^{3,4} The incidence of delirium after LT has been reported to vary, between 13 % and 42 %.^{1,5-7} Post-transplant delirium is highly associated with mortality and morbidity, and increases medical expenses due to a prolonged intensive care unit stay and hospital stay.^{3,8} Cognitive impairment has been observed for at least several days to weeks, although the course is reversible. Therefore, it is important to identify a group of patients with a high risk of postoperative delirium and to correct the adjustable risk factors at an earlier stage.

It is reported that the use of narcotic analgesics postoperatively decreases the activity of acetylcholine, while increase the activity of dopamine, thereby causing delirium.⁹ However, even if proper pain control is not performed, delirium is also likely to occur.^{10,11} Patient-controlled intravenous analgesia (PCIA) makes it easy to control pain after surgery thereby reducing the extent of usage of narcotic analgesics. The purpose of this study is to compare the incidence of delirium in patients with and without the PCIA after LT.

MATERIALS AND METHODS

This study was approved by the hospital clinical research committee (IRB No. 05-2019-034) and

the requirement for written informed consent was waived by the IRB. The computerized data of medical records of 260 patients who underwent LT from January 1, 2010 to July 31, 2017 were evaluated and the results are presented in Figure 1. After excluding 7 patients who underwent re-transplantation or additional surgery, and missing data, the study cohort consisted of 253 patients and was divided into two groups: patients who had used PCIA (P group, n = 71) and those who did not use PCIA (C group, n = 182) after LT in the ICU.

Data collection

Through computerized data collection, basic demographic information of patients, details of laboratory tests and treatments were extracted before, during, and after surgery. Patient records were collected through preoperative anesthetic records, anesthetic records, intensive care unit records, progress notes, nursing records and discharge notes.

The definitions of variables are as follows. For preoperative examination, tests performed within 1 day before surgery were used. Post-surgical laboratory tests used tests performed within 1 day of surgery. Postoperative complications were collected based on discharge records.

Delirium was defined as patients with symptoms and signs consistent with the DSM-IV criteria who were treated with a haloperidol or other medication, or patients who were diagnosed in psychiatry by using the mini-mental status examination and confusion assessment method in the nursing records, prescription records, and consulting records.

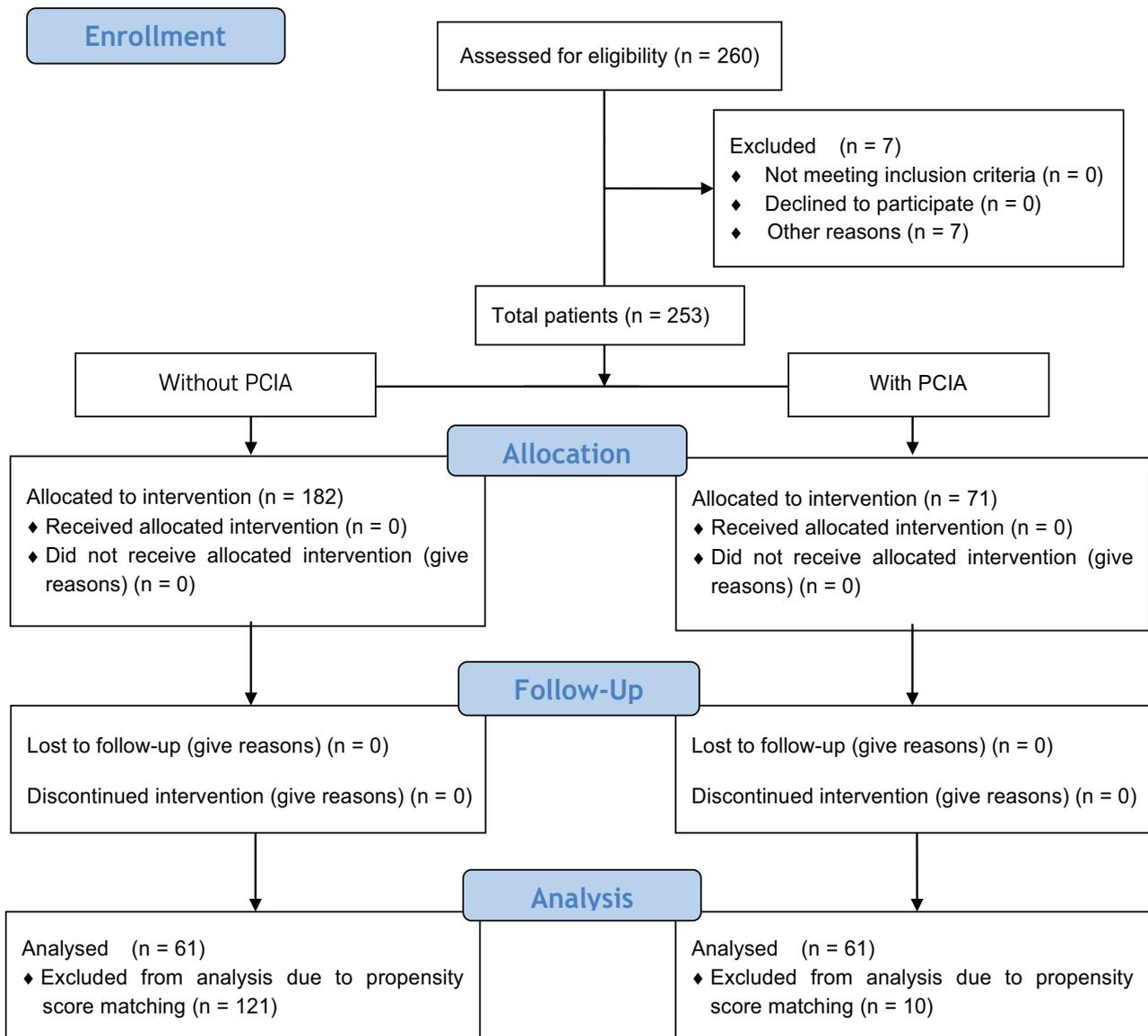


Fig. 1. Flow diagram in this study.

Cardiac complications were defined as cases of heart-related diseases such as arrhythmia and angina pectoris, and respiratory complications were defined as cases of respiratory infections such as pneumonia. Neurological complications were the cases with a record of treatment for a neurological problem such as brain hemorrhage. In the case of infection, it was defined as the occurrence of infection at the surgical site. Death was defined as death during hospitalization after

surgery. Acute rejection after LT was confirmed by pathological examination within 6 months after transplantation.

Management Protocol

LT and anesthesia were performed using conventional methods. General anesthesia was induced using 1 – 2 mg/kg of propofol and muscle relaxant such as 0.6 – 1 mg/kg of rocuronium or 0.1 – 0.2 mg/kg of cisatracurium. Inhaled anes-

thetic gases of sevoflurane or desflurane were treated with an oxygen/air mixture of 40 – 50 % fraction of inspired oxygen. Remifentanyl (range, 0.5 – 10 mcg/kg/h) and muscle relaxant (rocuronium: range, 0.3 – 0.6 mg/kg/h; or cisatracurium: range, 0.1 – 0.2 mg/kg/h) were infused during the operation. All patients had standard monitoring with electrocardiography, along with observation of end-tidal carbon dioxide concentration, bispectral index, peripheral oxygen saturation, and cerebral blood oxygenation, and invasive arterial monitoring with radial and femoral artery were applied. Central venous oxygen saturation monitoring (PreSep, Edwards Lifesciences, Irvine, Calif., USA) was performed to evaluate the volume status using an EV1000 monitoring platform (Edwards Lifesciences) to monitor stroke volume, stroke volume index, cardiac output, cardiac index, central venous oxygen saturation, and systemic vascular resistance. Blood transfusion was performed to maintain the hematocrit level at 25 – 30 %, and blood pressure was maintained with a systolic blood pressure of 90 mmHg and an average arterial pressure of 60 mmHg or more using norepinephrine (0.01 - 0.4 mcg/kg/min). If norepinephrine was ineffective, dobutamine, vasopressin and epinephrine were considered. After the completion of surgery, the patient was moved to the ICU.

The patients in group P used disposable PCIA device (Accufuser Plus®, WooYoung Medical, Korea) containing 1,500 µg of fentanyl diluted to 100 ml in normal saline; the basal rate was set to 1 ml/h, with a bolus of 1 ml and a lock-out

time of 15 min. The patients in group C received intravenous fentanyl whenever pain control was needed. All patients were given enough fentanyl until the pain score on the numeric rating scale was 3 or less.

Statistical analysis

Data were analyzed using Statistical Analysis System version 9.3 (SAS Institute, USA) and R software version 3.3.2 (R Project for Statistical Computing, Austria). Data are expressed as mean ± standard deviation, median (25 to 75 percentile), or the number of patients (%). The normality test was performed with the Shapiro-Wilk W test or Kolmogorov-Smirnov. The independent t-test or Wilcoxon rank-sum test was used for continuous variables for comparison between the two groups. The chi-square test or Fisher's exact test was used for categorical variables. To investigate the effect of the PCIA on the incidence of delirium, 1:1 matching was performed using the nearest neighbour matching method using the propensity score. After 1:1 propensity score matching, continuous variables were compared by paired t-test or Wilcoxon signed-rank test, and categorical variables by McNemar's test. The effect of the PCIA on the incidence of delirium was analysed using univariate analysis and multivariate analysis were analyzed. A *P* value < 0.05 was considered statistically significant.

RESULTS

The characteristics of patients undergoing LT

were analyzed and presented in Table 1. Among patients who underwent LT, 36 / 253 (14.23%) patients were diagnosed with delirium after surgery. Typically, 26 / 182 (14.29 %) patients in Group C and 10/71 (14.09 %) patients in Group P developed postoperative delirium after LT. There was no difference between the two groups ($P = 0.967$). Patients in Group P had hypertension ($P = 0.047$) and diabetes mellitus (DM) ($P = 0.017$) more frequently than those in Group C, but there was no difference between the two groups after matching.

Preoperative laboratory data and perioperative factors in patients undergoing LT are shown in

Table 2. Preoperative serum creatinine (Cr) was higher ($P = 0.016$) and anesthetic duration was longer ($P = 0.014$) in Group P compared to Group C, but preoperative sodium was higher ($P = 0.030$) in Group C than in Group P. However, there were no differences except for anesthetic duration ($P < 0.0001$) between the two groups after matching.

Postoperative data of patients undergoing LT are described in Table 3. Postoperative hemoglobin (Hb) ($P = 0.001$) and sodium ($P = 0.001$) were higher in Group C than in Group P and ICU stay was longer ($P = 0.007$) in Group C. However, after matching, no differences were ob-

Table 1. Characteristics of patients undergoing LT

	Before propensity score matching				After propensity score matching			
	Group C (n = 182)	Group P (n = 71)	SMD	<i>P</i> value	Group C (n = 61)	Group P (n = 61)	SMD	<i>P</i> value†
Age (years)	53.40 ± 7.36	54.14 ± 10.07	0.084	0.572	53.33 ± 7.86	53.80 ± 10.27	0.052	0.775
Sex (F/M)	50 (27.47)	20 (28.17)	0.016	0.911	33 (27.05)	16 (26.23)	0.037	0.839
	132 (72.53)	51 (71.83)			89 (72.95)	45 (73.77)		
BMI (kg/m ²)	22.52 (2.99)	22.00 (3.76)	0.153	0.299	21.93 (2.36)	22.12 (3.88)	0.06	0.739
Cause of LT			0.226	0.569			0.273	0.714
Alcoholic cirrhosis	38 (20.88)	15 (21.13)			13 (21.31)	9 (14.75)		
HBV and HCV	123 (67.58)	45 (63.38)			41 (67.21)	42 (68.85)		
NBNC LC	5 (2.75)	5 (7.04)			2 (3.28)	4 (6.56)		
Toxic hepatitis	11 (6.04)	5 (7.04)			3 (4.92)	5 (8.2)		
Primary biliary cirrhosis	5 (2.75)	1 (1.41)			2 (3.28)	1 (1.64)		
MELD score	17.92 ± 10.88	19.85 ± 11.86	0.169	0.220	19.44 ± 12.37	17.85 ± 10.63	0.138	0.448
HTN	31 (17.03)	20 (28.17)	0.269	0.047*	15 (24.59)	16 (26.23)	0.038	0.835
DM	40 (21.98)	26 (36.62)	0.326	0.017*	18 (29.51)	19 (31.15)	0.036	0.844
IHD	2 (0.55)	1 (1.41)	0.087	0.483	1 (0.82)	0 (0.00)	0.183	1.000
CHF	2 (1.10)	0 (0.00)	0.149	1.000	0 (0.00)	0 (0.00)	-	-
Diuretics	30 (16.48)	15 (21.13)	0.119	0.311	11 (18.03)	13 (21.31)	0.083	0.649
Insulin	4 (2.2)	4 (5.63)	0.178	0.154	1 (1.64)	3 (4.92)	0.185	0.619
Sleep disorder	21 (11.54)	5 (7.04)	0.232	0.702	7 (11.48)	4 (6.56)	0	0.343

Values are presented as mean ± SD, median (25–75 percentile) or number (%). Group C, those who did not use PCIA; Group P, those who used PCIA; SMD, standardized mean difference; BMI, body mass index; LT, liver transplantation; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC LC, non-HBV non-HCV liver cirrhosis; MELD, model for end-stage liver disease; HTN, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; CHF, congestive heart failure. * $P < 0.05$ compared between the two groups. †Propensity score-matched values.

Table 2. Preoperative laboratory data and perioperative factors in patients undergoing LT.

	Before propensity score matching			After propensity score matching		
	Group C (n = 182)	Group P (n = 71)	SMD <i>P</i> value	Group C (n = 61)	Group P (n = 61)	SMD <i>P</i> value†
Hb (g/dl)	10.85 ± 2.24	10.56 ± 2.28	0.130 0.352	10.5 ± 2.18	10.71 ± 2.3	0.092 0.612
Bil (µmol/l)	2.4 (0.40, 47.30)	3.2 (0.40, 72.00)	0.266 0.105	2.1 (0.40, 45.50)	3.1 (0.40, 62.00)	0.046 0.439
Albumin (g/dl)	3.15 ± 0.52	3.06 ± 0.62	0.171 0.206	3.06 ± 0.55	3.10 ± 0.58	0.079 0.665
Cr (mg/dl)	0.80 (0.30, 3.50)	0.9 (0.20, 6.50)	0.373 0.016*	0.84 (0.26, 3.52)	0.80 (0.20, 3.70)	0.174 0.898
Na (mEq/l)	137.50 ± 5.54	135.9 ± 4.97	0.313 0.030*	137.0 ± 5.87	136.61 ± 4.73	0.074 0.685
K (mEq/l)	3.94 (0.49)	4.07 (0.66)	0.229 0.082	3.9 (0.54)	3.96 (0.46)	0.131 0.472
Anesthetic Duration (h)	11.00 (7.00, 28.00)	10.00 (6.50, 18.00)	0.405 0.014*	10.00 (7.15, 18)	10.3 (6.5, 15.00)	0.09 0.000*
EBL (L)	3.92 ± 3.20	3.58 ± 2.46	0.116 0.379	3.75 ± 2.86	3.54 ± 2.47	0.04 0.078
Total fluid intake (L)	7.08 (2.00, 38.0)	7.77 (2.50, 32.95)	0.114 0.204	7.50 (2.00, 30.66)	7.90 (2.93, 32.95)	0.09 0.122
pRBC (unit)	4.00 (0.00, 93.00)	5.00 (0.00, 20.00)	0.042 0.271	5.00 (0.00, 30.00)	5.00 (0.00, 20.00)	0.02 0.058

Values are expressed as mean ± SD or median (25–75 percentile). Group C, those who did not use PCIA; Group P, those who used PCIA; SMD, standardized mean difference; Hb, hemoglobin; Bil, bilirubin; Cr, creatinine; Na, sodium; K, potassium; EBL, estimated blood loss; pRBC, packed red blood cells. **P* < 0.05 compared between the two groups. †Propensity score matched values.

Table 3. Postoperative data of patients undergoing LT.

	Before propensity score matching			After propensity score matching		
	Group C (n = 182)	Group P (n = 71)	SMD <i>P</i> value	Group C (n = 61)	Group P (n = 61)	SMD <i>P</i> value†
Hb (g/dl)	9.15 ± 1.47	8.46 ± 1.38	0.26 0.001*	9.16 ± 1.36	8.39 ± 1.43	0.05 0.003*
Bil (µmol/l)	4.0 (0.80, 28.10)	4.3 (0.90, 41.70)	0.31 0.774	4.2 (0.80, 21.10)	4.3 (0.90, 41.70)	0.08 0.575
Na (mEq/l)	140.20 ± 3.83	138.50 ± 3.78	0.02 0.001*	139.66 ± 4.23	138.67 ± 3.88	0.10 0.183
K (mEq/l)	4.01 ± 0.44	3.98 ± 0.38	0.26 0.655	4.03 ± 0.47	3.93 ± 0.39	0.07 0.430
ICU stay (days)	9.00 (2.00, 64.00)	6.00 (2.00, 49.00)	0.26 0.007*	7.00 (2.00, 64.00)	6.00 (2.00, 49.00)	0.08 0.081
Time from surgery to discharge (days)	28.00 (10.00, 624.00)	26.00 (5.00, 143.00)	0.23 0.245	28.00 (15.00, 118.00)	26.00 (5.00, 143.00)	0.14 0.261
Postoperative complication						
Cardiac complication	4 (2.2)	1 (1.41)	0.059 1.000	2 (3.28)	1 (1.64)	1.000
Respiratory complication	18 (9.89)	6 (8.45)	0.050 0.726	5 (8.2)	5 (8.2)	1.000
Neurologic complication						
Hemorrhage	1 (0.55)	0 (0.00)	0.105 1.000	0 (0.00)	0 (0.00)	- -
Seizure	1 (0.55)	0 (0.00)	0.105 1.000	0 (0.00)	0 (0.00)	- -
Brain damage	3 (1.65)	1 (1.41)	0.020 1.000	0 (0.00)	1 (1.64)	0.183 1.000
Infection	2 (1.1)	4 (5.63)	0.253 0.054	0 (0.00)	4 (6.56)	0.375 0.119
Death	8 (4.4)	5 (7.04)	0.114 0.526	4 (6.56)	5 (8.2)	0.063 1.000
Sepsis	5 (2.75)	1 (1.41)	0.094 1.000	3 (4.92)	1 (1.64)	0.185 0.619
Acute rejection	5 (2.75)	21 (1.41)	0.094 1.000	3 (4.92)	0 (0.00)	0.260 0.496

Values are expressed as mean ± SD, number (%) or median (25–75 percentile). Group C, those who did not use PCIA; Group P, those who used PCIA; SMD, standardized mean difference; Hb, hemoglobin; Bil, bilirubin; Na, sodium; K, potassium; ICU, intensive care unit. **P* < 0.05 compared between the two groups. †Propensity score-matched values.

Table 4. Logistic regression analysis with crude data.

Variables	OR	95% CI		<i>P</i> value*	OR	95% CI		<i>P</i> value†
		Lower	Upper			Lower	Upper	
PCIA	0.984	0.448	2.161	0.967	0.779	0.325	1.870	0.577
Age	1.016	0.972	1.063	0.479				
Sex	0.849	0.393	1.832	0.676				
BMI	0.901	0.802	1.013	0.081				
HTN	0.949	0.390	2.309	0.908				
DM	0.412	0.153	1.110	0.080				
MELD score	1.051	1.021	1.082	0.001*	1.014	0.966	1.064	0.582
Diuretics	2.000	0.886	4.514	0.095				
Insulin	2.069	0.401	10.673	0.385				
Sleep disorder	2.253	0.880	5.768	0.090				
Psychiatric medication	5.302	1.352	20.789	0.017*	3.216	0.705	14.664	0.131
Hb before surgery	0.775	0.646	0.931	0.006*	0.876	0.709	1.083	0.222
Albumin before surgery	0.698	0.367	1.328	0.273				
Cr before surgery	1.504	1.058	2.138	0.023*	1.178	0.745	1.863	0.482
Anesthetic duration	1.034	0.923	1.158	0.568				
Intraoperative EBL	1.130	1.023	1.249	0.017*	1.043	0.894	1.216	0.595
pRBC	1.039	1.002	1.077	0.038*	1.015	0.963	1.070	0.586
Hb after surgery	0.934	0.729	1.195	0.586				
Albumin after surgery	0.819	0.378	1.774	0.613				
Bil after surgery	1.087	1.021	1.158	0.010*	1.035	0.952	1.124	0.420
Na after surgery	0.994	0.908	1.089	0.898				
K after surgery	1.443	0.640	3.251	0.377				

PCIA, patient controlled intravenous analgesia; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; MELD, model for end-stage liver disease; Hb, hemoglobin; Bil, bilirubin; Cr, creatinine; EBL, estimated blood loss; pRBC, packed red blood cells; Na, sodium; K, potassium; ICU, intensive care unit. **P* value of univariate-crude data. †*P* value of multivariate-crude data.

served between the groups except for postoperative Hb ($P = 0.003$) between the two groups. There were no differences in postoperative complications between the two groups.

A logistic regression analysis was performed and PCIA with a *P* value of 0.1 or less in univariate analysis, body mass index, DM, model for end-stage liver disease (MELD) score, diuretics, sleep disorder, psychiatric medication, Hb before surgery, serum Cr before surgery, intraoperative

estimated blood loss, packed red blood cells usage, and bilirubin after surgery were defined (Table 4). Subsequently, multivariate analysis was performed and it was identified that PCIA was not associated with postoperative delirium in univariate analysis ($P = 0.967$) and multivariate analysis ($P = 0.577$) (Table 5).

DISCUSSION

Table 5. Comparison of the incidence of delirium depending on the use of PCIA

	Before propensity score matching				After propensity score matching			
	Total (n = 253)	Group C (n = 182)	Group P (n = 71)	<i>P value</i>	Total (n = 122)	Group C (n = 61)	Group P (n = 61)	<i>P value</i>
Incidence of delirium (%)	36 (14.23)	26 (14.29)	10 (14.09)	0.967	19(15.57)	12(19.67)	7(11.48)	0.359

Values are expressed as number (%). Group C, those who did not use PCIA; Group P, those who used PCIA;

In this retrospective review of LT recipients, it was identified that the use of PCIA after surgery was not associated with the incidence of postoperative delirium.

Delirium is an acute change in neurologic state with alteration in the levels of consciousness and attention. Risk factors for postoperative delirium include age 65 years and older, men, impaired cognitive function, hearing and vision impairment, dehydration, nutritional deficiency, psychiatric drugs, chronic internal disease, chronic kidney disease, chronic liver disease, pain, and sleep disorders.^{7,10,12,13} Furthermore, the condition might be triggered in cases of severe acute diseases such as infection, trauma, surgery, myocardial infarction, electrolyte imbalance, anemia, hypoglycemia, and emotional compression.^{4,14} Regulatory factors affecting postoperative delirium include postoperative body restraint placement, correcting metabolic and electrolyte abnormalities, use of suppressing drugs such as anesthetics, anticholinergics, benzodiazepine, narcotic analgesics, and anti-Parkinson drugs, controlling moderate pain, blood loss during surgery and blood transfusions, postoperative low albumin levels, less than 30% hematocrit, and oxygen deficiency.¹¹

Postoperative delirium and cognitive decline occur frequently in the patients after LT and cause a prolonged stay at ICU and prolonged mechanical ventilation, as well as increased mortality. Longer stays on the bed, which slows the onset of post-operative exercise, thereby creates difficulties in getting early rehabilitation treatment.¹⁵ Usually the course of postoperative delirium is reversible and has been demonstrated to be associated with long-term neurologic deterioration such as cognitive impairment and dementia.^{16,17} As a result, delirium after LT is associated with an increase in post-transplant mortality and morbidity, and rising medical expenses. Recently, with an increase in the number of patients undergoing LT and the survival rate of recipients, interest in post-transplant management has also increased. It is necessary to predict a group of patients who are likely to develop postoperative delirium and to correct the adjustable risk factors at an earlier stage.

Both postoperative pain and the use of narcotic analgesics have been reported to cause postoperative delirium.¹⁸⁻²⁰ Severe preoperative resting pain and an increase in the level of pain during postoperative day one were identified to be independently associated with the risk for the de-

velopment of postoperative delirium. Reducing pain after surgery can help in reducing delirium. In clinical practice, narcotic analgesics are considered as the most appropriate drugs for acute postoperative pain despite the major side effects of respiratory depression, neurologic alteration including delirium, and constipation, etc. It is almost impossible to avoid the use of narcotic analgesics at all in the post-transplant period, as non-opioid analgesics are not potent enough to alleviate acute surgical pain. However, fentanyl undergoes hepatic biotransformation into inactive metabolites and eliminates through kidney, patients with hepatic and renal insufficiency have increased risk of side effects of this drug.²¹ Therefore, pain management by using PCIA can effectively control pain while reducing the side effects of bolus injected narcotic analgesics such as transient respiratory depression or hemodynamic instability. Also, using PCIA can reduce the time difference between when pain control is required and when pain medication is administered. It is controversial whether it is safe to use PCIA for postoperative pain control in patients undergoing LT. However, in our study, postoperative PCIA was not an issue in terms of safety in patients undergoing LT.

The prevention and early detection of delirium are important for the treatment and management of liver transplant patients to decrease post LT morbidity and mortality. One of the characteristic aspects of postoperative delirium is that there is a time difference between the operation and the delirium. The patients present with no apparent mental symptoms during the conscious clarity

period, and delirium mainly develops within the first 24-48 hours after LT; recovery has been reported to occur within 5 days after surgery.²² There exist numerous diagnostic methods that serve as a standard for diagnosing postoperative delirium, among which DSM - IV and ICD - 10 are widely used.²³ In this study, DSM-IV criteria were used to diagnose delirium along with psychiatric cooperation. The possible explanation behind recovery from delirium within 5 days is postoperative normalization of liver function and clearance of metabolites from the transplanted liver in the first few days.²⁴

This study has some limitations. First, the study possibly lacks some variables that can potentially cause delirium after LT due to the retrospective nature of the study. The occurrence of postoperative delirium is likely a multifactorial phenomenon and it is not clear if the effects of various precipitating factors are additive or multiplicative. And total amount of fentanyl used was not investigated. Second, this is a single center study and the included number of cases is small which is insufficient to generalize the relation between PCIA and postoperative delirium. Third, as we focused on delirium in the early postoperative period, incidents of later onset delirium might have been neglected.

In conclusion, it was identified that patients with PCIA after LT were not related to postoperative delirium. Therefore, it is necessary to actively control postoperative pain using PCIA after LT. As our study was limited by its retrospective design, prospective randomized control studies are recommended in the future to confirm

our results on PCIA and postoperative delirium in LT recipients. Further study is required to identify modifiable preoperative or postoperative risk factors of delirium after LT.

REFERENCES

1. Vizzini G, Asaro M, Miraglia R, Gruttadauria S, Fili D, D'Antoni A, et al. Changing picture of central nervous system complications in liver transplant recipients. *Liver Transpl* 2011;17:1279-85.
2. Belcher JM, Garcia-Tsao G, Sanyal AJ, Bhoagal H, Lim JK, Ansari N, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology* 2013;57:753-62.
3. Lescot T, Karvellas CJ, Chaudhury P, Tchervenkov J, Paraskevas S, Barkun J, et al. Postoperative delirium in the intensive care unit predicts worse outcomes in liver transplant recipients. *Can J Gastroenterol* 2013;27:207-12.
4. Rompianesi G, Montalti R, Cautero N, De Ruvo N, Stafford A, Bronzoni C, et al. Neurological complications after liver transplantation as a consequence of immunosuppression: univariate and multivariate analysis of risk factors. *Transpl Int* 2015;28:864-9.
5. Mueller AR, Platz KP, Krause P, Kahl A, Rayes N, Glanemann M, et al. Perioperative factors influencing patient outcome after liver transplantation. *Transpl Int* 2000;13 Suppl 1:S158-61.
6. Lewis MB, Howdle PD. Neurologic complications of liver transplantation in adults. *Neurology* 2003;61:1174-8.
7. Haugen CE, Mountford A, Warsame F, Berkowitz R, Bae S, Thomas AG, et al. Incidence, Risk Factors, and Sequelae of Post-kidney Transplant Delirium. *J Am Soc Nephrol* 2018;29:1752-9.
8. Chiu NM, Chen CL, Cheng AT. Psychiatric consultation for post-liver-transplantation patients. *Psychiatry Clin Neurosci* 2009;63:471-7.
9. Pisani MA, Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med* 2009;37:177-83.
10. Choi JG. Delirium in the intensive care unit. *Korean J Anesthesiol* 2013;65:195-202.
11. Tilouche N, Hassen MF, Ali HBS, Jaoued O, Gharbi R, El Atrous SS. Delirium in the Intensive Care Unit: Incidence, Risk Factors, and Impact on Outcome. *Indian J Crit Care Med* 2018;22:144-9.
12. Mody K, Kaur S, Mauer EA, Gerber LM, Greenwald BM, Silver G, et al. Benzodiazepines and Development of Delirium in Critically Ill Children: Estimating the Causal Effect. *Crit Care Med* 2018;46:1486-91.
13. Clegg A, Siddiqi N, Heaven A, Young J, Holt R. Interventions for preventing delirium in older people in institutional long-term care. *Cochrane Database Syst Rev* 2014:CD009537.
14. Balderramo D, Prieto J, Cárdenas A,

- Navasa M. Hepatic encephalopathy and post-transplant hyponatremia predict early calcineurin inhibitor-induced neurotoxicity after liver transplantation. *Transpl Int* 2011; 24:812-9.
15. Yoon JS, Kim YR, Choi JW, Ko JS, Gwak MS, Kim GS. Risk factors of postoperative delirium following liver transplantation. *Korean J Anesthesiol* 2009;57:584-9.
 16. Jackson JC, Ely EW. Cognitive impairment after critical illness: etiologies, risk factors, and future directions. *Semin Respir Crit Care Med* 2013;34:216-22.
 17. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306-16.
 18. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. *Anesth Analg* 2006;102:1267-73.
 19. Leung JM, Sands LP, Paul S, Joseph T, Kinjo S, Tsai T. Does postoperative delirium limit the use of patient-controlled analgesia in older surgical patients? *Anesthesiology* 2009;111:625-31.
 20. Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM. The effects of postoperative pain and its management on postoperative cognitive dysfunction. *Am J Geriatr Psychiatry* 2007;15:50-9.
 21. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg* 2006;102:1255-66.
 22. Piñero F, Cheang Y, Mendizabal M, Cagliani J, Gonzalez Campaña A, Pages J, et al. Incidence, risk factors, and outcomes related with neurological events after liver transplantation in adult and pediatric recipients. *Pediatr Transplant* 2018;22:e13159.
 23. Boettger S, Nuñez DG, Meyer R, Richter A, Fernandez SF, Rudiger A, et al. Delirium in the intensive care setting: A reevaluation of the validity of the CAM-ICU and ICDSC versus the DSM-IV-TR in determining a diagnosis of delirium as part of the daily clinical routine. *Palliat Support Care* 2017;15:675-83.
 24. Lee H, Oh SY, Yu JH, Kim J, Yoon S, Ryu HG. Risk Factors of Postoperative Delirium in the Intensive Care Unit After Liver Transplantation. *World J Surg* 2018;42:2992-9.