



Prolonged Mechanical Ventilation Predictors in Patients Undergoing Liver Transplantation

Meltem Güner CAN¹, Ali ÖZER²

¹Acibadem Mehmet Ali Aydınlar University Atakent Hospital, Department of Anesthesia and Reanimation, İstanbul, Turkey

²Acibadem Mehmet Ali Aydınlar University Atakent Hospital, Department of Organ Transplantation, İstanbul, Turkey

ABSTRACT

Objective: Liver transplantation is the current treatment modality for end-stage liver disease. While there is increasing drive towards early extubation in patients undergoing liver transplantation, prolonged mechanical ventilation (PMV) related to various factors can be observed. We tried to determine the risk factors associated with PMV.

Methods: One hundred twenty five patients (age>18 years) of with the American Society of Anesthesiology (ASA) III-IV group undergoing liver transplantation were enrolled in this retrospective study. Patient charts, intraoperative and intensive care unit follow-up forms, and electronic medical recording system were used for data collection. Patients were categorized as having received (with) or not received (without) prolonged mechanical ventilation (>24 hours), and perioperative risk factors were attempted to determine.

Results: No significant intergroup differences were found in demographic variables but ASA and model for end-stage liver disease (MELD) scores were significantly higher in the with- than in the without-PMV group. Total amount of suspension of erythrocytes suspension, fresh frozen plasma, and cell-saver blood used intraoperatively was higher in the with-PMV group but difference did not reach statistical significance. Patients with-PMV had significantly higher cryoprecipitate transfusion rates than did those without-PMV (p=0.007). While no significant intergroup differences were found in mortality and length of hospital stay; length of intensive care unit (ICU) stay was higher in the with- PMV group (p=0.001). Extravascular lung water index, global ecosystem dynamics investigation, and pulse volume index values obtained from pulse contour cardiac output (PiCCO) monitorization were significantly lower in the with- than in the without-PMV group.

Conclusion: We found that preoperative high ASA and MELD scores, high blood product transfusion rates, and hypovolemia supported by the PiCCO measurements are closely related to PMV and long length of ICU stay.

Keywords: Liver transplantation, weaning, prolonged mechanical ventilation

Introduction

Liver transplantation is a safe and effective way of treating end-stage liver disease (ESLD) due to better understanding of the pathology of liver diseases, the development of organ protection techniques, the use of safer and effective immunosuppressive drugs, advances in surgical techniques, anesthesia and monitorization. With these improvements, both perioperative complication and mortality rates have decreased significantly, and 1-year life expectancy has exceeded 90%.

Liver transplant candidates are often characterized by a hyperdynamic circulatory state of cirrhotic cardiomyopathy (1) and a complex process in which all systems are affected. Need for massive transfusion due to severe surgical blood loss and intravascular volume shift, surgical large vein maneuvers and the effects of current coagulopathy, metabolic dysfunction, hemodynamic instability and reperfusion on systems require intraoperative detailed monitorization (2). In addition to standard monitorization, cardiac output monitorization is required for the

Address for Correspondence: Ali ÖZER, Acibadem Mehmet Ali Aydınlar University Atakent Hospital, Department of Organ Transplantation, İstanbul, Turkey

Phone: +90 533 212 23 24 **E-mail:** draliozerr@gmail.com **ORCID ID:** orcid.org/0000-0003-4736-3418

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management of intraoperative hemodynamic changes. For this reason, nowadays, pulse contour cardiac output (PiCCO) ve hemodynamic monitor methods which combine thermodilution and arterial waveform analysis methods, have less complication rates than pulmonary artery catheter and are less invasive, have gained importance. PiCCO, also used in our clinic on a routine basis, is an invasive hemodynamic monitoring method which uses the combination of these two techniques and shows important parameters such as cardiac index (CI), stroke volume index (SVI), global end-diastolic index (GEDI), stroke volume variation (SVV), global ejection fraction, systemic vascular resistance index (SVRI), extravascular lung water index (ELWI) and pulmonary vascular permeability index (PVPI).

Although early extubation trend increases in most of the centers where liver transplantation is performed due to improvements in perioperative care (3,4), prolonged mechanical ventilation is required due to various factors such as massive blood transfusion, pulmonary edema, lung damage, acid, capillary leakage, primary pulmonary and heart disease (5). In this study, we aimed to determine the risk factors associated with prolonged mechanical ventilation requirement in patients undergoing liver transplantation.

Methods

Anesthesia

After obtaining ethics committee approval, American Society of Anesthesiologists (ASA) III-IV 125 patients aged over 18 years who underwent liver transplantation between 2015 and 2017 were included in this retrospective study. Patients whose preoperative anesthetic evaluations were completed one day before, were taken to the operation room without premedication and heart rate, noninvasive blood pressure, SpO₂, body temperature and EtCO₂ monitorizations were performed. After induction of anesthesia, invasive arterial pressure, central venous pressure (with right internal jugular catheterization accompanied by ultrasound) and PiCCO monitorization (with right femoral artery catheterization using the existing central venous catheter and PiCCO catheter with special thermistor) were performed. Propofol and fentanyl was used for induction of anesthesia and cis-atracurium was used for muscle relaxation. After endotracheal intubation, desfluran (6-8%) was given in 40-50% oxygen-air mixture and intravenous infusion of remifentanyl [0.05-0,25 µg kg⁻¹ minimum (min)⁻¹] was used for maintenance of anesthesia. Muscle relaxation was maintained with cis-atracurium infusion. Mechanical ventilation parameters were adjusted to keep PaCO₂ values between 30-35 mmHg, tidal volume 6-8 mL kg⁻¹, respiration rate 10-14/min and peep 4-6 mmHg. Restrictive fluid management was performed in patients. The replacement of albumin was determined according to the level of albumin of the patients. Erythrocyte suspension (ES) replacement was performed to keep hematocrit values at 26-28%. In our study, thromboelastography was not used and fresh frozen plasma (FFP), cryoprecipitate or platelet replacement (complete blood count and prothrombin time, activated partial thromboplastin time, international normalized ratio and fibrinogen levels measured in standard dissection phase

and anhepatic and neohepatic phases). Inotrop/vasopressor agents were initiated due to the data of invasive hemodynamic monitorization (blood pressure, heart rate, cardiac flow, SVRI) and the presence of hemodynamic instability. The patients were heated with lower heating blankets and blown heating systems. In addition, hypothermia was prevented by using fluid heating systems for all intravenous fluids and blood products. In order to prevent rejection, all patients were administered 10 mg kg⁻¹ methyl prednisolone intravenously prior to perfusion during anhepatic period. Blood glucose levels of patients were kept between 80-160 mg/dL. Acibadem Mehmet Ali Aydınlar University ATADEK-2017/16.

Surgical Technique

The patients were operated with bilateral subcostal incision or inverted L incision. Graft implantation was started with the main hepatic vein (left/right hepatic vein) and vena cava anastomoses were performed under partial clamp using piggy-back method. Then, if available, other vein anastomoses (segment 5-8 or inferior vein) were made by parachute technique on openings on vena cava. Portal vein anastomosis was performed end-to-end, if possible and anhepatic phase was completed and graft perfusion stage was initiated. Following perfusion, the hepatic artery anastomosis was made preferably anatomical and in case of a problem in recipient artery, extra-anatomic arterial anastomosis was made. Gallbladder anastomosis was performed by end-to-end/hepatico-jejunostomy method. In none of the patients portacaval shunt was used. After anastomoses were ultrasonographically shown as open and flow was shown as good by the radiologist, bleeding control was done and surgery was completed.

Intensive Care and Extubation

The patients were sent to intensive care unit as intubated at the end of the operation and they were followed up with electrocardiography, heart rate, invasive blood pressure, central venous pressure, EtCO₂ and temperature monitorizations. Analgesia and sedation management were performed for each patient in accordance with the patient's own intensive care process. When intensive care patients met the standard criteria (Table 1), they were extubated with T-tube method, one of spontaneous breathing methods (Table 2) by the intensive care team (6). Mechanical ventilation was accepted as prolonged mechanical ventilation when the duration of the ventilation exceeded 24 hours.

Data Collection

Anesthesia preoperative evaluation forms, intraoperative monitoring forms, intensive care monitoring forms, consultation notes, and epicrisis were examined and the following data were recorded.

Preoperative Data: Demographic data, comorbid diseases, smoking habit, etiology of end-stage liver disease, model for end-stage liver disease (MELD) scores, presence and degree of preoperative encephalopathy, presence of hepatopulmonary and hepatorenal syndrome.

Intraoperative Data: Intraoperative fluid amounts, blood and blood product transfusion amounts, hemodynamic data (heart rate, invasive arterial pressures, central venous pressures) and PiCCO data (CI, SVI, SVV, GEDI, SVRI ELWI, PVPI), inotrop-vasopressor needs, anhepatic phase and surgery durations.

Postoperative Data: Duration on mechanical ventilator in intensive care unit and stay in intensive care unit-hospital, need for retransplantation, mortality and morbidity.

Patients were divided into two groups based on the time periods for mechanical ventilation determined in the previous studies (7,8): Patients needing prolonged mechanical ventilation (>24 hours) and patients not needing prolonged mechanical ventilation (<24 hours) and the risk factors for prolonged duration of mechanical ventilation were determined.

Table 1. Standard extubation criteria

Objective criteria	<ul style="list-style-type: none"> Adequate oxygenation (PO₂>60 mmHg when FiO₂<0.4 and PEEP: 5-10 cm H₂O, PO₂/FiO₂>150-300 Stable hemodynamic status (heart rate <140 beats/min, stable blood pressure without vasopressor or with minimal vasopressor support) Fever <38 °C The absence of respiratory acidosis Adequate hemoglobin level (8-10 g/dL) Stable mental status (GCS >13, no sedative infusion) Stable metabolic status (electrolyte, blood glucose...) Amelioration of acute phase of disease
Subjective clinical evaluation	<ul style="list-style-type: none"> Clinician considering suitability for extubation Adequate cough reflex

GCS: Glasgow coma scale, PEEP: Positive end-expiratory pressure

Statistical Analysis

Statistical analysis was performed using the SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY). Two-tailed tests were used in all statistical analyses. In comparisons between the two groups, independent samples t test was used in evaluation of parametric data and Pearson’s chi-square and Fisher’s exact test, if needed, were used in evaluation of non-parametric data. The relationship between etiological factors and prolonged mechanical ventilation was examined by Bivariate correlation test. Categorical data were expressed as mean ± standard deviation, non-categorical data were expressed as number (n) and percent (%). A p value less than 0.05 was considered statistically significant.

Results

The data and files of 125 patients over 18 years of age who underwent liver transplantation from living donor were retrospectively analyzed. All data of 10 patients could be reached and 115 patients were included in the study. In 10 (8.69%) of 115 patients, prolonged mechanical ventilation need was observed. Demographic data and ASA and MELD scores of the patients were summarized in Table 3. ASA and MELD scores were significantly higher in the prolonged mechanical ventilation group than in the other group. There was no difference between the groups in terms of the presence of comorbid disease, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension and hepatic encephalopathy and etiological factors.

When intraoperative variables were examined, there was no significant difference between the groups in terms of the amount of crystalloid and albumin given with restrictive liquid approach. Although ES, FFP, cell saver blood and platelet amounts were higher in the prolonged mechanical ventilation group, statistical significance was not found (Figure 1). The amount of cryoprecipitate used (1.67±3.39 U) was significantly higher in the prolonged mechanical ventilation group than in the other

Table 2. Weaning methods

Method	Advantage	Disadvantage
T-tube method	<ul style="list-style-type: none"> - Testing patient’s spontaneous breathing ability - Allow working/resting periods - Faster weaning than SIMV - Synchronization - Increased patient comfort 	<ul style="list-style-type: none"> - Sudden loading of respiratory work to patient - Endotracheal tube resistance - Disabled alarm systems - Careful observation requirement
Pressure support ventilation (PSV)	<ul style="list-style-type: none"> - Slow loading of respiratory work on the patient - Faster weaning than SIMV - Prevention of muscle fatigue 	<ul style="list-style-type: none"> - Observation of major changes in minute ventilation
Synchronized intermittent mandatory ventilation (SIMV)	<ul style="list-style-type: none"> - Guaranteed minimum minute ventilation - Use of alarm systems - Applicability with PSV/CPAP 	<ul style="list-style-type: none"> - Desynchronization - Long weaning process - Increased muscle fatigue
CPAP	<ul style="list-style-type: none"> - Allowing tidal volume monitoring 	<ul style="list-style-type: none"> - Sudden loading of respiratory work to patient

SIMV: Synchronized intermittent mandatory ventilation, PSV: Pressure support ventilation, CPAP: Continuous positive airway pressure

group (0.21 ± 1.27 U) ($p=0.007$). The duration of the surgery was 495 ± 76 min, the duration of the anhepatic phase was 95 ± 41 min in the prolonged mechanical ventilation group and the duration of the surgery was 529 ± 125 min, the duration of the anhepatic phase was 90 ± 34 min in the other group. Differences in terms of duration of the surgery and the anhepatic phase between groups were not statistically significant.

The results of PiCCO measurements in dissection phase, anhepatic phase and neohepatic phase were summarized in Table 4.

In our study, 10 of 115 patients died and one had a need for retransplantation. There was no difference between the groups in terms of mortality and hospital stay, whereas the duration of stay in intensive care unit was 8.10 ± 9.0 days in the prolonged mechanical ventilation group and 3.13 ± 3.51 days in the other group ($p=0.001$).

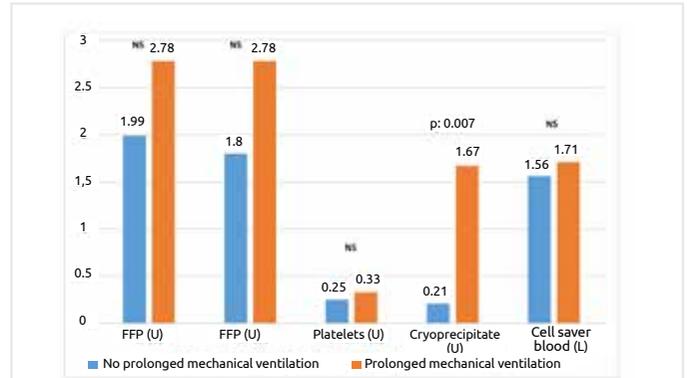


Figure 1. Blood product utilization rates in patients undergoing liver transplantation

ES: Erythrocyte suspension, FFP: Fresh frozen plasma, NS: Not significant

Table 3. Demographic data and risk scores

	Prolonged mechanical ventilation No (n= 105)	Yes (n= 10)	p value
Age (year)	49.61±12.64	47.10±16.03	0.558
Weight (kg)	73.99±15.75	66.35±23.20	0.164
Height (cm)	168.07±12.48	165.30±13.87	0.507
BMI (kg/m²)	25.75±4.77	23.56±6.36	0.179
ASA (I-V)	3.18±0.386	3.60±0.516	0.002
MELD	18.71±4.24	22.55±5.89	0.013

ASA: American Society of Anesthesiologists, MELD: Model for end-stage liver disease, BMI: Body mass index

Table 4. Intraoperative hemodynamic monitorization data in patients undergoing liver transplantation

	Prolonged MV	Dissection phase	p	Anhepatic phase	p	Neohepatic phase	p
CI	Yes	4.03±0.8	0.443	3.31±0.95	0.144	3.99±0.85	0.018
	No	4.28±1.02		3.82±1.04		4.75±0.96	
SVI	Yes	46.00±11.12	0.027	32.70±11.05	0.008	41.60±11.80	0.000
	No	53.89±10.56		43.76±12.37		55.01±11.10	
GEDI	Yes	592.70±134.64	0.028	483.40±143.89	0.006	510.50±139.15	0.010
	No	681.94±119.98		588.05±108.94		621.66±127.40	
SVV	Yes	7.10±4.41	0.556	12.80±6.65	0.073	11.10±5.53	0.004
	No	6.34±3.83		9.27±5.82		6.66±4.45	
GEF	Yes	29.63±10.34	0.057	29.70±5.21	0.389	32.40±6.15	0.022
	No	33.47±5.50		31.63±6.87		37.08±6.07	
SVRI	Yes	1506±468	0.631	1925±498	0.732	1337±328	0.357
	No	1433±452		1848±691		1230±350	
ELWI	Yes	7.50±1.65	0.003	8.25±1.72	0.016	7.40±1.43	0.008
	No	9.25±1.76		12.00±1.51		8.88±1.68	
PVPI	Yes	1.86±0.38	0.424	2.01±0.41	0.802	2.09±0.50	0.723
	No	1.96±0.37		2.05±0.49		2.04±0.42	
CVP	Yes	12.50±4.28	0.633	10.20±4.59	0.480	11.6±5.76	0.399
	No	13.10±3.71		9.30±3.76		12.65±3.53	

CI: Cardiac index, ELWI: Extravascular lung water index, GEDI: Global end-diastolic index, GEF: Global ejection fraction, PVPI: Pulmonary vascular permeability index, SVI: Stroke volume index, SVRI: Systemic vascular resistance index, SVV: Stroke volume variation, CVP: Entral venous pressure MV: Mechanical ventilation

Discussion

In patients undergoing major surgery, it may be necessary to maintain mechanical ventilation support in intensive care unit. The duration of prolonged mechanical ventilation in these patients is accepted as 48 hours in some clinical studies (9,10) and as 24 hours in some studies (7,8). In our study, we accepted mechanical ventilation for more than 24 hours as "prolonged mechanical ventilation need". Prolonged mechanical ventilation after major surgery is found to be associated with increased morbidity and mortality (11,12). The need for prolonged mechanical ventilation in patients undergoing liver transplantation, although traditionally considered as a postoperative pulmonary complication, may occur as a result of graft dysfunction, impairment of consciousness, preoperative sedentary condition, hemodynamic instability, bleeding diathesis, residual anesthetic effect, heart failure and prolonged surgical process. For this reason, general practice in patients undergoing liver transplantation during the postoperative period is to monitor the patient in the mechanical ventilator for a while.

Weaning is the gradual reduction of mechanical ventilator support until the patient has spontaneous and sufficient breathing. In this process, the physician should gradually increase the patient's effort, reduce mechanical ventilator support, and initiate the weaning process at the appropriate time. Weaning types are summarized in Table 2. Studies show that early and inappropriate weaning tryings are associated with increased cardiac ischemia risk and prolonged mechanical ventilation durations. When appropriate clinical and laboratory findings were obtained and when the weaning indexes were suitable for extubation in our intensive care unit, patients were extubated frequently using T-tube method.

In our study, we found that postoperative mechanical ventilation support was prolonged (>24 hours) in 8.69% of adult patients undergoing liver transplantation. The preoperative ASA and MELD scores and ES, FFP, cell saver blood, platelet and cryoprecipitate amounts used in the operation were higher in the prolonged mechanical ventilation group than the other group.

In patients undergoing liver transplantation, it may be necessary to give blood and blood products in serious amounts to the patients for various reasons during the intraoperative and postoperative periods. Therefore, high bleeding rate and high amount of transfusion of blood products during perioperative period are among the most important factors responsible for prolongation of mechanical ventilation support and increased mortality and morbidity after liver transplantation (13). In a recent study by Prasad et al. (14) the volume of blood products used in patients undergoing orthotopic liver transplantation was found to be a significant predictor of postoperative poor outcome. In our study, although the amount of transfusion of erythrocyte suspension and FFP was very low compared with the other studies (15,16), it was found to be higher in the prolonged mechanical ventilation group than the other group without reaching statistical significance. On the other hand, the use of cryoprecipitate was found to be statistically significantly higher

in the prolonged mechanical ventilation group. Therefore, we believe that high blood transfusion rates should be a stimulant for prolonged mechanical ventilation, so that blood conservation techniques and intraoperative autologous transfusions will affect patient outcomes.

Pulmonary edema, another risk factor for prolonged mechanical ventilation after liver transplantation, may be hydrostatic or non-hydrostatic. Alveolocapillary membrane integrity is impaired and this impairment may be aggravated by ischemia-reperfusion damage during transplantation in patients with ESLD (17,18). The clinical outcome is the increase of protein-rich extravascular fluid in the lung. Measurement of parameters showing the integrity of this liquid and alveolocapillary membrane may provide important information to clinician. In the literature, there are studies showing that ELWI and PVPI values obtained by PiCCO monitoring had prognostic value in terms of results in critical patients, and that PVPI values could be used effectively to differentiate hydrostatic pulmonary edema from non-hydrostatic pulmonary edema (19-21). In those study, high ELWI levels were associated with decreased survival, and PVPI was defined as a good indicator for results in patients in intensive care units. However, studies on the use of these parameters during the perioperative period are limited. Garutti and colleagues showed that ELWI values ≥ 12 mL/kg and PVPI values ≥ 2.3 obtained by PiCCO measurements made at the end of surgery in patients with liver transplantation, were associated with longer mechanical ventilation and longer duration of hospital stay (22). In our study, we found that ELWI values were lower in all three phases of transplantation in the prolonged mechanical ventilation group than the other group and that there was no significant difference between the two groups in terms of PVPI values. In support of these results, GEDI ve SVI values obtained in all three phases of surgery were found to be lower in the prolonged mechanical ventilation group. Contrary to the results of the studies in the literature which showed that high ELWI, PVPI and GEDI levels were risk factors for prolonged mechanical ventilation; low values found in our study seems to be a stimulating factor. Prolonged mechanical ventilation may be due to having lower intravascular volumes of these patients or it may be due to having greater fluid and blood transfusion need during surgery in these patients, as well as it may be due to organ damage caused by hypoperfusion due to inadequate fluid resuscitation.

Another risk factor for prolonged mechanical ventilation is preoperative poor condition. There are many studies in the literature that show that high ASA and MELD scores are associated with poor outcomes (14,15,23). In our study, ASA and MELD scores were significantly higher in the prolonged mechanical ventilation group, but the effect of age, gender and comorbid disease on mechanical ventilation duration was not shown.

There were a number of limitations in our study. One of these was the retrospective design of our study. In addition to this, a low number of patients who needed prolonged mechanical ventilation might be a parameter that seemed to affect the statistical value of the results. In addition, the results of arterial wave analysis and

PiCCO measurements might have been unexpectedly affected by vascular impedance and compliance, which have been impaired in ESLD. It is well known that the current-dependent invasive hemodynamic monitorization methods have no proven effects on the results, mortality and morbidity.

Study Limitations

One limitation of our study was the retrospective design of the study. In addition, the dose and duration of the analgesic and sedative agents, which directly affect the duration of ventilation support, were not known. However, patients undergoing liver transplantation in our center were monitored by the same team using standard protocols in intensive care unit.

Conclusion

We observed that preoperatively high ASA and MELD scores in patients undergoing liver transplantation, and the use of blood and blood products in intraoperative period and hypovolemia observed in PiCCO measurements extended the duration of stay in mechanical ventilation and in intensive care unit during the postoperative period. Since prolonged duration of mechanical ventilation and stay in the intensive care unit are known to be directly correlated with morbidity and mortality; the determination of factors that constitute a risk to the need for prolonged mechanical ventilation and the determination of appropriate treatment strategies by taking the necessary measures will reduce the duration of hospitalization in the intensive care unit and mortality and morbidity rates. We believe that there is a need to work more for it.

Ethics

Ethics Committee Approval: Acıbadem Mehmet Ali Aydınlar University ATADEK-2017/16.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.G.C., Design: M.G.C., A.Ö., Data Collection or Processing: M.G.C., A.Ö., Analysis or Interpretation: M.G.C., A.Ö., Literature Search: M.G.C., Writing: M.G.C., A.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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