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MINIREVIEWS

Fast track anesthesia for liver transplantation: Review of the current practice

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Abstract

Historically, patients undergoing liver transplantation were left intubated and extubated in the intensive care unit (ICU) after a period of recovery. Proponents of this practice argued that these patients were critically ill and need time to be properly optimized from a physiological and pain standpoint prior to extubation. Recently, there has been a growing movement toward early extubation in transplant centers worldwide. Initially fueled by research into early extubation following cardiac surgery, extubation in the operating room or soon after arrival to the ICU, has been shown to be safe with proper patient selection. Additionally, as experience at determining appropriate candidates has improved, some institutions have developed systems to allow select patients to bypass the ICU entirely and be admitted to the surgical ward after transplant. We discuss the history of early extubation and the arguments in favor and against fast track anesthesia. We also described our practice of fast track anesthesia at Mayo Clinic Florida, in which, we extubate approximately 60% of our patients in the operating room and send them to the surgical ward after a period of time in the post anesthesia recovery unit.

Key words: Liver transplant; Fast track anesthesia; Early extubation; Intensive care; Liver failure

Core tip: With proper patient selection, early extubation and bypassing of the intensive care unit is possible for patients undergoing liver transplantation. This needs a multidisciplinary approach and institutional support to be effective and can improve patient outcomes, as well as, improving resource utilization.

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INTRODUCTION

Historically, patients undergoing liver transplantation have been recovered in intensive care units (ICUs) following surgery to ensure a smooth transition through the recovery period. Advocates of this practice argue that these surgeries are associated with large fluid shifts and patients often have multiple significant comorbidities necessitating a slow, controlled emergence with close supervision[1-3]. However, as surgical and anesthetic techniques have improved, a growing number of centers worldwide have begun the practice of early extubation following transplantation. Some centers have even developed processes allowing select patients to completely bypass the ICU and be directly admitted to the surgical ward after transplantation. This article aims to discuss the history and techniques involved in fast track liver anesthesia.

LITERATURE SEARCH

We performed a PubMed and MEDLINE search using the terms fast track anesthesia, early extubation, liver transplant, abdominal transplantation, ICU, transplant anesthesia. Articles included original studies and review articles were reviewed for significance and additional articles were identified from the reviewed articles.

HISTORY

The idea of early extubation following major surgery was first described in cardiac anesthesia by Prakash *et al*[4] in 1977. In his study, Prakash found that 123 of 142 adult patients could spontaneously breath either immediately after or within 3 h following open-heart surgery. Furthermore, the group realized that the careful pre- and intra-operative assessment of potential candidates was needed to ensure success with this approach. More investigators followed, and as the literature supporting and refining the process of early extubation in cardiac anesthesia grew, anesthesiologists began exploring its application in liver transplantation (Table 1). Similar to the cardiac anesthesia experience, liver transplant teams began the arduous task of trying to determine which patients were most likely to succeed with this new approach. Rossaint *et al*[5], in 1990, suggested that patients who have been given minimal fluids may be good candidates. In their study, fluid was administered only when there was a fall in the cardiac index and ventricular filling pressures. This resulted in 5/36 patients being extubated immediately after surgery and an average time to extubation of 6 h for the remainder. Mandell and her team were successful at defining criteria for early extubation by examining patients that were successfully extubated within 8 h after surgery[6]. After deriving a list of extubation criteria and retrospectively comparing their success rates to another university program, they found that patients with good donor liver function, hemodynamic stability, an alveolar-arterial gradient of < 150 mmHg, and no encephalopathy tended to do well with immediate extubation. Criteria that did not significantly affect extubation were age > 50, United Network for Organ Sharing status 2-4, intraoperative transfusion requirements, and coexisting diseases. That same year, Neelakanta *et al*[7] published a paper describing the immediate extubation of 18 patients after liver transplantation followed by ICU admission. There were no incidents of reintubation. When the extubation group was retrospectively compared to matched controls, no differences in outcomes were discovered. Plevak *et al*[8] reported that an integrated plan encompassing all levels of care for the first 48 h after liver transplant reduced the time to extubation and shortened ICU stays without the need to change personnel and intraoperative protocols.

Over the next several years, researchers continued to refine which criteria best predicted success with early extubation. As the popularity with early extubation grew, transplant programs developed internal protocols to streamline the perioperative process and the percentages of patients given the opportunity for early extubation increased. Experience bred confidence, which in turn lead to more early extubations, better outcomes and improved patient selection. Biancofiore showed an increase in the extubation rate from an initial rate of 19% to 82% over 5 years as the anesthesia team became more confident with the process[1]. Similarly, the overall trend had been an increase in rates reported in the published studies from the same time era. Starting with success rates of 18.7% in 2001, multiple studies now describe rates closer to 90% as of 2010[9-12]. Today many centers around the world participate in early extubation of liver transplant patients, some have even progressed to bypassing the ICU altogether[2,13]. For the purpose of this paper, the process of bypassing the ICU and going directly from the postoperative care unit to the surgical ward is termed "fast tracking".

ARGUMENTS FOR AND AGAINST FAST TRACK ANESTHESIA

Proponents and advocates of fast track anesthesia have raised several points to support their arguments (Table 2). Early investigators believed that prolonged intubation following complex surgeries, such as liver transplant, allowed the patients to adequately "recovery" from the stress of surgery. Additionally, this period theoretically allowed the physicians caring for the patient in the postoperative phase to adequately optimize hemodynamic and pulmonary parameters prior to extubation and ideally improve outcomes. Advocates for early extubation have argued that it may be beneficial for the new graft to limit the exposure to mechanical ventilation. Kaisers *et al*[14] reported the deleterious effects of positive end expiratory pressure (PEEP) on liver graft hemodynamics. They found that a PEEP of

Table 1 Early extubation in adult liver transplant recipients

Ref.	Patients (*n*)	Anesthesia	Criteria for extubation	Findings
Rossaint *et al*[5]	5/39	Fentanyl infusion, methohexital infusion, thiopental, pancuronium	"According to established criteria" but not clearly delineated	
Mandell *et al*[3]	University of Colorado: 16/67 early extubation; UCSF: 25/106 early extubation	Thiopental, succinylcholine, isoflurane or desflurane, fentanyl, lorazepam, doxacurium	Preoperative: UNOS status 3 or 4; No coexistent disease; Age < 50 yr; No Encephalopathy; Intraoperative: Good donor liver function; < 10 units of red blood cells administered; No vasoactive support at end of surgery; A-a gradient < 150 mmHg	University of Colorado: 0/16 reintubations; UCSF: 2/25 reintubations (hypoventilation/ respiratory failure)
Neelakanta *et al*[7]	35 total patients: 18 extubated in OR; 17 extubated in ICU	Midazolam, thiopental, succinylcholine, isoflurane, fentanyl, morphine, pancuronium	Good nutritional status, no significant cardiac or pulmonary disease, uneventful surgical course, < 3 units of red blood cells transfused, sign of early graft function, normothermia. Decision was made by anesthesiologist after consultation with surgeon	O reintubations for either group. No difference in ICU length of stay; Immediate extubation group had more respiratory acidosis on admission to ICU
Biancofiore *et al*[1]	365 total patients: Group A: 211 extubated in OR; Group B: 113 extubated < 24 h; Group C: 41 extubated > 24 h	Fentanyl, thiopental, cisatracurium, sevoflurane, remifentanil	Awake, following commands, clinical evidence of neuromuscular reversal, normocarbia, respiratory rate < 25, adequate oxygenation (pulse oximetry > 95% with FiO_2 < 0.5), hemodynamic stability	Group A: 2/211 reintubations (surgical bleeding, pneumonia); Group C: 4/41 reintubations (surgical bleeding, pneumonia, hepatic artery thrombosis). Non-invasive ventilation performed in 11/211 Group A and 6/113 in Group B
Glanemann *et al*[9]	546 total patients: Group 1: 102 extubated in OR; Group 2: 383 extubated < 24 h; Group 3: 61 extubated > 24 h	Fentanyl, methohexital, pancuronium	Hemodynamic stability, normothermia, tidal volume of 5-8 mL/kg, respiratory rate < 20/ min, adequate minute ventilation, positive gag reflex, awake and responsive	Group 1: 9/102 reintubated; Group 2: 50/383 reintubated; Group 3: 22/61 reintubated; Survival at 5 yr greatly reduced in Group 3 and in patients whom underwent reintubation. Liver graft reperfusion injury significantly influenced success and time to extubation
Skurzak *et al*[10]	652 total patients: 575 extubation in OR; 77 nonextubated patients	Varied: Isoflurane or sevoflurane, fentanyl, remifentanil, sufentanil, pancuronim, atracurium, cis-atracurium. Extubated in OR	Conventional criteria used to determine for extubation. Contraindications to early extubation: active bleeding with a need for abdominal packing, preoperative mechanical ventilation, grade 4 encephalopathy, graft dysfunction (acidosis, persistent coagulopathy, hemodynamic instability)	30/575 reintubations within 48 h (surgical interventions, oversedation, pulmonary failure, pulmonary edema, cerebral ischemia, hepatic/renal failure)
Mandell *et al*[2]	147 total patients: 111 extubated in OR; 23 no attempt at extubation; 13 failed to meet extubation criteria	Thiopental, succinylcholine, isoflurane or desflurane, fentanyl, lorazepam, doxacurium	Awake, following commands, positive gag reflex, tidal volumes > 8 mL/kg, respiratory rate < 20/min, normocarbia, adequate neuromuscular reversal, hemodynamic stability	2/111 reintubations within 48 (portal vein thrombosis, oversedation)

UNOS: United Network for Organ Sharing; ICU: Intensive care unit; UCSF: University of California San Francisco.

Table 2 Arguments for/against fast track anesthesia

Pro	Con
Improved graft blood flow	Need for recovery after surgical stress
Decreased complications from mechanical ventilation	Time to optimize cardiopulmonary parameters
Patient comfort	Chance of failed extubation
Less chest radiographs	Absence of large prospective studies showing benefit
Improved resource utilization	Chance of reoperation
Cost containment	

10 mbar significantly reduced cardiac index, SvO2 and widened the arteriovenous oxygen content difference when measured with a pulmonary artery catheter placed percutaneously into the hepatic veins. It has been hypothesized that this may be due to retrograde blood accumulation in the liver circulation due to an increased backpressure transmitted from the pulmonary circulation[15]. Several small animal studies lend support to these claims[16,17]. More recently, however, these findings have been challenged. Saner observed that PEEP values up to 10 mbar produced no significant

change in hepatic arterial and venous flow as measured by Doppler in deceased donor rescue liver transplant and living donor liver transplant recipients[15,18]. Holland *et al*[19], examined patients undergoing cardiac surgery and requiring mechanical ventilation postoperatively. His group found that a PEEP of 10 mbar did not influence the disappearance of indocyanine green, a flow dependent marker of liver function. Nonetheless, while there is controversy about the effect of ventilation on hepatic blood flow and graft function, there is strong evidence that unnecessary mechanical ventilation is associated with several complications, including muscle deconditioning, tracheal injury, and pulmonary infections, the incidence of which can be lessened with early extubation[3,20,21].

Early extubation and fast track anesthesia has been shown to decrease the total cost for hospitalization by either reducing the length of intensive care or bypassing the ICU completely[6,13,22]. Taner *et al*[13], showed a reduction in total room charges, as well as, a decrease in the amount of chest radiographs and arterial blood sampling. This translates to better resource utilization and may be beneficial in areas with limited resources and in environments where cost containment is important[12].

Early extubation is not without significant risk, especially when dealing with patients possessing significant comorbidities. In a review of 11 studies by Wu *et al*[12], reintubation rates ranged from 3% to 35%. A variety of reasons including respiratory insufficiency, pneumonia, and reoperations were cited as common reasons for reintubation. Glanemann found an 11.7% reintubation rate among patients extubated in the operating room *vs* a 36% rate in patient extubated in the ICU[9]. Additionally, they found a higher incidence of tracheostomy in the ICU group. In the study, patients with acute liver failure, retransplantation, Child C status, and complicated surgeries requiring more than 6 units of packed red blood cells had an increased risk for prolonged postoperative mechanical ventilation[9].

ANESTHESIA FOR FAST TRACK

Most early studies have employed a balanced anesthetic approach[1,6,7,9-11,23,24]. This typically consisted of thiopental or propofol combined with opioids at induction, followed by inhalational agents and narcotics for maintenance. Concern has been raised over the use of propofol infusions for liver transplantation based on the fact that concentrations appear to increase during the anhepatic phase[25,26]. This may result in unpredictable levels and interfere with the ability to ensure a rapid emergence. The use of bispectral index monitoring may help offset this side effect by preventing overdosage[27-29].

Isoflurane, desflurane, and sevoflurane have been used in studies evaluating early extubation. Dose requirements for both desflurane and isoflurane have been shown to decrease during the anhepatic phase[30,31]. Increasing Model for End-stage Liver Disease (MELD) score also appears to be inversely proportional to volatile agent requirements[30]. These findings necessitate careful titration of these agents in patients planning to undergo early extubation and fast track anesthesia to prevent prolonged emergence.

Most often, neuromuscular blockade is achieved with atracurium or cis-atracurium, however vecuronium, rocuronium, and pancuronium have all been employed in studies evaluating early extubation[12]. As vecuronium, rocuronium, and pancuronium utilize hepatic metabolism to variable degrees, caution should be used when these medications. Delayed and primary graft nonfunction may result in prolonged neuromuscular block. Neuromuscular monitoring is an absolute requirement to ensure adequate return of muscle strength prior to extubation.

Adequate postoperative pain control without respiratory depression is a key component to anesthesia for fast track candidates, therefore an astute understanding of analgesic pharmacology in the care of the liver transplant patients is important. Liver transplantation recipients have reported decreased perioperative opioid requirements when compared to patients without liver disease undergoing other types of major abdominal surgeries, as the majority of opioid metabolism is liver-dependent. The severity of the liver disease and the process of the transplantation itself may alter the effects of different pain medications[32-34]. For example, when comparing healthy living liver donors undergoing graft procurement to patients with liver cirrhosis from chronic hepatitis B or C infection or hepatocellular carcinoma undergoing hepatectomy, the latter showed significantly lower morphine requirement on postoperative day 1[32]. Additional studies have shown that morphine usage was significantly less in patients undergoing liver transplant than in other liver operations, especially during the first three postoperative days[35-37]. Proper dosage of medications is crucial in achieving both adequate intraoperative anesthetic depth and postoperative pain control while avoiding over-sedation which increases the risk of prolonged postoperative mechanical ventilation.

At our institution, approximately 60% of 150 yearly liver transplant patients undergo fast track anesthesia and bypass the ICU completely. We typically induce anesthesia with propofol, fentanyl, midazolam, and succinylcholine. After intubation, anesthesia is maintained with isoflurane, fentanyl, and cis-atracurium. We limit our fentanyl dosage to 1000 micrograms unless the patient is opioid tolerant. If additional opioids are needed, we limit them to incremental dosing of up to 250 mg fentanyl aliquots. Postoperatively, patient-controlled hydromorphone is administered to manage incisional pain. Bispectral index monitoring is typically not used and our average operative time is 238 min for a primary liver transplantation. At the time of transplant, 30% have a raw MELD of 21-30 and 20% have a MELD of 31-40. Prior to extubation every attempt to ensure adequate hemostasis is attempted by the surgeon and anesthesia team using real time thromboelastrography and careful examination of the surgical field. Transfusion goals are a stable hemoglobin of 8-10 mg/dL, an international normalization ratio of 1.5-2, a fibrinogen level greater that 170, and a platelet count of approximately 100.

We do not utilize set fast track criteria *per se*; rather all of the anesthesiologists base our determination on clinical experience after consultation with the operating surgeon. Typically redo transplants and patients requiring vasopressors or postoperative dialysis are admitted to the ICU after surgery. High volume transfusions are not an indication for ICU admission unless there is significant concomitant coagulopathy and a high likelihood of needing to transfuse more than 2 units of blood products per hour. Likewise, MELD score itself is not an indication for intensive care, although higher MELDs are more likely to be associated with significant comorbidities. We usually make our determination after graft reperfusion to give either the ICU or surgical ward time to prepare for the admission. On admission to the postoperative care unit, the anesthesia team evaluates relevant blood labs, an electrocardiogram, and a chest radiograph. After clearance from the anesthesia team, the patient is transferred to the surgical ward where the patient initially receives 1:1 nursing care for the first 24 h and further evaluation from the transplant hepatology team[13].

CONCLUSION

In summary, early extubation for large surgical cases started in cardiac surgery and is gaining popularity within the liver transplant anesthesia community. The practice of fast track anesthesia may decrease the incidence of pulmonary complications and improve graft function, and result in better resource management. As experience grows within our field, transplant teams have become better able to determine patients that can benefit from this practice[24]. Careful coordination and communication between the surgeons, anesthesiologists, and ward teams needs to be in place to ensure safe delivery of care.

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