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MINIREVIEWS

Analgesia after liver transplantation

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Abstract

This article addresses postoperative analgesia in patients with end-stage liver disease who have undergone liver transplantation (LT). Postoperative analgesia determines how patients perceive LT. Although important, this topic is underrepresented in the current literature. With an increased frequency of fast tracking in LT, efficient intra- and postoperative analgesia are undergoing changes. We herein review the current literature, compare the benefits and disadvantages of the therapeutic options, and make recommendations based on the current literature and clinical experience.

Key words: Liver transplant; Analgesia; Fast-track; Opioid; Postoperative

Core tip: Based on several papers published over the last two decades, there is a general assumption that pain following liver transplantation (LT) is less intense than pain following other major abdominal procedures and that the postoperative opioid consumption is lower than for other hepatobiliary procedures. There is also an assumption that patient-controlled opioid analgesia is the only mode of postoperative analgesia for this group of patients. In this paper, we challenged that opinion and addressed the specificity of postoperative pain intensity and treatment in LT patients. We also explored all options in pain control, in addition to patient-controlled analgesia, including epidural analgesia, transversus abdominis plane block and wound catheter infiltration.

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INTRODUCTION

Liver transplantation (LT) is a major surgery performed in very ill patients with end-stage liver disease. In terms of hemodynamic variations, fluid shift and replacement, metabolic derangements, bleeding tendency, duration, and potential complications, it is probably the most challenging abdominal operation. Although there is an abundance of material in the literature on LT and on

certain aspects of anesthesia, there are very few reports regarding postoperative analgesia following LT.

Based on several papers published over the last two decades, there seems to be a general assumption that pain following LT is less intense than pain following other major abdominal procedures and that consequently the postoperative opioid consumption is lower than for other hepatobiliary procedures[1-3]. There is also an assumption that patient-controlled opioid analgesia (PCA) is the only mode of postoperative analgesia for this group of patients. Improvements in perioperative care and fast tracking require changes in intra- and postoperative analgesia[4]. In this paper, we will address the specificity of postoperative pain intensity and treatment in LT. We will also explore all options in pain control.

SPECIFICITY OF PAIN INTENSITY FOLLOWING LT SURGERY

There is a general assumption among LT experts that postoperative pain is not so severe and that analgesia requirements are lower than for other major abdominal procedures; however, several factors have been identified as contributing to a high analgesia requirement following LT. First, the large "Mercedes-Benz incision" that is routinely used for LT is one of the longest and, consequently, most painful incisions[5]. The subcostal component of that incision is particularly painful during deep breaths, coughing, and movement. Second, the long surgical time, the use of surgical retractors, and the pressure applied to the lower ribs with the retractors contribute to an intensely painful sensation following surgery[6]. Third, the hyperdynamic circulation characteristics of end-stage liver disease are associated with a higher distribution clearance of analgesic medications administered intraoperatively[7]. Consequently, the intraoperative analgesia requirement is increased in patients with end-stage liver disease undergoing LT. Fourth, when massive blood loss and transfusion occur during surgery, there is a need for more analgesia simply because some analgesic drugs will be lost with blood loss. Fifth, when the newly transplanted liver is working, analgesic drug metabolism will be higher than that in the pretransplant state. Sixth, some patients undergoing LT experience chronic pain preoperatively. Consequently, management of postoperative pain is as complex as for any other patient with chronic pain. Finally, although less frequent, factors associated with a high analgesia requirement still exist, such as the fact that a small proportion of LT recipients are methadone-maintained and require significantly more intra- and postoperative analgesia[8].

There are also factors that might be expected to contribute to lower analgesia requirements following LT. First, patients with more severe end-stage liver disease generally require less analgesia[9]. Second, during the anhepatic phase, there is no analgesic drug metabolism and thus a decreased need for analgesic medication[10]. Third, when there is primary nonfunction of the transplanted liver or delayed recovery of liver function post-LT, analgesia requirements are decreased. In addition, renal impairment may prolong the action of morphine, in part due to slower excretion of the active metabolites of morphine[11].

Historically, patients undergoing LT were kept sedated and ventilated for at least 12 h, when the pain is the most intense. During that time, they were given generous continuous infusions of opioids that provided sufficient analgesia. When patients woke up, they had already passed the most painful postoperative phase. However, with recent fast tracking in up to 90% of patients undergoing LT, patients are awake within a couple of hours of LT, when postoperative pain is most intense[4].

INTENSITY OF PAIN: THE EVIDENCE

Pain intensity assessed by measuring pain

There are very little data in the literature about pain intensity following LT. No single study has focused on the intensity of postoperative pain. We could only extract data from a control group of a retrospective study on 16 patients who had received morphine PCA for postoperative analgesia, where patients were in the intensive care unit (ICU) and nurses recorded pain scores hourly[12]. The median pain score was 2/(0-3), equivalent to a visual analog scale (VAS) score of 7.5, at 24 h postsurgery[12]. These results were from a transplant center that intended to keep patients asleep for the shortest possible time and that had a track record of fast tracking 25% of patients[13]. This study showed high pain scores in first 24 h following LT. In contrast, another retrospective study by Chen *et al*[3] reported a mean VAS score of 3 on postoperative day 1 and < 3 on postoperative days 2 and 3 following LT.

Pain intensity assessed by opioid consumption

A few retrospective studies have assessed morphine consumption post-LT. One study comparing morphine requirements after liver resection *vs* morphine requirements after LT found slightly lower morphine consumption only on the first postoperative day in the LT group[2]. A small retrospective study of 16 patients who were fast-tracked and then monitored in the ICU revealed that the total amount of morphine consumption over 24 h was 71.8 ± 39.9 mg. Apart from the high morphine consumption, large variation in the morphine dosage was noted[12].

Intraoperative analgesia in LT

One of the many factors that can affect postoperative analgesia following LT surgery is intraoperative analgesia. The type of intraoperative analgesia used depends on the transplantation center or the individual anesthetist's preferences. According to the current literature, most use a continuous infusion or boluses

of fentanyl followed by remifentanil infusion[14]. A small proportion of LT recipients, approximately 10% to 24%, is eligible for intraoperative epidural analgesia[15].

Fentanyl is still the most commonly used intraoperative opioid. The amount of intraoperatively administered fentanyl varies largely from 0.11 μg/kg per minute in Moretti's study[2] to "not to exceed 10 μg/kg" in the Taner study[16] or 100 μg/h until 1 h before surgery in Biancifore's study[17]. Intraoperative fentanyl administration has been reduced for fast tracking post-LT: for example, from 50 μg/kg in the control and 20 μg/kg in the fast-track group[18], with the same analgesic effect.

In the past, a large dose of fentanyl administered intraoperatively delayed the initial request for postoperative analgesia. For example, in Eisenach's study[1], the first request for postoperative analgesia was 725 ± 267 min after the end of surgery. Their patients had 1695 ± 157 μg of fentanyl intraoperatively. When they measured plasma fentanyl levels postoperatively, it took 6 h for plasma fentanyl to be fully eliminated and become undetectable[1]. Such high intraoperative fentanyl administration could explain the low postoperative demand for analgesia in patients undergoing LT before the fast-tracking era.

Although the pharmacokinetic properties of remifentanil are suitable for fast tracking, only a small proportion of LT anesthetists use remifentanil intraoperatively[19]. Changes in anesthetic practices by reducing fentanyl dosing or replacing fentanyl with remifentanil has the potential to facilitate fast tracking following LT[19].

TYPES OF POSTOPERATIVE ANALGESIA FOLLOWING LT

Postoperative analgesia is multimodal, with opioid PCA (fentanyl, remifentanil, morphine, buprenorphine, tramadol, oxycodone) as the main component[20].

Ketamine and clonidine are sometimes used to enhance the opioid effects of PCA. Other components of multimodal analgesia include paracetamol, nonsteroidal anti-inflammatory drugs, and various other analgesics in the transitional period from PCA or epidural analgesia to regular or as-required analgesia. Other options that are rarely used include epidural analgesia or the transversus abdominis plane (TAP) block in addition to PCA[12].

Epidural analgesia and LT

Thoracic epidural analgesia (TEA) has been used as a mode of postoperative pain relief for LT in a select group of patients. It is not widely practiced because of the impaired hemostasis associated with end-stage liver disease and severe unpredictable intraoperative coagulopathy. TEA in LT may not be the technique of choice for routine administration of postoperative analgesia, but can be considered in patients who have normal coagulation profiles preoperatively. Safe conduct of TEA in LT involves anesthetic expertise and stringent monitoring in the postoperative period[6,15].

TAP block and LT

An ultrasound-guided subcostal TAP block can be used as a part of multimodal postoperative analgesia in patients undergoing LT. A retrospective study by Milan *et al*[12] showed a significantly lower 24-h morphine consumption when a TAP block was performed (46 ± 24 mg) than when a TAP block was not performed (72 ± 40 mg), as well as lower pain scores and median times to extubation.

Local anesthetic infiltration via wound catheter infusion

Although there are no reports on the application of wound catheter infiltration for postoperative analgesia in patients undergoing LT, there are some promising results in patients undergoing live donor and live resection. A recent prospective randomized study of 40 patients compared the quality of postoperative analgesia and its side effects when using local anesthetic-based analgesia (PainBuster) with the efficacy of opioid-based analgesia (intrathecal morphine with intravenous fentanyl) in liver donors. The researchers found more satisfactory analgesia with intrathecal opioids and fentanyl than with PainBuster during the first 12 h after surgery and comparable analgesia after that. The side effects were similar. Bowel recovery was faster with PainBuster[21].

Moreover, a recent meta-analysis showed that local anesthetic infiltration *via* wound catheters combined with PCA provided pain relief comparable to continuous epidural analgesia except for the first postoperative day. Both techniques were associated with a similar hospital stay duration, and opioid use with a wound catheter was associated with a lower complication rate[22].

DISCUSSION

There has been a general belief that patients undergoing LT require less postoperative analgesia than do patients undergoing "lesser" hepatobiliary surgery. Everyday practice, however, does not always support this belief. When we reviewed the literature, we found a few publications that had assessed opioid consumption rather than pain intensity[1-3]. Additionally, each publication included no more than 10 patients undergoing LT, and the studies were performed several decades ago[1-3].

Historically, patients undergoing LT received generous intraoperative analgesia with fentanyl. There is evidence that it takes at least 6 h for intraoperatively administered fentanyl to be eliminated from the bloodstream[1]. Additionally, patients were kept asleep for at least 12 h following LT, but sometimes they were kept asleep for days, particularly patients with acute liver failure. By the time the patients were awake, the most severe postoperative pain had resolved, and a significant

proportion of patients had no recollection of any pain or had low pain intensity. Additionally, pain control in sedated and ventilated patients was safe in terms of respiratory depression, which allowed the intensivist to be rather generous with opioid infusion because pain assessment in ventilated and sedated patients is not accurate.

With the relatively recent and expanding trend of fast tracking patients undergoing LT, management of the postoperative pain has changed. First, fast tracking requires a 60% reduction in intraoperative analgesia with fentanyl[18]. Second, intraoperative fentanyl infusion is stopped earlier, approximately 1 h before the end of surgery[18]. Although remifentanil, a shorter-acting synthetic opioid, was supposed to replace fentanyl for intraoperative analgesia, there is no confirmation that this is happening; indeed, more papers describe the intraoperative use of fentanyl than remifentanil[19]. The price of remifentanil for long surgical procedures and its known hyperanalgesic effects may be to blame for this[23].

When it comes to postoperative analgesic methods, little seems to have changed from morphine PCA[19]. There are now more options for PCA, including tramadol, buprenorphine, oxycodone, fentanyl, and, rarely and for short periods of time, remifentanil.

Epidural analgesia should not be ruled out as an option, but only about 10% of patients undergoing LT meet the criteria for normal preoperative clotting results[15]. Logistic issues, such as the lack of competent staff for following patients with epidural catheters, medico-legal issues, and anesthetists' reluctance, are likely the real reasons why epidural analgesia is not popular in LT. Although no publications have addressed epidural hematomas following epidural analgesia for LT, anesthetists have not been proactive in introducing the method for postoperative analgesia. Unknown metabolic pathways of local anesthetics in the anhepatic phase and in patients with deranged liver function are probably additional reasons for anesthetists' reluctance.

There is also modest experience with alternative techniques, such as the TAP block (a small retrospective study on 15 patients and 15 controls)[12] and wound catheter use in postoperative analgesia for LT (unpublished data), which is not likely to motivate LT anesthetists to apply these alternative techniques more often.

In conclusion, it seems that the time has come to reassess pain intensity following LT, the type and quantity of analgesics, and additions to opioid PCA analgesia as part of multimodal analgesia. There is also a need to explore regional anesthesia techniques for postoperative analgesia in patients undergoing LT.

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