

Opioid-Reducing Pain Management in Adult Liver Transplant Recipients

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ABSTRACT

Liver transplants are surgically and medically challenging in the perioperative timeframe. Liver transplant recipients often have multiple systemic illnesses and comorbidities that contribute to this complexity. Pain management in the perioperative period is one particular area that is challenging but being increasingly explored. With a growing emphasis on early extubation and worse outcomes associated with poor pain control, there is a need to identify and better understand which opioid-reducing pain regimens provide the best analgesia in liver transplant recipients. This has stirred new research on regional nerve blocks and other non-opioid pain medication regimens. Therefore, the purpose of this study is to provide a concise, analytical review of the progress being made in applying regional anesthesia, alternative medicine, and other opioid-reducing pain regimens to adult liver transplant recipients.

Keywords: Liver recipient; Perioperative pain, Liver transplant; Regional anesthesia; Opioid-reducing.

INTRODUCTION

The number of liver transplants performed per year continues to steadily increase both in the United States and globally. In 2021, a total of 9,234 adult and pediatric liver transplants were performed [1]. These patients have severe acute or chronic conditions including hepatitis C infection, alcoholic liver disease, cholestatic disease, hepatocellular carcinoma, and nonalcoholic fatty liver disease. Liver failure patients have many systemic and local pathophysiological changes that can manifest as hepatic encephalopathy, intracranial hypertension, thrombocytopenia, anemia, acute renal failure, pneumonia, pulmonary edema, and hyponatremia or other electrolyte abnormalities (Figure 1). These multisystem illnesses compounded with other patient comorbidities

makes management of liver transplant patients complex. Such complexity brings many challenges both surgically and medically in the perioperative period. One underappreciated aspect in particular that continues to be challenging for patients undergoing liver transplant surgery is optimizing perioperative pain control.

There are many reasons why pain management is unique in this population. For example, liver transplant patients often have altered levels of albumin, which binds to certain medications [2]. Low levels of albumin can result in increased levels of free medication and thus a higher risk of toxicity and adverse effects. Moreover, many analgesics are metabolized and/or excreted by the hepatobiliary system, and thus liver transplant patients have altered pharmacokinetics and

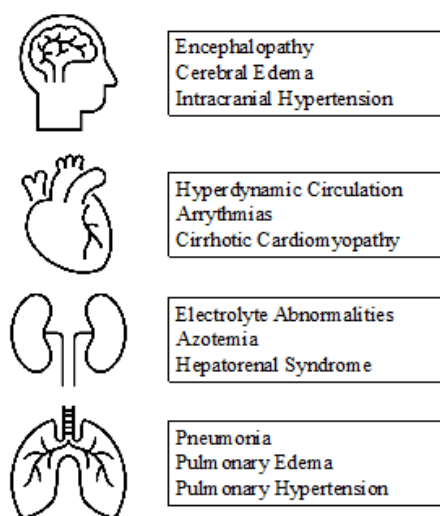


Figure 1: Systemic dysfunction in the setting of liver failure.



Figure 2: Opioid reducing pain management for liver transplant recipients.

pharmacodynamics for many medications. Furthermore, commonly used medications for perioperative pain control such as opioids, ibuprofen, and acetaminophen have many risks and limitations in patients with liver disease. For example, although opioids are not necessarily directly toxic to liver cells, pre-operative opioid use at the time of liver transplant has been found to be associated with mortality and graft loss [3], thereby leading to some practitioners’ hesitancy in prescribing opioid therapy. Likewise, non-steroidal anti-inflammatory drugs (NSAIDs) can cause idiosyncratic drug-induced liver injury [4]. Although uncommon, it can be severe enough to result in liver transplantation, warranting

awareness of its associated risks in liver transplant patients [5]. Additionally, acetaminophen can directly cause hepatotoxicity through its toxic metabolites that lead to oxidative stress and DNA damage. These risks are generally known in the medical field but are especially important in the liver transplant population in the settings of hepatic dysfunction and need for graft survival. Lastly, it is important to be aware that liver transplant recipients have such unique underlying pathophysiology and pharmacokinetics that several studies found that these patients often have less postoperative analgesia requirements compared to those undergoing open hepatic resection and other large

Author	Regional Anesthesia	Sample Size	Demographics (% Male)	Study Design	Block	Key Pain Findings
Assefi 2023	TAP	210	76.2%	Retrospective Before-And-After Study	Single Shot	Lower cumulative opioid consumption within 48h
Milan 2011	TAP	34	64.7%	Retrospective Cohort Study	Single Shot	Lower morphine consumption in TAPB No significant difference in pain scores
Hausken 2021	TEA	685	60.0%	Retrospective Cohort Study	Continuous	Low pain scores Low complications
Trzebicki 2010	TEA	67	49%	Retrospective Study	Continuous	Low rate of unsatisfactory analgesia No complications
Nair 2019	ESP	1	0%	Case Report	Continuous	Acceptable postoperative supplemental analgesia

TAP = transversus abdominis plane; TEA = thoracic epidural analgesia; ESP = erector spinae plane

Table 1: Regional Anesthesia in Adult Liver Transplant Recipients.

abdominal surgeries despite having a more extensive surgery [6-9]. These findings highlight the need for pain research that is focused specifically on isolated populations of liver transplant recipients.

Perioperative pain control for liver transplant recipients is important for a multitude of reasons. Effective pain control can enhance postoperative recovery in many ways, such as by accelerating the time to extubation, early mobilization, and oral intake. Early extubation is especially important as it has been shown to decrease costs, hospital length of stay,

pulmonary complications, and even mortality after liver transplantation [10-12]. Clinical protocols emphasizing adequate analgesia to promote early extubation have been developed and successfully implemented in practice [10]. Additionally, chronic postsurgical pain has been shown to be a risk factor for mortality after liver transplant [13]. Although several studies suggest that liver transplant recipients may have less postoperative pain compared to patients undergoing other major abdominal surgeries, the aforementioned studies highlight the need for physicians to prioritize effective perioperative analgesia in this patient population [6-8]. It is

necessary for physicians and other healthcare professionals taking care of liver transplant patients to be aware of the advances being made in opioid-avoidant pain management strategies for this population in order to provide the highest quality of care. Therefore, the purpose of this review is to concisely highlight research on regional analgesia and other opioid-reducing pain regimens for liver transplant recipients to inform physicians and guide future research (Figure 2).

REGIONAL ANESTHESIA FOR PAIN MANAGEMENT

Standard perioperative strategy typically involves frequent and large amounts of postoperative opioid use for pain management. This is often administered by intravenous patient-controlled analgesia (IV PCA) or IV pushes as needed. However, opioids carry a high risk for misuse, abuse, and dependency [14,15]. One study found that almost 15% of liver transplant recipients who did not use preoperative opioids and 43% of those who did use preoperative opioids had continued to use opioids one year after surgery [13]. Additionally, side effects such as vomiting, sedation, constipation, respiratory depression, and urinary retention are common and can negatively impact postoperative recovery. In order to help reduce opioid consumption, clinicians have been highly interested in using alternative analgesia methods such as regional nerve blocks. For liver transplant patients, blocks that are being explored and utilized are thoracic epidural analgesia (TEA), transversus abdominis plane (TAP) block, and the erector spinae plane (ESP) block (Table 1).

Epidural Block

Epidural analgesia, particularly TEA, is utilized for select patients undergoing liver transplant surgery. One of the major risks of epidural analgesia is a spinal epidural hematoma that forms from bleeding into the epidural space, which can result in neurological deficits and require surgery. Given the platelet and hemostatic abnormalities seen with hepatic dysfunction, there is a theoretically increased risk of a spinal epidural hematoma in liver transplant recipients [16,17]. Thus, in addition to the risks of an abscess, infection, and dural puncture, physicians are particularly cautious when using TEA in this patient population. Nonetheless, here we highlight the limited research examining its safety and/or efficacy in pain control for liver transplant recipients [18,19].

Hausken et al conducted a retrospective, single-center study evaluating TEA's safety and efficacy among adult liver transplant recipients [19]. The authors compared several outcomes between 327 patients who received TEA and 358

patients who did not. TEA was only offered to those without coagulopathy (INR < 1.5 and platelets > 100x10⁹/L). Most importantly, both groups had very low numeric rating scale (NRS) pain scores (median less than 2) postoperatively, demonstrating TEA's utility in pain control. Moreover, the TEA group had significantly lower rates of pneumonia, readmission to the ICU, and need for reintubation. However, non-TEA patients had significantly higher MELD scores and had a significantly higher percentage of patients who had an ICU stay before the liver transplant. This study demonstrates that TEA can be useful for pain control in select liver transplant recipients without severe coagulopathy [19].

An older study by Trzebicki et al assessed the safety of TEA in liver transplant recipients without severe coagulopathy, defined in the study as those with an INR < 1.5, PTT < 45, and platelets > 70 g/L [18]. In an analysis of 67 patients who received TEA, no patients developed an epidural hematoma, abscess, chronic back pain, or focal neurological deficits, although there were five patients who did not have satisfactory analgesia. The authors did not report pain scores or compare these outcomes to another treatment or control group. This study provided early evidence showing that TEA is feasible in liver transplant recipients without severe coagulopathy [18].

Transversus Abdominis Plane Block

The TAP block is a fascial plane block performed by injecting local anesthetic in the plane between the transversus abdominis and internal oblique muscles under ultrasound guidance. This targets the nerves derived from the anterior rami of thoracolumbar spinal nerves to provide postoperative analgesia. The most significant concern is the possibility of local anesthetic systemic toxicity due to the vascularity within this region and the volume of anesthetic used. As a fascial plane block, this concern is ameliorated with lower concentration local anesthetic than used for perineural blocks. Nevertheless, TAP blocks are technically easy to perform, relatively safe, and used as adjuncts to multimodal analgesic regimens. The safety and efficacy of TAP blocks is well-established for other large surgeries such as bariatric surgery, caesarean section, and hernia surgery [20-22]. However, only two studies have explored its utility in an isolated population of liver transplant recipients.

One of the earliest studies exploring TAP blocks for liver transplant recipients was published by Milan et al [23]. The authors conducted a pilot study comparing 17 patients who received bilateral subcostal TAP blocks (levobupivacaine) postoperatively with morphine patient-controlled analgesia

(PCA) and 17 patients who had only morphine PCA. The authors found that those that received TAP blocks with morphine PCA had significantly less total morphine consumption (45.9 mg) within 24 hours of surgery compared to controls (71.8 mg). However, there was no significant difference in pain scores between both groups. This study showed that TAP blocks may not change subjective pain scores, but they can meet the objective of reducing opioid consumption [23].

One of the most recent studies exploring TAP blocks for liver transplant recipients was published by Assefi et al [24]. The authors conducted a retrospective, before-and-after study using 210 patients, of which 78 received bilateral, single-shot subcostal TAP blocks and 132 did not receive a TAP block. The authors found that those that received TAP blocks had no complications related to the blocks and had significantly less cumulative opioid consumption (median oral morphine equivalent (OME) consumption 50 mg) within 48 hours of surgery compared to the non-TAP block group (median OME consumption 74 mg). However, there was no significant difference in pain scores between both groups. This study also confirmed that TAP blocks can help reduce opioid use [24].

Erector Spinae Plane Block

The ESP block is a fascial plane block that involves injection of local anesthetic between the tip of the transverse process of the thoracic or lumbar vertebra and the anterior fascia of the erector spinae muscles. The injected anesthetic acts on the dorsal and ventral rami of the spinal nerves to achieve a multi-dermatomal sensory block. It has primarily been used to provide analgesia for thoraco-abdominal procedures as it is a potentially safer alternative to epidural techniques [25]. This is largely because needle placement for ESP blocks does not pass the transverse process, making it more superficial and further away from the spinal cord and other major vascular structures, resulting in a lower risk of intrathecal injection, neurologic injury, and bleeding [26-28]. Moreover, the ESP block may be a promising alternative for postoperative pain management in liver transplant recipients, as it is easy to perform with minimal or no sedation.

To the best of our knowledge, only one study has reported on the use of ESP blocks for adult liver transplant recipients. Nair et al published a case series on the use of ESP blocks for major hepatopancreaticobiliary surgery, of which one 58-year-old female patient with autoimmune hepatitis underwent orthotopic liver transplant [29]. Following skin closure, their team placed bilateral ESP blocks. The authors

did not report specific pain scores but reported that the patient used an acceptable amount of supplemental analgesia for pain control throughout their postoperative course [29]. The positive results seen with this case warrant larger, well-designed studies.

There are two studies describing ESP blocks in pediatric liver transplant patients that we would like to raise awareness of due to the sparsity of literature in adult liver transplant recipients. The first study by Moore et al. described the successful use of continuous bilateral ESP blocks in two pediatric liver transplant cases: one in a 12-year-old male who had maple syrup urine disease and one in an 8-year-old male with glycogen storage disease type 1A [30]. The second study by Dewey et al is a retrospective cohort study of twenty-two patients that showed that ESP blocks are safe, lowered opioid requirements, and facilitated a fast return of bowel function [31]. As highlighted by the aforementioned studies, there is an imminent need to explore the safety and efficacy of ESP blocks in a large population of adult liver transplant recipients and to compare those outcomes to other regional analgesia methods.

Local Anesthetic Infusion

Lidocaine local anesthetic intravenous infusions have been performed for hepatobiliary and other abdominal surgery patient analgesia [32-34]. Their use is limited in the liver failure population as lidocaine and its metabolites are metabolized via hepatic metabolism. This can be toxic and fatal in the end-stage liver disease patient. However, a recent study showed that a continuous intraoperative infusion of lidocaine hydrochloride at 1 mg/kg/hr for adult patients undergoing open partial hepatectomy for liver donation that was stopped at the end of surgery does not result in unsafe lidocaine levels and could possibly be used more routinely in this population [35]. Further research is needed to consider the safety and efficacy of lidocaine infusions for select perioperative liver transplant recipients.

NON-CONVENTIONAL PAIN MANAGEMENT

As highlighted above, TEA, TAP blocks, and ESP blocks are being explored for their utility in pain control in liver transplant recipients. In addition to these blocks, other non-conventional options that could supplement or replace conventional opioid therapy are being explored.

For example, the use of a single preoperative dose of pregabalin for post-operative analgesia in liver transplant recipients was recently explored by Knorr et al [36]. The authors conducted a single-center, retrospective study that included 101 patients: 44

received a single dose of 150 mg of pregabalin before orthotopic liver transplantation (OLT) and 57 served as controls who received the standard of care. Preoperative pregabalin reduced opioid consumption by nearly 70% within the first 24 hours and by 54% within 24 to 72 hours post-OLT compared to controls. Additionally, a significantly greater proportion of patients in the pregabalin group reported their maximum level of pain as mild in the first 24 hours postoperatively. Overall, this study highlights that preoperative pregabalin can significantly reduce opioid consumption after OLT [36].

One study even explored the utility of hand massage as an adjunctive therapy for postoperative pain and anxiety management in liver transplant recipients [37]. The study consisted of 80 adult patients who had a liver transplant, of which 40 received a hand massage and 40 did not. The Visual Analog Scale (VAS) score was used as a measure of pain intensity and the State-Trait Anxiety Inventory (STAI) was used to assess anxiety. The authors found that both the average VAS score (pain) and average STAI-S score were significantly lower in the hand massage group compared to controls. Indicating that pain and anxiety levels can be decreased through hand massage after liver transplantation. This study shows that non-pharmaceutical alternatives such as hand massage could be clinically useful by providing postoperative pain and anxiety relief in liver transplant patients [37].

Another study explored the utility of a back massage twice a day for pain control after liver transplantation [38]. There were 84 patients included in the study with 42 receiving a back massage and the other 42 serving as controls. The authors found that the average VAS score was significantly higher in the control group compared to the back massage group. This shows that back massage is a unique alternative therapy that can help with postoperative pain control in liver transplant patients [38].

Additional alternative therapies, such as capsaicin cream and music therapy, have demonstrated pain relief in patients undergoing other surgeries and should also be explored further for liver transplant patients [39,40].

DISCUSSION

Pain management in liver transplant is challenging given the hepatobiliary abnormalities and systemic inflammation that results in altered pharmacokinetics and pharmacodynamics with an increased risk for complications. However, effective pain control is necessary in these patients to decrease postoperative

complications and costs and improve graft survival and patient satisfaction. Regional analgesia techniques and other opioid-reducing techniques have the potential to significantly improve pain management in this population while concomitantly reducing opioid use. There is a need to identify the best multimodal regimen for liver transplant recipients in the setting of coagulopathy, risks of infection, and ongoing encephalopathy concerns.

As described earlier in this review, good outcomes in pain control have been demonstrated using TAP blocks, ESP blocks, and TEA, with each technique having its own risks and benefits. There have been several studies comparing and contrasting these techniques in other abdominal surgeries [41-45]. Given the physiological, medical, and surgical differences from other abdominal surgery patients, there is a need to compare and contrast these techniques within the liver transplant recipient population to better understand which is most effective. To the best of our knowledge, there has been no published study comparing these techniques within liver transplant recipients. Even within the liver transplant donor literature, there has only been 1 published study comparing specific regional anesthesia techniques (TEA vs ESP) [46]. It is possible that certain blocks are better in certain sub-populations of liver transplant patients, which needs to be studied further. For example, there may be racial differences, gender differences, or age-stratified differences in pain outcomes based on the type of block utilized. Additionally, the influence of other variables on pain control such as incision technique and surgical approach needs to be explored. Likewise, differences in outcomes between single injection and continuous blocks need to be evaluated. Moreover, pain control in the preoperative setting needs to be more thoroughly researched, as preoperative opioid use has been shown to increase the risk of mortality following liver transplantation [47].

CONCLUSION

Nerve blocks, alternative medicine, and other opioid-reducing perioperative pain management techniques are continually being investigated for liver transplant recipients. Physicians should be aware of the promising outcomes demonstrated by these initial studies and consider integrating such techniques into their clinical practice. Further large-scale, standardized, preferably prospective, randomized controlled trials in patients undergoing liver transplant surgery are needed to ensure high quality evidence results in robust, standardized opioid-reducing pain protocols for liver transplant recipients.

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