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Review

Multimodal Pain Management of Liver Transplantation: What Is New?

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Abstract

Liver transplantation (LT) is a life-saving treatment representing the only viable option for patients suffering from end-stage liver disease (ESLD) or acute liver failure. Patients who undergo LT require a multidisciplinary approach to postoperative pain management. However, pain management in this context is often inadequately explored. Limited options exist for proper pain control in patients with hepatic failure, mainly due to the increased risk of kidney and multi-organ failure. In LT candidates, specific analgesics may elevate the risk of side effects, such as hepatic encephalopathy, acute renal failure, and gastrointestinal bleeding, consequently increasing overall morbidity and mortality. In the case of LT, the post-operative pain might be underestimated since the demand for analgesics is typically lower than other major abdominal surgeries. Consequently, there is a lack of studies addressing post-operative pain management. This review aims to outline current strategies for pain management in LT, with a particular focus on opioid-free approaches, and to introduce forthcoming developments in this field.

Keywords
Enhanced recovery after surgery; opioid-free anesthesia; model for end-stage liver disease

1. Introduction

Liver transplantation (LT) is a complex abdominal surgery characterized by extended duration and considerable surgical stress. The management of post-operative pain following LT should take into account factors such as the stage of liver cirrhosis, surgical technique, and the duration of the procedure [1]. Ensuring adequate pain control is crucial as it enhances patient comfort and facilitates early mobilization, ultimately contributing to a more rapid overall recovery. Also, respiratory independence is paramount for LT patients, as delayed weaning from mechanical ventilation can adversely impact outcomes [2]. The subcostal incision required for accessing the surgical site can lead to discomfort, especially during activities like deep breathing, coughing, and mobilization. Residual post-LT pain may be attributed to surgical retractors' extended surgical duration and pressure applied to the lower ribs [3]. Although there are limited reports regarding post-operative pain management following LT, the severity of pain is generally low, with some recipients requiring minimal analgesic intervention [4]. Managing pain in the context of LT can be challenging, particularly considering the risks of neuropathic pain syndromes and the potential for opioid withdrawal in transplant candidates with dependency issues [5]. Furthermore, pain management in patients with cirrhosis presents additional complexities due to the heightened risk of adverse events. Uncompensated liver disease, as observed in Acute on Chronic Liver Failure (ACLF) cases, may be associated with encephalopathy, portal hypertensive bleeding, and hepatorenal syndrome [6]. Some analgesics may produce undesirable effects, such as excessive sedation and renal dysfunction, due to altered drug metabolism in individuals with chronic liver disease and ACLF [5, 6]. A comprehensive understanding of the pharmacokinetics and pharmacodynamics of analgesic medications in severe liver disease is essential to achieve adequate analgesia while minimizing the risk of adverse outcomes. Changes in the distribution, metabolism, and elimination of pain medications can result in excessive sedation and prolonged mechanical ventilation. Despite the absence of randomized trials and established guidelines, ensuring adequate pain control post-LT remains a pivotal aspect of enhancing patient satisfaction, expediting post-operative recovery, and improving overall survival [7].

2. Materials and Methods

This review represents an expert opinion on pain management in the perioperative liver transplantation (LT) setting, conducted by the Transplant Anesthesia and Critical Care team at the University School of Medicine in Pisa. The Transplantation Unit in Pisa has performed an average of 150 LT procedures annually, with a cumulative total of 2787 LT procedures since 1996. This review aims to compare the outcomes of our unit with existing recommendations, with a specific focus on the approach to post-operative pain management and the pharmacological considerations for cirrhotic patients. No ethics committee approval was deemed necessary for this research.

3. Results

The perioperative management of transplant recipients has undergone recent changes. In the past, patients were often kept sedated and on mechanical ventilation for the initial twelve hours following liver transplantation (LT), a period when postoperative pain tended to be more intense. In contrast, our transplant unit now advocates for the early discontinuation of sedative medications and mechanical ventilation within the first six hours after LT. This shift underscores the importance of optimizing postoperative pain management. Such early recovery efforts align with the principles outlined in Enhanced Recovery After Surgery (ERAS) protocols, which have demonstrated potential benefits in improving postoperative outcomes [2]. Table 1 summarizes factors that may influence the analgesic requirements of patients affected by end-stage liver disease (ESLD) undergoing LT [2, 8].

Table 1 Factors that increase or decrease postoperative pain and analgesics demand.

Factors that increase postoperative pain and/or increase analgesics demand	Factors that reduce postoperative pain and/or decrease analgesics demand
"Mercedes-Benz" type incision	Renal failure decreases the excretion of opioid drugs
Extended surgical time	Nephrotoxicity from immunosuppressive agents
Hyperdynamic circulation in Liver cirrhosis increases the distribution and clearance of analgesic drugs	PNF\Delayed recovery of liver function after LT
Bleeding and transfusions	High levels of peripheral methionine-enkephalin
The neo-hepatic stage of LT: the metabolism of the analgesic drugs is higher	The anhepatic phase of LT: there is no metabolism of analgesic drugs
Methadone therapy before surgery	The severity of ESLD
Presence of chronic pain even before surgery	MELD score >20 and Child-Pugh C

ESLD: end-stage liver disease; PNF: primary non-function; MELD: Model for End-stage Liver Disease.

3.1 Management of Perioperative Analgesia

3.1.1 Postoperative Opioid Therapy Management

Managing patients with end-stage liver disease (ESLD) using opioid therapy during postoperative recovery can be complex. The use of opioid medications before liver transplantation (LT) represents a risk factor for readmission. It has been demonstrated that patients with a history of opioid abuse can benefit from early intervention to prevent relapse. One complication that may lead to re-hospitalization is the exacerbation of hepatic encephalopathy resulting from opioid administration. In the perioperative setting, opioids can slow the recovery of intestinal motility, reducing the effectiveness of treatments for encephalopathy [9]. The effects of many drugs that act on the central nervous system are modulated in ESLD patients due to altered pharmacodynamics. This alteration may be attributed to changes in the permeability of the blood-brain barrier and increased neurotransmission mediated by gamma-aminobutyric acid. Compared to patients without severe liver disease, those with high Model for End-Stage Liver Disease (MELD)

and Child-Pugh scores require lower analgesics doses to prevent hepatic encephalopathy worsening. In these patients, careful titration of opioid doses is essential [5]. Titration may also be influenced by delays in graft function and the achievement of steady-state opioid levels. In patients undergoing LT, there is an increase in plasma levels of methionine-enkephalin (ME), which leads to a reduced need for perioperative analgesics [8]. The higher ME concentration results from reduced hepatic degradation and biliary excretion of neuropeptides. In patients with ESLD, the decreased need for opioids is associated with increased plasma levels of endogenous opioid neuropeptides [10]. Furthermore, patients with high MELD scores (>20) required significantly less fentanyl while maintaining lower pain scores in the first three days after LT. Reduced demand for post-operative pain control was observed in fentanyl patient-controlled analgesia (PCA) with maximum doses <50 mcg/h [10]. Hypoalbuminemia is a common consequence of cirrhosis that affects the protein binding of many drugs, including opioids — reduced protein binding results in increased opioid bioavailability. When LT was performed without opioids during the pre-anhepatic and anhepatic phases, the need for inhalation anesthetics decreased with increasing severity of liver disease (MELD score >20) [11].

3.1.2 Alternative Strategies to Systemic Opioids

Impairment of liver function results in alteration in pharmacokinetics. Therefore, it is advisable to adopt a multimodal approach to pain management for LT. This approach includes the use of opioids, along with adjuvants such as ketamine, clonidine, acetaminophen, non-steroidal anti-inflammatory drugs (NSAID's), tramadol, and gabapentin. Additionally, locoregional analgesic techniques, such as epidural analgesia or truncal abdominal blocks like Transversus Abdominis Plane (TAP) blocks, have been described [3, 12-15].

3.2 Pharmacological Strategy

The possible pharmacological treatments alternative to the opioid medications already mentioned, include acetaminophen, NSAIDs, tramadol, gabapentin, pregabalin, and ketamine.

3.2.1 Acetaminophen

In patients with glutathione deficiencies, which can occur due to malnutrition, chronic disease, or alcoholism, the abuse of acetaminophen increases the risk of acute liver failure. Current recommendations suggest a maximum daily dose of 2-3 grams of acetaminophen. However, in patients affected by cirrhosis, doses ranging from 1 to 4 grams per day are generally well tolerated, even in cases with a history of alcohol abuse. Typically, acetaminophen is metabolized in the liver by CYP450 enzymes into an intermediate metabolite, which is subsequently conjugated with glutathione for elimination. Although the half-life of acetaminophen may be prolonged in cirrhotic patients, the content of CYP450 enzymes is not increased, and glutathione stores are usually adequate to prevent paracetamol hepatotoxicity. No substantial evidence indicates that acetaminophen significantly worsens liver failure in patients with end-stage liver disease (ESLD). Due to its established safety profile, absence of sedative effects, and lack of nephrotoxicity, acetaminophen remains a reasonable option for pain management in ESLD patients [5].

3.2.2 NSAIDs - Non-Steroidal Anti-Inflammatory Drugs

NSAIDs in major abdominal surgery are recommended to reduce opioid requirements and mitigate their associated adverse effects. NSAIDs undergo metabolism in the liver through oxidative and conjugative pathways, but it's essential to acknowledge their potential to cause liver failure through known immunological idiosyncrasies. Additionally, NSAIDs have antiplatelet activity, inhibit prostaglandin synthesis in the gastric mucosa, and can increase bleeding time. Furthermore, NSAIDs can potentially induce renal dysfunction due to factors such as hemodynamic compromise, dehydration, and immunosuppression. In patients affected by end-stage liver disease (ESLD), creatinine may not be an accurate renal failure marker. Therefore, careful consideration should be given to these medications, which can precipitate acute kidney injury (AKI) in patients with subclinical or unknown renal dysfunction [4, 12]. It is advisable to exercise caution or even refrain from using NSAIDs in liver transplant (LT) recipients.

3.2.3 Tramadol

Tramadol is an opioid that exerts its analgesic effects through central actions and spinal monoaminergic inhibition of pain. The inhibition of serotonin, norepinephrine, and monoaminergic reuptake further enhances these effects. Unlike some other opioid drugs, tramadol, at equi-analgesic doses, activates μ receptors to a lesser extent. This characteristic may result in reduced sedation, respiratory depression, and the potential for lower tolerance development. In patients with end-stage liver disease (ESLD), the analgesic effectiveness of tramadol may be less pronounced than expected due to the liver's conversion of tramadol into active metabolites via CYP2D6. Therefore, it is advisable to increase the interval between doses of oral tramadol when impaired liver function is present. For patients with a history of epilepsy, it's crucial to note that tramadol can lower the seizure threshold. Thus, it should not be combined with anticonvulsants, selective serotonin reuptake inhibitors, tricyclic antidepressants, or morphine to avoid the risk of serotonin syndrome [8]. Tramadol can effectively manage moderate postoperative pain, whether administered orally or intravenously. In the context of LT, unlike major abdominal surgery, tramadol may prove effective when given as boluses or as a continuous infusion. Combining tramadol with acetaminophen allows for a reduction in the tramadol dose and enhances analgesia while reducing the incidence of opioid-related adverse effects [4].

3.2.4 Gabapentin and Pregabalin

Gabapentin and pregabalin are typically prescribed for the management of painful neuropathies. These medications undergo minimal hepatic metabolism, exhibit low protein binding, and are excreted unchanged by the kidneys. Common side effects include sedation, dizziness, and edema [5]. In the context of liver transplantation (LT), a multimodal pain management approach combining gabapentin and acetaminophen has shown promise in reducing perioperative opioid usage [13].

3.2.5 Ketamine

Ketamine, an NMDA receptor antagonist, exerts its analgesic effects in a dose-dependent manner. One notable feature of ketamine is its ability to induce "dissociative anesthesia," which

may not necessarily result in a loss of consciousness but is characterized by amnesia and possible agitation or catatonia while preserving respiratory function. However, ketamine infusion in the intraoperative and post-operative LT setting may be associated with adverse effects, including fever and pulmonary hypertension [16]. Other reported adverse effects of ketamine include cerebral vasodilation, increased cerebral oxygen consumption, and elevated intracranial pressure at both high and low doses. It may be prudent to avoid the use of ketamine in cases of Acute or Chronic Liver Failure (ACLF) to mitigate the risk of brain edema and increased intracranial pressure [8].

3.3 Non Pharmacological Strategy

Alternative nonpharmacological strategies for pain management of LT are epidural analgesia and regional anesthesia.

3.3.1 Epidural Analgesia

Epidural analgesia is frequently impractical in patients with end-stage liver disease (ESLD) due to factors like thrombocytopenia, impaired coagulation factor synthesis, and shifts in perioperative coagulation balance. The utilization of the thoracic epidural approach remains a topic of debate, particularly as less invasive techniques can often suffice for managing moderate postoperative pain. However, it's important not to automatically rule out thoracic epidural analgesia (TEA) in these patients [4]. TEA can indeed be a viable option in LT recipients who do not exhibit severe hepatic coagulopathy. In a comprehensive study involving 327 patients who underwent TEA, no severe complications such as epidural hematoma or epidural abscess/infection were reported. Notably, the TEA group said lower pain scores during the first 5 days post-surgery [14]. In ESLD, the hemostatic balance can be unpredictable, given the simultaneous reduction of both pro- and anti-coagulant factors. Consequently, the prolonged International Normalized Ratio (INR) does not necessarily explain an increased bleeding risk. Further investigation is needed in these patients to establish validated thresholds for the safe application of neuraxial techniques in line with recommended published guidelines [17, 18].

3.3.2 TAP - Transversus Abdominis Plane - Block

TAP and other truncal blocks have shown opioid-sparing effects in major abdominal surgery, primarily when performed under ultrasound guidance [19]. Two key approaches are commonly employed: the classic and the subcostal techniques. The classic TAP technique is utilized mainly as part of multimodal analgesia for managing post-operative pain in lower abdominal surgery. It involves the injection of a local anesthetic into the fascial plane between the internal oblique and transverse abdominal muscles, where the thoracolumbar nerves extend from T6 to L1 before innervating the anterior abdominal wall. By interrupting the pain signals originating from the skin of the abdomen, subcutaneous tissue, and peritoneum through the separation of these layers, effective pain relief is achieved.

On the other hand, the subcostal TAP technique provides analgesia from dermatomes T7 to L1 and is often employed to manage pain in upper abdominal surgery [20]. In liver transplantation, subcostal TAP block has been associated with reduced morphine consumption, earlier withdrawal

from mechanical ventilation compared to opioid-only control groups, and decreased post-operative nausea and vomiting [20].

4. Discussion

The evaluation of the severity of ESLD is most commonly based on the MELD score. Advances in surgical techniques and ex vivo organ support have expanded the opportunities for transplantation, even for sicker patients with higher MELD scores [21]. In this context, providing customized analgesia is imperative. Mild to moderate pain is typical after LT and peaks on the second post-operative day. Implementing a fast-track post-operative pain control approach can enhance the quality of care, boost patient satisfaction, and reduce the length of hospital stays [7]. Given the unpredictable metabolism of drugs in patients with ESLD, LT necessitates multimodal pain management strategies. Employing opioid-sparing techniques has demonstrated efficacy in the post-transplant recovery of organ function. Among these techniques, locoregional approaches have shown promise, although their application has been limited and not sufficiently documented [22].

Nevertheless, locoregional techniques present excellent alternatives for achieving early recovery, particularly in ESLD patients without severe impairment, typically characterized by a MELD score of less than 20. Conversely, for individuals with severe ESLD and higher MELD scores, current evidence does not firmly support the benefits of locoregional analgesia strategies after LT. We conjecture that this group might benefit from a locoregional approach involving perifascial catheters or catheter blocks with continuous drug infusion, which could reduce the need for intravenous drugs. Additionally, alternative strategies such as wound infiltration of local anesthetic via catheter infusion, patient-controlled analgesia (PCA), and hand massage have successfully reduced opioid consumption compared to control groups [23].

5. Conclusions

We advocate for further clinical trials explicitly targeting pain control management in the LT cohort to enhance immediate postoperative recovery. The pain management of LT should be tailored individually, taking into account the severity of ESLD. We recommend prioritizing using locoregional techniques to minimize the pharmacological impact on the graft.

Abbreviations

LT	Liver Transplantation
ACLF	Acute on Chronic Liver Failure
ESLD	End-stage Liver Disease
ERAS	Enhanced Recovery After Surgery
ME	Methionine-Enkephalin
PCA	Patient Controlled Analgesia
PNF	Primary Non Function
MELD	Model for End stage Liver Disease
NSAID	Non-Steroidal Anti-Inflammatory Drugs
TAP	Transversus Abdominis Plane Block

AKI Acute Kidney Injury
TEA Thoracic Epidural Analgesia

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Author Contributions

Niccolò Castellani Nicolini and Jacopo Belfiore equally contribute to this work.

Competing Interests

The authors have declared that no competing interests exist.

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