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Early extubation practices following liver transplantation: a review of the literature

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Abstract: *Background*: Early extubation and fast-tracking after liver transplantation (LT) has become increasingly popular worldwide. It has been suggested that avoidance of prolonged intubation has beneficial effects on postoperative outcome in general, and on pulmonary complications and liver graft function in particular, but literature data are inconsistent.
Objectives: Our aim was to evaluate the definition, incidence, outcomes, anesthetic management and criteria for immediate or early extubation after LT.
Methods: A literature search in Pubmed, Medline and Embase was performed using the following MeSH terms: liver transplantation, early extubation, fast-tracking, enhanced recovery.
Results: The definition of early extubation ranges between immediate extubation at the end of surgery and extubation within 8 hours after surgery. There is great variability between centers for the incidence of early extubation. Several publications show that it is feasible and safe to extubate selected patients immediately or within a few hours after liver transplantation, but the beneficial effects on postoperative outcome remain controversial. In some centers immediate extubation reduced the length of stay in the intensive care unit (ICU) and the total hospital length of stay, and bypassing the ICU reduced the cost. Several factors precluding a successful immediate or early extubation after LT have been identified, but most centers do not have a standardized protocol to select good candidates. In contrast with standardized enhanced recovery after surgery protocols for major procedures, there is no standardized anesthetic management for fast-tracking after LT.
Conclusions: Immediate or early extubation after LT is feasible, safe, and possibly associated with a better postoperative outcome in selected patients. A criteria-based, center-specific, multidisciplinary designed protocol could result in more liver recipients benefitting from immediate or early extubation. Prospective, well-designed trials are warranted to improve immediate or very early extubation practices after LT.

Keywords: Early extubation; liver transplantation; fast-tracking.

Introduction

In the last few decades, there has been an evolution in the postoperative management of liver transplant recipients. Historically, these patients remained mechanically ventilated for a prolonged period in the intensive care unit (ICU). Arguments in favor of this practice are a need for optimization and stabilization of hemodynamics, coagulation, metabolic status and analgesia in these critically ill patients. In analogy with cardiac and major liver surgery, several centers successfully extubated patients immediately or within a few hours after liver transplantation. It has been suggested that avoiding unnecessarily prolonged ventilation has beneficial effects on outcome (reduced pulmonary infections, improved graft function), better use of resources, reduced length of intensive care and hospital stay.

The literature regarding early extubation after LT mainly consists of small case series, retrospective studies and reviews. Several questions remain unanswered. We performed a review of the literature to evaluate a few aspects associated with early extubation after LT in adult receptors: the definition and incidence of early extubation, early extubation and postoperative outcome, anesthetic management and criteria for early extubation.

Methods

We conducted a literature search using Pubmed, Medline and Embase with the terms ‘liver transplantation’, ‘early extubation’, ‘fast-tracking’, ‘enhanced recovery’. Additional articles were ad-

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ded by relevance or identified from the reviewed articles. We selected 21 retrospective trials, 2 case series, 12 prospective trials and 4 reviews (2 systematic reviews, 2 narrative reviews).

Results

Definition and incidence of early extubation

The definition of early extubation after LT varies throughout the literature, ranging from immediate extubation (in the operating room, post-anesthesia care unit (PACU) or ICU) to tracheal extubation within 8 hours postoperatively. In most papers the term "immediate" referred to extubation in the operating room at the end of surgery.

In 1990, Rossaint et al. published the first case series of early extubation after orthotopic liver transplantation (OLT) in adult recipients. They successfully extubated 5/39 patients (12.8 %) immediately postoperatively, after implementing an intraoperative restrictive fluid management protocol. Fluids were only administered after a decrease in cardiac index and ventricular filling pressures (1).

In the following years, the feasibility and safety of immediate or very early extubation after liver transplantation was further explored in several publications.

Mandell et al. retrospectively identified pre- and intraoperative criteria for immediate postoperative extubation. The subsequent application of these criteria in selected patients in 2 centers was successful in 16/67 patients (23.9 %) in one center and in 25/106 patients (23.6 %) in the other center (2). The anesthetic technique was determined by the attending anesthesiologist, but the total dose of benzodiazepines and narcotics was limited.

Biancofiore et al. retrospectively reviewed data from 181 unselected consecutive liver transplant recipients (3). Tracheal extubation was successful in 63,5 % of patients within 3 hours of surgery and in 74,0 % of patients within 8 hours of surgery. All patients received a similar balanced anesthesia.

Table 1

Incidence of early extubation

References	Period of data collection (publication date)	Type of study	Early extubation rate	Extubation timing
Rossaint et al. (1)	1988-1989 (1990)	Case series	5/39 (12%)	Immediate
Mandell et al. (2)	1995 (1997)	Prospective (UC) Retrospective (UCSF)	16/67 (23.9%) 25/106 (23.6%)	< 8 h (UC) Immediate (UCSF)
Ferraz Neto et al. (6)	1995-1998 (1999)	Retrospective	27/40 (67.5%)	< 3 h
Biancofiore et al. (3)	1997-1999 (2001)	Retrospective	115/181 (73.6%) 19/181 (10.5%)	< 3 h > 3 - < 8 h
Glanemann et al. (7)	1992-1996 (2001)	Retrospective	102/546 (18.7%)	Immediate
Ulukaya et al. (8)	2002	Retrospective	40/60 (66.7%)	Immediate
Mandell et al. (4)	1996-1998 (2002)	Prospective	111/147 (75.5%)	Immediate
Cammu et al. (9)	2003	Case series	4/6 (66.6%)	Immediate
Biancofiore et al. (10)	1999-2004 (2005)	Prospective	211/365 (57.8%)	Immediate
Zeyneloglu et al. (11)	2004-2006 (2007)	Retrospective	52/100 (52%)	Immediate
Glanemann et al. (12)	1997-2005 (2007)	Retrospective	643/837 (76.8%)	Immediate
Mandell et al. (5)	2-year period (2007)	Prospective, Multicenter	5-67% (total 391/1270 patients)	< 1 h
Skurzak et al. (13)	1997-2002 (2010)	Retrospective	575/652 (88.2%)	Immediate
Taner et al. (14)	2003-2007 (2012)	Retrospective	523/870 (60.10%)	Immediate/PACU
Bulatao et al. (15)	2003-2010 (2014)	Retrospective	704/1296 (54.3%)	Immediate/PACU
Lee et al. (16)	2011-2012 (2014)	Retrospective	66/107 (61.7%)	< 1 h
Blaszcyck et al. (17)	2000-2015 (2016)	Retrospective	371/506 (73.7%)	< 45 min.
Chae et al. (18)	2011-2017 (2019)	Retrospective	101/255 (39.6%)	Immediate
Acho et al. (19)	2014-2017	Retrospective	80/279 (28.6%)	Immediate
Haque et al. (20)	2009-2017	Retrospective	371/1378 (26.9%)	< 4 h

In 2002, a first report on successfully bypassing the ICU after LT was published. The group of Mandell et al. successfully extubated 111/174 patients (75.5 %) in the operating room and 74.7% of these patients went directly to the surgical ward after conventional PACU admission (4). A standardized anesthetic technique minimizing benzodiazepines and narcotics was used.

Despite a change in allocation practices, with priority based on MELD score as an objective parameter of severity of liver disease, Mandell et al. confirmed the safety and feasibility of early tracheal extubation within 1 hour after LT in a multicenter prospective trial, reporting early extubation in 391 out of 1270 patients (30.8 %) (5). There was, however, a huge difference between the participating centers for the incidence of extubation within 1 hour after surgery: between 5 and 67% of the patients met the criteria for early extubation. The anesthesia technique was similar for the different centers, but not strictly standardized.

From then on a growing body of literature on early extubation after liver transplantation emerged. Table 1 lists the incidence of early extubation for the papers we identified for this review.

Early extubation and postoperative outcome

In the study by Mandell et al., immediate postoperative extubation of selected patients (preoperative exclusion criteria) was associated with a significantly shorter ICU stay (20.4 ± 7.4 vs. 35 ± 8.0, $p < 0.05$). Reintubation was required in 2 out of 25 patients in one center, whereas no reintubations were necessary in the other center (0/16). There was a significant cost reduction for patients who were extubated immediately postoperatively as compared to patients who remained ventilated for a longer period of time (2).

Neelakanta et al. retrospectively compared data from a group of adult patients who were extubated immediately after LT (n = 18) and a control group of patients who were not immediately extubated and had ≤ 3 units of blood transfused during LT (n = 17). There were no significant differences between groups with regard to discharge times from the ICU (50.6 ± 2.7 hours in the immediate extubation group vs. 61.2 ± 4.7 in the control group, $p = 0.06$), or discharge from the hospital (14.8 ± 1.6 days in the immediate extubation group vs. 21.3 ± 3 days in the control group, $p = 0.06$) (21). Of the 18 patients who were extubated in the operating room, none required reintubation.

Ferraz-Neto et al. reported a reintubation rate of 2 out of 27 patients (11.8 %) who were extubated within 3 hours of LT. Both patients died (6).

In a retrospective study by Glanemann et al., 81 of 546 adult patients (14.8 %) required reintubation with reinstitution of mechanical ventilation after successful early postoperative extubation (7). The reintubation rate was significantly higher in the group of patients extubated > 24 hours postoperatively than in any of the other 2 groups (immediate extubation and extubation < 24 hours): 22/61 patients (36.1 %) in the > 24 hours group vs. 9/102 patients (8.8 %) in the immediate postoperative extubation group and 50/383 patients (13.1 %) in the < 24 hours group.

There was no statistically significant difference in reintubation rate between the immediate and < 24 hours extubation groups. Long-term survival was significantly reduced in patients who required prolonged ventilation (> 24 hours) when compared to patients who were extubated immediately or within 24 hours ($p < 0.001$). Survival rates at 1, 2, 3 and 5 years after orthotopic liver transplantation (OLT) were 93.1%, 90.9%, 89.5% and 84.8% respectively, in the immediate extubation group, vs. 91.5%, 89.4%, 87.5% and 86.1% in the early extubation group (< 24 hours) and 72.1%, 70.1%, 70.1% and 65.1% in the late extubation group. There was no significant difference in survival between the immediate and early extubation group ($p = 0.835$).

Biancofiore et al. demonstrated that early extubation after LT was safe in patients without major blood transfusion, without hemodynamic instability and without renal or neurological impairment. The length of stay in the ICU was significantly shorter for patients extubated within 3 hours after surgery than for patients extubated > 3 hours postoperatively. Hospital length of stay, as well as mortality after 3 and 6 months was significantly better for recipients who were tracheally extubated within 3 hours after OLT compared to patients who required prolonged intubation (> 24 hours). There was a low incidence of tracheal reintubation in patients extubated within 3 hours after surgery: 9/115 patients (7.8 %). In the group of patients extubated between 3 and 24 hours after surgery 5/29 patients (17.2 %) required reintubation, and 10/36 patients (27.8 %) needed reintubation after initial prolonged intubation (> 24 hours). The reintubation rate was significantly less for patients extubated within 3 hours than for patients extubated after prolonged intubation (> 24 hours) ($p < 0.05$) (3).

Findlay et al. examined the effect of "fast-track anesthesia" (shorter-acting drugs, fentanyl

limited to a maximum of 20 µg/kg) on the duration of postoperative mechanical ventilation and length of ICU stay after LT in preoperatively selected patients (22). Patients with repeat LT, multiple organ transplantation, acute liver failure, renal replacement therapy, pulmonary hypertension, hepatopulmonary syndrome, and patients intubated preoperatively were excluded. Postoperative mechanical ventilation was significantly shorter in the fast-track group than in the traditional group (mean 553.5 min with a range of 0-1740 min vs. 1018 min with a range of 175-5280 min respectively, $p < 0.001$). There was no significant difference in ICU length of stay between the groups.

In 2002, Ulukaya et al. retrospectively evaluated allograft function and respiratory complication rate in 40 adult OLT recipients (out of 60 consecutive liver transplants) who were extubated immediately at the end of surgery and admitted to the ICU. Six patients (15 %) required reintubation, 5 due to a reoperation and 1 for acute respiratory distress syndrome. The patients who required reoperations were extubated again in the operating room. Fifteen patients (37%) had respiratory complications not requiring reintubation. No allograft dysfunction (primary nonfunction or delayed graft function) occurred, as measured by AST, ALT and PT values, which all normalized within one week postoperatively (8).

Biancofiore et al. prospectively investigated the safety of immediate postoperative extubation after LT in selected patients (10). Preoperative exclusion criteria were acute hepatic failure, emergency retransplantation, and preoperative mechanical ventilation. The reintubation rate was low: 2/211 (1 %) of liver recipients who were immediately extubated and 4/41 (9.7%) who were extubated more than 24 hours after surgery. Non-invasive ventilation was indicated in 17/354 transplant recipients (4.8 %): 11/211 (5.2 %) in the immediate extubation group and 6/113 (5.3 %) in the group of patients extubated < 24 hours after surgery. Mortality was significantly higher in the group extubated > 24 hours than in the other 2 groups ($p = 0.001$): 2/211 (1 %) in the immediate extubation group, 4/113 (3.5 %) in the group extubated within 24 hours and 11/41 (26.8 %) in the group extubated after 24 hours.

A multicenter prospective evaluation of the safety of immediate postoperative extubation (< 1 hour postoperatively) in selected liver transplant recipients was performed in 2007. Patients with coronary artery disease, pulmonary vascular disease, retransplantation, multiorgan transplantations, and patients with Grade 4 encephalopathy were excluded. The authors reported an incidence of 32 adverse events occurring within 72 hours of surgery in 391 patients (7.7 %) who were extubated within 1 hour after surgery. Most adverse events were pulmonary (10/32, 31.2 %) or surgically related (7/32, 21.8 %). Pulmonary complications were usually minor: 9 patients experienced transient hypoxemia (treated with supplementary oxygen) and 1 patient with persistent hypoxemia required reintubation. Six patients required a reoperation within 36 hours. Two patients died on the third postoperative day. Adverse events occurring > 36 hours after surgery were generally more severe than adverse events occurring within 36 hours of surgery (5).

Zeyneloglu et al. retrospectively reviewed data from all patients (n = 100) who underwent OLT between January 2004 and June 2006 at their institution. The length of stay in the ICU was significantly shortened in patients who were immediately extubated postoperatively compared to patients who were extubated in the ICU: mean 2.5 ± standard deviation (SD) 1.2 days vs. mean 4.1 ± SD 4.5 days, respectively ($p = 0.01$). Results on duration of hospital stay showed no difference between the two groups: immediate extubation 29.6 ± 27.0 days vs. ICU extubation 29.6 ± 26.3 days ($p = 1.000$) (11).

Taner et al. retrospectively reviewed data from selected adult liver recipients. Five hundred and twenty-three of 870 patients (60.10 %) were fast-tracked to the surgical ward after immediate extubation in the operating room or in the PACU, and 347 (39.90 %) patients were admitted to the ICU after OLT. The fast-track failure rate was 1.9 %: after initial immediate extubation 10 patients were admitted to the ICU from the surgical ward within 3 days after liver transplantation. Postoperative hospital length of stay was significantly shorter in fast-track patients: 8.26 ± 7.77 days vs. 18.76 ± 26.10 days, $p < 0.001$. The 30-day mortality rates were not significantly different for the 2 groups: 4 patients (0.80 %) in the fast-track group and 6 patients (1.70 %) in the ICU group died within the first 30 days after LT. Long-term patient survival rates were significantly higher for fast-track patients than for ICU patients at 1 year (94.5 % vs. 89.6 %, $p = 0.007$), 3 years (87.0 % vs. 82.4 %, $p = 0.005$), and 5 years (81.3 % vs. 74.7 %, $p = 0.003$). The 1 year graft survival rate was higher for the fast-track group than for the ICU group (89.7 % vs. 85.3 %, $p = 0.043$), but there was no significant difference between both groups for the 3 and 5 year graft survival rate (14).

Bulatao et al. compared survival in selected liver transplant recipients fast-tracked to the surgical ward to those who were admitted to the ICU. Median follow-up was 5.2 years (range: 1 day to 9.7 years). Overall patient survival (relative risk (RR) 0.75, 95 % confidence interval (CI): 0.6-0.96, p = 0.020) and graft survival (RR 0.78, 95 % CI: 0.62-0.98, p = 0.032) were significantly better in the fast-track patients (15).

In a retrospective analysis of 107 adult patients post living donor liver transplantation (LDLT), patients who were extubated within 1 hour post-transplant (n = 66, 61.7 %) stayed in the hospital (24.4 vs. 31.0 days, p < 0.05) and ICU (5.7 vs. 8.8 days, p < 0.05) for shorter periods than those who were extubated later than 14 hours after surgery (n = 41, 38.3 %). No intergroup difference was found in mortality (1 vs. 1), reintubation rate (1 vs. 4), graft dysfunction (1 vs. 3) and bleeding episodes (1 vs. 4) (early vs. non-early extubation groups). The incidence of reoperation (1 vs. 5, p = 0.03), infectious complication (5 vs. 9, p = 0.032) and vascular thrombosis (0 vs. 2, p < 0.001) was significantly lower in the early extubation group (16).

Pocknall et al. retrospectively applied the fast-track scoring system developed by Bulatao et al. to 30 consecutive liver transplant recipients (with the exclusion of patients in acute liver failure or patients preoperatively mechanically ventilated). There was a statistically significant correlation between the fast-track score predictive of a successful early extubation and the duration of postoperative mechanical ventilation (23).

A small case series in India retrospectively evaluated 15 LDLT recipients who were extubated on table. None required reintubation postoperatively (24).

A recent trial retrospectively reviewed post-operative outcomes of 255 male patients after LDLT. As compared with patients in the conventional extubation group (n = 154), patients in the immediate extubation group (n = 101) required a shorter ICU length of stay: median 7 days (5-7) vs. 7 days (6-8), p = 0.008. The incidence of pneumonia (4 % vs. 16.9 %) and early allograft dysfunction (2 % vs. 16.9 %) was significantly lower in the immediate extubation group. Hospital length of stay and reintubation rates did not statistically differ between the two groups (18).

In a prospective, single-blinded, randomized study, Rao et al. investigated the effects of a fast-track protocol on postoperative outcome after LT in selected patients. Exclusion criteria were age ≤ 16 and ≥ 70 years, retransplantation, radiofrequency ablation or hepatic artery infusion chemotherapy. They observed a significantly shorter ICU length of stay and hospital length of stay in the fast-track group compared to the control group. The median ICU length of stay was 2 days (range 1-7 days) in the fast-track group and 5 days (range 3-12 days) in the control group (p < 0.01). The hospital length of stay was 18 days (range 15-32 days) in the fast-track group and 28 days (range 23-35 days) in the control group (p < 0.01). There was no significant difference in overall postoperative complication rate between the groups. There were no postoperative readmissions or mortality in any of the groups within 3 months after surgery (25).

In a small-scale prospective study, Brustia et al. investigated the feasibility of a fast-track protocol for LT (26). Ten adult fast-track patients were each matched (MELD score, BMI, age and gender) with 2 historical controls. Preoperative exclusion criteria were multiple organ transplantation, fulminant liver failure, retransplantation, split or living donor LT, or MELD score > 26. A fast-track protocol was developed, based on enhanced recovery protocols for liver surgery. Fast-track patients were extubated within 6 hours of surgery. Compliance with the fast-track protocol was 72.9 %. ICU length of stay was significantly shorter in the fast-track patients: median 3 days (2.0-4.0) vs. 4.5 days (3.0-8.3), p = 0.005. Total length of stay was reduced by 47 % in the fast-track group as compared to the control group: 9.5 days (9.0-10.5) vs. 18.0 days (14.3-24.3), p < 0.001. There were no differences between both groups for postoperative complications and 30 days readmission rates after discharge.

Acho et al. recently demonstrated that immediate postoperative extubation leads to a decrease in pulmonary complications after LT. They compared postoperative outcomes of seventy two patients who were extubated in the operating room to a matched control group (n = 72) consisting of patients who were extubated later.

The late extubation group suffered from a significantly higher rate of pulmonary complications (27.8% vs. 11.1%, p = 0.012) which included pneumonia, symptomatic pleural effusion or pulmonary edema requiring treatment or increased respiratory support. Reintubation rates (2.8% vs. 2.8%, p > 0.9) and 90-day graft survival rates (98.6% vs. 95.8%, p = 0.31) did not differ between the two groups. Total ICU stay (2 vs. 3 days, p = 0.082) and cost ($5700 vs. $7710, p = 0.11) were lower in the immediate extubation group but this did not reach statistical significance (19).

Criteria for early extubation

Independent pre- and intraoperative variables predictive of prolonged intubation after LT in different recipient populations were retrospectively identified in multiple studies (Table 2).

Some studies excluded patients for early extubation by using predetermined criteria based on expert opinion: recipients with preoperative coexistent diseases, age > 50 years, encephalopathy or who were classified as United Network for Organ Sharing (UNOS) status 1 or 2, were initially found to be unsuitable candidates for early postoperative extubation. Good donor liver function, < 10 units packed red blood cells (PRBC) administered intraoperatively, no persistent need of vasoactive support at the end of surgery and an alveolar-arterial oxygen gradient < 150-200 mmHg are the intraoperative criteria which had to be met before early extubation was attempted (2,9).

The definitive decision to extubate was generally based on widely employed criteria for extubation after major surgery: adequate mental status, good respiratory parameters (tidal volume, respiratory rate, end-tidal CO_2, O_2 saturation), stable hemodynamic parameters, normothermia, evidence of reversal of neuromuscular blockade (often subjective).

In 2010, Skurzak et al. proposed the 'safe operating room extubation after liver transplantation (SORELT) score' (13). This prognostic score was intended as an objective aid in the decision process for safe early extubation after LT. It was based on a retrospective comparison of data (preoperative, intraoperative, graft related) from patients successfully extubated in the operating room with data from non-extubated patients. The authors identified 2 major and 3 minor criteria as independent predictors for nonextubation (Table 2). Immediate extubation could be considered if less than 2 major criteria, 1 major plus 2 minor criteria or 3 minor criteria were present.

Bulatao et al. developed a scoring system to determine the probability of successful fast-tracking (immediate extubation and bypassing the ICU) of liver transplant recipients (15).

The score was based on a combination of 9 preoperative and intraoperative parameters: receptor age, receptor BMI, receptor gender, MELD score at time of transplantation, pretransplant length of hospital stay, transplant number, intraoperative packed red blood cell (PRBC) transfusion, operative time and vasopressor administration during the last hour of surgery.

The probability score was derived from retrospectively analyzed data from 1269 liver recipients, and subsequently validated in an independent group of 372 selected (exclusion criteria were applied) liver recipients.

Haque et al. retrospectively applied the fast-track probability score developed by Bulatao to data from 1378 liver receptors in a single center. The predictive accuracy in this group of patients was less than in the original publication by Bulatao. When the authors adapted the original Bulatao score to their patient population, the predictive value improved (20).

Anesthesia management

While many, but not all, authors report the use of a standardized anesthesia technique, most protocols were not specifically designed for early extubation. A vast majority of centers routinely used a balanced anesthesia technique with an inhalation anesthetic; only 3 centers consistently used a total intravenous technique (9, 17, 27). In older studies, generally longer-acting anesthetic agents and narcotics were used. In more recent years, propofol has been the induction agent of choice and there has been an increase in the use of remifentanil during LT (9-11, 13, 16, 27, 28).

There are only a few studies investigating the influence of anesthesia on early extubation after LT.

In 2002, Findlay et al. showed that the use of a tailored anesthetic regimen significantly shortened the duration of postoperative mechanical ventilation (22). Postoperative ventilation time was significantly shorter in the "fast-track" anesthesia group (propofol, cisatracurium, midazolam, 20 µg/kg fentanyl, isoflurane/N_2O) than in the group of patients who received a traditional anesthetic technique (thiopental, pancuronium, lorazepam, 50 µg/kg fentanyl, isoflurane): mean 553.5 minutes (median, 390 minutes) versus mean 1.081 minutes (median, 855 minute), $p < 0.001$. There was no difference between groups in length of ICU stay.

A few authors investigated if BIS monitoring as a method for titrating anesthetic agents during LT had an effect on extubation time.

In a retrospective study, Schumann et al. investigated if BIS monitoring as a method for titrating anesthetic agents in liver transplant recipients had an effect on the time to extubation (29). Patients in the BIS group (n = 41) received less isoflurane at each phase during LT than the control group (n = 42), but the difference was statistically significant only during the anhepatic phase (end-

Table 2

Independent pre- and intraoperative variables predictive of prolonged intubation after LT in different recipient populations

Reference (year of publication)	Predictors of prolonged intubation	Patients excluded from data analysis
Biancofiore et al. (3) (2001)	PGD, renal failure, cardiovascular failure, serious neurological impairment, > 12 units PRBC transfused intraoperatively, pulmonary edema	None
Glanemann et al. (7) (2001)	ALF, MV prior to OLT, massive intraoperative bleeding (> 15 units PRBC and FFP transfused), PRS, retransplantation	Pediatric recipients, intraoperative death
Mandell et al. (4) (2002)	Encephalopathy, BMI ≥ 35	Retransplantation, multi-organ transplantation, UNOS status 1, LDLT, intraoperative death
Biancofiore et al. (10) (2005)	MELD > 11	ALF, emergency retransplantation, intraoperative death or death in the first 24 postoperative hours, preoperative MV
Glanemann et al. (12) (2007)	ALF, retransplantation, Child C status, > 6 units PRBC transfused intraoperatively	None
Zeyneloglu et al. (11) (2007)	Emergent OLT, intraoperative hypotension	None
Skurzak et al. (13) (2010)	PRBC transfusion ≥ 7U, lactate ≥ 3.4mmol/L at the end of surgery, hospitalized patient before OLT, surgical duration ≥ 5h, Dopamine > 5 µg/kg/min or NE > 0.05 µg/kg/min at end of surgery	Fulminant hepatic failure, retransplantation due to primary nonfunction, preoperative MV, pediatric recipients, HPS, liver-kidney transplant, intraoperative death
Taner et al. (14) (2012)	High MELD score at the time of OLT, long operative time, high intraoperative transfusion requirements, high recipient age, high recipient BMI, absence of HCC/CCA	Intraoperative death, partial liver graft recipients, preoperative ICU admission, intraoperative RRT, multi-organ transplantation, combinated OLT and cardiac surgery
Lee et al. (16) (2014)	> 7 units PRBC transfused, last measured lactate > 8.2 mmol/L	Retransplantation
Bulatao et al. (15) (2014)	Fast tracking probability score based on: age, BMI, gender, MELD, pretransplant length of stay, transplant number, PRBC, vasopressor last hour, operative time	Multi-organ transplantation, combined cardiac surgery and OLT, intraoperative death, partial liver graft recipients, preoperative ICU admission, intraoperative RRT, fast-track failures
Blaszczyk et al. (17) (2016)	Low preoperative Hb level, no use of TEA, perioperative PRBC and FFP transfusion	None
Chae et al. (18) (2019)	Preoperative: low PMI Intraoperative: RRT, PRS , FFP transfusion	Emergency LDLT, encephalopathy (Westhaven IIII-IV), female
Acho et al. (19) (2020)	Anhepatic time > 75 minutes, MELD > 20, encephalopathy, total intraoperative PRBC-FFP-autologous transfusion ≥ 12 units	Retransplantation, multivisceral transplantation, preoperative MV, intraoperative deaths

Abbreviations: PGD, primary graft dysfunction; PRBC, packed red blood cells; ALF, acute liver failure; MV, mechanical ventilation; OLT, orthotopic liver transplantation; FFP, fresh frozen plasma; BMI, body mass index; UNOS, United Network for Organ Sharing; LDLT, living donor liver transplantation; MELD, Model of End-Stage Liver disease; NE, norepinephrine; HPS, hepatopulmonary syndrome; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; RRT, renal replacement therapy; TEA, thoracic epidural anesthesia; PMI, psoas muscle index; PRS, post reperfusion syndrome.

tidal isoflurane concentration 0.52 vs. 0.65 %, p = 0.026), and it is not likely that this difference was clinically important. There was no statistically significant difference between the BIS group and the control group for time to extubation (4.9 vs. 2.4 days respectively, p = 0.08).

One center recommends the use of a combined general and thoracic epidural anesthesia in patients with no contraindications (17): Blaszczyk et al. retrospectively looked for independent predictors of early extubation after LT. They identified the perioperative use of epidural analgesia as an anesthesia-related predictor of early extubation. Epidural catheters (placed at T6-T8) were placed in 61/371 (16.4 %) patients of the early extubation group and in 12/135 (8.9 %) patients of the late extubation group (p = 0.032). Intraoperatively, epidural analgesia was obtained with a mixture of a local anesthetic and an opioid. All patients received a total intravenous anesthesia. After continuous

epidural analgesia was initiated, intravenous opioids were administered only if needed, but the authors provide no data on the amount of opioids administered in patients with epidurals in comparison to patients without epidurals. There were no reports on complications associated with an epidural (e.g. epidural hematomas).

Discussion

Traditionally, liver transplant recipients remained intubated and mechanically ventilated in the ICU for a prolonged period of time. Proponents of this practice argued that these critically ill patients needed time for physiological optimization and adequate analgesia after major surgery. Since several years, more and more centers avoid prolonged ventilation after LT and extubate recipients immediately, in the operating room, or very early after surgery. Potential arguments in favor of immediate or very early extubation after LT are a reduced incidence of pneumonia, a reduced incidence of graft failure and better use of financial and human resources due to a reduced length of stay in the ICU and in the hospital. In some centers the ICU is bypassed after immediate extubation in the operating room, and patients are fast-tracked to the PACU and the surgical ward (4, 14, 15).

Early extubation and fast-track perioperative management have been widely and successfully adopted for major procedures such as cardiac, thoracic and pancreatic surgery and for partial liver resections.

The implementation of Enhanced Recovery After Surgery (ERAS) protocols for cardiothoracic, pancreatic or major hepatic surgery reduced hospital resource utilization and total cost without increasing complication rates (30, 31). For these procedures there are standardized ERAS protocols consisting of multimodal and multidisciplinary preoperative, intraoperative and postoperative components.

Immediate postoperative extubation after LT was first reported for selected patients in the early nineties (1). Further development of anesthetic and surgical techniques fueled this approach, leading to high early extubation rates in several centers (3). In contrast with other major surgical procedures there are no generally accepted standardized protocols for immediate/early extubation or for fast-tracking after LT.

The literature on immediate or early extubation after LT consists mainly of retrospective studies or small case series, and many questions regarding early extubation after LT remain. In this review, we attempted to clarify the following subjects: the definition and incidence of early extubation, early extubation and postoperative outcome, anesthetic management and early extubation, and criteria for early extubation.

Many liver transplant centers aim for early extubation, but the timing ranges from immediate extubation in the operating room to extubation within 8 hours after surgery. The term fast-tracking in LT usually refers to immediate extubation in the operating room and bypassing of the ICU. Centers fast-tracking liver transplant recipients generally monitor these patients in the PACU for a short period of time before transferring them to a step-down unit with more extensive monitoring and a higher nurse:patient ratio than in a regular surgical ward. Other centers send all the patients after LT to an ICU, where extubation is attempted as soon as possible. It seems that the differences in early extubation practices after LT are center-specific and often depend on institutional practices and organization.

The early extubation (within 8 hours of surgery) rate after LT varies widely, ranging from 12 % to 88 %. There are several explanations for this broad range. Some centers only considered highly preselected patients as candidates for early extubation, thus including only the healthiest liver receptors, while other centers excluded only extremely sick patients (e.g. patients with acute liver failure or patients mechanically ventilated before transplantation). Organizational differences may also play an important role. Liver transplant programs with the resources allowing to bypass the ICU are probably more likely to attempt immediate extubation. It seems that centers with a dedicated group of anesthesiologists for LT are more prone to aim for immediate or very early extubation after surgery. Maybe there is also a learning curve or a confidence building period involved. Obviously, immediate or early extubation of liver transplant recipients is only indicated if it is safe.

Several publications examined outcome parameters after immediate or early extubation: reintubation rates, adverse events, allograft dysfunction, mortality, length of ICU stay, ICU cost, and length of hospital stay.

Reintubation rates in patients extubated immediately or early after LT are generally low and vary between 0 and 15 % (2-4,6-8,16,18,21,24). There appears to be no difference between patients extubated immediately or early (< 8 hours) after surgery. Postoperative reintubation rates after LT were higher after prolonged intubation than after

immediate or early extubation (3, 7). These results are not surprising, considering that patients remaining intubated for a prolonged period after LT were generally in poor clinical condition preoperatively (e.g. acute liver failure, preoperative mechanical ventilation, encephalopathy, extreme frailty), had difficult surgery or graft dysfunction (7).

Several studies show that the rate of adverse events is low for selected liver recipients extubated immediately or early after transplantation (5, 8, 10). A few publications reported a lower incidence of reoperations, infectious complications, vascular thrombosis, or pulmonary complications in patients extubated immediately or early after LT (16, 18, 19).

It has been suggested that prolonged mechanical ventilation might have a negative effect on liver allograft function, but this has not been well studied. Chae et al. retrospectively documented a lower incidence of allograft dysfunction in patients who were immediately extubated, but this was not supported by other data (16, 18).

Mortality during initial hospitalization is low for patients extubated immediately after surgery (5, 10, 25). Long-term patient survival rates are similar for patients extubated immediately or within 24 hours after surgery, but are significantly lower for patients who remained intubated longer than 24 hours after surgery (3, 7). As mentioned earlier, patients remaining intubated longer than 24 hours after LT are generally patients at higher risk for complications due to preoperative morbidity or intraoperative problems. Retrospective comparison of data from fast-track patients bypassing the ICU after LT with data from patients who were directly admitted to the ICU show similar short-time survival rates for both patient groups, but higher long-term (up to 5 years) survival rates for successfully fast-tracked patients (14, 15).

Patients who were extubated immediately or very early after surgery had a significantly reduced length of stay in the ICU or bypassed the ICU in comparison with patients who remained ventilated for a longer period (2, 3, 11, 16, 18, 25, 26). Other studies showed no difference for ICU length of stay between immediate/early and late extubation, or between fast-track and non fast-track patients (19, 21, 22). Unfortunately, most studies are retrospective chart reviews, and it is not clear if strict criteria for discharge from the ICU were applied in all centers.

Also, while some authors only examined data from liver recipients selected on the basis of strict preoperative criteria, other authors included almost all patients and excluded only the very sick (acute liver failure, preoperative mechanical ventilation).

Immediate extubation after LT was associated with a significant ICU cost reduction in a few studies (2, 19).

Postoperative hospital length of stay was reduced in immediate/early extubated patients in some studies (3, 14, 16, 25, 26) while other studies, including some with a reduced ICU length of stay, did not detect a difference with patients who remained intubated longer (11, 18, 19, 21).

Many studies show that immediate or early extubation after LT is not associated with increased morbidity and mortality in selected patients. A few studies demonstrate that immediate or early extubation is favorable in terms of adverse events, ICU length of stay, hospital length of stay and ICU cost of in comparison with prolonged intubation, but this is not confirmed by other studies. There are no data indicating if it makes a difference if patients are extubated immediately after LT or within a few hours of surgery. The decision to extubate immediately after surgery, in the operating room, often depends on institutional organizational structures.

Centers promoting this practice, generally have a step-down unit. Patients extubated in the operating room bypass the ICU and are admitted to a step-down unit after staying a few hours in the PACU. It is probably not clinically important if patients are extubated immediately or very early after LT, as long as unnecessary prolonged intubation is avoided.

Immediate or early extubation after LT is feasible, safe, and perhaps beneficial in selected patients, but it is important to carefully select good candidates and to identify patients at risk for prolonged intubation. Some centers evaluate almost every liver recipient, except the extremely sick, for immediate/early extubation, while other centers only consider receptors without major comorbidity and with a low MELD score.

Several authors analysed data from liver transplant recipients to identify risk factors for prolonged mechanical ventilation after LT, but most studies are retrospective and the results are not always consistent. Generally accepted preoperative risk factors for prolonged intubation after LT are severe encephalopathy, mechanical ventilation or ICU admission prior to transplantation, acute liver failure, emergency retransplantation, multi-organ transplantation, and LT combined with cardiac surgery (3, 4, 7, 12-15, 19). If any of these factors is present, receptors are generally not considered for immediate/early extubation. Many patients listed for LT suffer from sarcopenia. In a recent study Chae et al. showed that the core muscle

mass 1 month prior to surgery was higher in the immediate extubation group after LDLT than in the conventional extubation group (18). Intraoperative risk factors for prolonged intubation are, most notably, major transfusion of PRBC, hemodynamic instability, renal dysfunction and signs of allograft dysfunction (3, 7, 11-16, 18, 19). Data on other receptor characteristics or intraoperative parameters as risk factors for prolonged intubation remain controversial: age, high body mass index, MELD score, duration of surgery (3-5, 11-16, 19).

A few centers developed scoring systems, based on selected preoperative patient characteristics and intraoperative data, to predict successful immediate/early extubation after LT, but experience with these scoring systems is limited (13, 15, 23). A scoring system successfully predicting immediate/early extubation in one center does not necessarily have the same predictive value in another center due to different patient characteristics and institutional practice (15). This indicates that a scoring system should be used cautiously, as a tool to help identify suitable candidates for immediate/early extubation, and that it should be used in combination with good clinical judgement.

While several preoperative and intraoperative factors precluding a successful immediate/early extubation have been identified, the final decision to extubate immediately or early after LT is often not based on uniform criteria or institutional guidelines. Most centers apply generally accepted requirements for extubation after major surgery (adequate neurological status, absence of residual neuromuscular block, good respiratory parameters, stable hemodynamics, normothermia), in addition to criteria relevant for transplant liver recipients (e.g. no evidence of allograft dysfunction, minimal vasopressor requirement).

It seems reasonable to expect that the choice of anesthetic technique and anesthesia-related drugs affects the success rate of immediate/early extubation after LT, but this has not been studied satisfactorily. Universally accepted ERAS guidelines for major surgery, including liver resections, recommend the use of (ultra)short- to intermediate-acting anesthesia-related drugs and to avoid high doses of opioids (32). There are no such ERAS guidelines for liver transplantation, but in recent years there is a tendency to use shorter-acting drugs (e.g. remifentanil) or limit the total dose of opioids. A few studies assessed the effect of a fast-track anesthesia protocol for LT, but these studies did not have strict guidelines on intraoperative anesthesia-related drugs (22). Also, studies employing a protocol similar to ERAS protocols for major surgery, did not include clear guidelines on intraoperative anesthesia (25, 26, 33). Most anesthesiologists use a balanced anesthesia technique for LT, while others prefer a total intravenous anesthesia; there are no data indicating that any of those techniques is superior for LT.

The need for inhalation anesthetics or propofol, as assessed by BIS monitoring, is reduced during the anhepatic phase of LT and in patients with a higher MELD score (34-38). It is not clear if this is relevant since the studies are small-scale and it seems that the reduction in anesthetic requirements is not clinically significant. In a small study retrospectively assessing the effect of BIS monitoring during LT, patients with BIS monitoring received significantly less isoflurane during the anhepatic phase than the control group, but the difference was clinically very small and there was no difference in time to extubation. BIS monitoring seems a plausible method to titrate anesthetic depth but there are no data demonstrating that this has a positive effect on the immediate or early extubation of patients after liver transplantation.

Despite the positive experience of one center with the use of thoracic epidural anesthesia during LT (17), the risk of bleeding diathesis possibly resulting in epidural hematomas should discourage such practice. Even in patients with adequate coagulation preoperatively there is always a risk of coagulation disturbances during surgery or postoperatively, due to massive transfusion and/or allograft dysfunction.

We conclude that immediate or early extubation after LT is feasible, safe, and possibly associated with a better postoperative outcome in selected patients. It is not clear if there is a difference in outcome between immediate or very early postoperative extubation, but there is no reason to keep well selected liver receptors postoperatively ventilated for hours. We know the risk factors for a prolonged intubation after LT, but most centers do not have a standardized protocol as an aid in identifying good candidates for immediate or very early extubation. A criteria-based, center-specific, multidisciplinary (involving anaesthesiologists, transplant surgeons, intensive care physicians) designed protocol could result in more liver recipients benefitting from immediate or early extubation. Prospective, well-designed trials are warranted to improve immediate or very early extubation practices after LT.

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