An Update on Postoperative Analgesia Following Lung Transplantation

One challenging and controversial aspect of the perioperative management of patients undergoing lung transplantation is managing postoperative pain. Because the etiologies for transplantation, the patient populations, the surgical approaches, and the use of mechanical assistance either as extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB) are so diverse, it is difficult to standardize a regimen for treating postsurgical pain in these patients.

The etiology of pain in this population is multifactorial and includes the type of incision, with the anterior submammary thoracosternotomy, also known as the clamshell incision, being the most painful, followed by the posteriolateral thoracotomy incision, with the anterolateral thoracotomy incision being the least painful; the duration of surgery, leading to prolonged rib retraction and stretching of intercostal muscles; the manipulation of lungs and pleura; the insertion of large-bore thoracostomy tubes; and patient factors. The patients who present for lung transplantation are generally debilitated, coupled by anxiety that may cause them to perceive pain differently. Many have been prescribed long-term preoperative analgesics or sedatives, which can increase their tolerance to postoperative angesics. Craven et al. discovered that up to 21% of candidates awaiting lung transplantation developed a psychiatric disorder, and Scott et al. found that anxiety was a significant predictor of postoperative pain.

Providing adequate pain control is essential because inadequate postoperative analgesia prevents deep breathing and graft expansion, combined with an inadequate cough response and impaired mucociliary function due to airway denervation, which can result in the retention of pulmonary secretions, atelectasis, and airway closure, eventually resulting in hypoxemia, pneumonia, graft failure, and prolonged mechanical ventilation.

In addition to pulmonary complications, incomplete postoperative analgesia is associated with hemodynamic, immunologic, metabolic, and hemostatic alterations, as well as the activation of the autonomic and stress response systems, which may result in the development of myocardial ischemia or arrhythmias, increased pulmonary vascular resistance, and reduced renal and splanchnic blood flow, increasing intensive care unit (ICU) length of stay. In the long term, there is a causal relationship between the intensity of acute post-thoracotomy pain and the development of chronic post-thoracotomy pain syndrome.

The treatment of post-thoracotomy pain improves respiratory effort, reduces atelectasis and other pulmonary complications, and facilitates weaning from mechanical ventilation, resulting in a decreased ICU length of stay and improved patient satisfaction. Lung transplant patients who are extubated earlier have been found to have lower extravascular lung water, lower mean pulmonary arterial pressures, lower vasoressor requirements, and higher arterial to inspired oxygen ratios in contrast to lung transplant patients who are extubated later.

There are 3 main modalities to treat postoperative pain in these patients; they include the use of a multimodal approach with the use of systemic opioids combined with nonopioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory agents, thoracic epidural analgesia (TEA) with a local anesthetic and/or opioid infusion, and, more recently, paravertebral catheters, either placed percutaneously or directly into the paravertebral space by the surgeons while the chest is open. The gold standard of providing analgesia after lung transplantation is TEA, which provides pain control while avoiding the excessive sedation associated with parenteral opioids.

In this issue of the Journal of Cardiothoracic and Vascular Anesthesia, McLean et al assess the benefits of preoperative thoracic epidural placement for lung transplantation, as opposed to postoperative placement. The authors retrospectively reviewed the charts of 163 patients who underwent lung transplantation during the period between May 2012 and October 2015 to evaluate specific outcomes, including the incidence of postoperative delirium, measured as return to coherent function, opioid usage, length of mechanical ventilation, and ICU and hospital length of stay. The patients who had received a thoracic epidural catheter preoperatively were designated by the term "PreTE." These patients were chosen based on clinician preference and had no contraindications for epidural placement, and there was sufficient...
time to place the epidural before surgery. Preoperative epidurals were placed within 2 hours of the procedure and were not activated until the patient arrived in the ICU. In the group in which epidurals were not placed preoperatively, or the “NoPreTE” group, epidurals were placed when the patient was deemed hemodynamically stable with no signs of bleeding or coagulopathy, and had adequate oxygenation and a normal neurologic examination. Also included in the NoPreTE group were those patients who did not require TEA for pain control or who developed complications and did not qualify for an epidural placement. Exclusions from the study included patients requiring preoperative mechanical assistance, such as an intra-aortic balloon pump or ECMO, those who were anticoagulated, or those for whom there was inadequate information available to evaluate the patient. Because pain scores were not available in the electronic record, opioid requirements, measured as morphine equivalents, were used as a surrogate for adequacy of analgesia. The patients were weaned from mechanical ventilation using a standardized extubation protocol, and the time to achieve coherency after surgery was assessed using the standardized Confusion Assessment Method for the ICU once every shift or every 12 hours up to the first Confusion Assessment Method for the ICU negative assessment and was used to determine adequacy for extubation as well as discharge from the ICU to the floor.

Out of 163 patients, 8 were excluded, resulting in a study size of 155 patients. The authors included patients undergoing both single-lung transplantation (SLT) and double-lung transplantation. The patient demographics were similar in respect to age, diagnosis, and lung allocation scores. Double-lung transplantation was performed using a clamshell incision, and SLT was performed using a thoracotomy incision. The majority of cases were performed using CPB. The number of double-lung transplants was higher and the CPB times were longer in the NoPreTE group, suggesting that this group contained patients who were more critically ill than in the PreTE group.

In the primary analysis, out of the 155 patients remaining, 56 were in the PreTE group and 99 were in the NoPreTE group. In the NoPreTE group, 60 patients had epidurals placed within 24 hours after ICU admission, 23 had epidurals placed after 24 hours of ICU admission, 6 had epidurals placed after 24 hours (with the last epidural placed on postoperative day 14), and 10 patients did not require TEA. The epidurals were activated with an infusion of 0.1% bupivacaine at 10 mL/h within a mean time of 13.5 hours from admission to the ICU in the PreTE group and a mean time of 19.6 hours in the NoPreTE group. After 96 hours, 22 patients did not meet the extubation criteria set by the authors’ institution and were excluded from the secondary analysis. No neurologic or hematologic complications due to epidural placement were noted. The authors suggest that preoperative epidural insertion and early activation may reduce postoperative opioid requirements, the time to become coherent, the length of mechanical ventilation, and ICU and hospital lengths of stay, but after controlling for the type of lung transplant and length of time on CPB, the time to become coherent and the ICU and hospital length of stays were not statistically significantly different between the 2 groups.

The benefits of TEA in lung transplantation have been well documented. Not only does TEA allow for early extubation, but the use of TEA has been associated with a reduced incidence of pulmonary complications and a reduction in surgical stress, protecting the heart by decreasing myocardial oxygen demand and maintaining coronary perfusion pressure through its blockade of the sympathetic cardioaccelerator fibers. In this article, the authors attempt to determine the optimal timing of placement of TEA in patients undergoing lung transplantation to maximize patient outcomes. Because this was a retrospective study in a diverse patient population, the authors could not standardize the timing of epidural placement. Patients in the NoPreTE group did not get a preoperative epidural if the patient was deemed too ill during the pretransplantation evaluation to attempt placement, if there was not enough time to place one before induction, or if the anesthesiologist assigned to that transplant did not place preoperative epidurals as part of his or her practice. Despite these pitfalls, the authors have demonstrated improved outcomes with earlier placement and activation of TEA in a select group of patients, most of whom required anticoagulation for CPB, with no adverse events, including epidural hematoma. One of the main issues in inserting a preoperative epidural catheter is the risk of epidural hematoma formation in a patient who is likely to receive anticoagulation either for ECMO or CPB. In a study by Ho et al., a total of 4,583 patients received TEA and were heparinized. No patient developed a thoracic epidural hematoma, and from their findings they estimated a minimum risk of hematoma formation to be 1:150,000.

The main disadvantage of TEA is the nonstandardization of the medications in, and the dosages and rates of the infusions administered through, the epidural. Primarily local anesthetic-based infusions can result in hypotension, bradycardia, and muscle impairment from blockade of the intercostal muscles, and primarily opioid-based infusions can cause respiratory depression, urinary retention, constipation, and pruritus. Inadequate analgesia can occur when the sympathectomy from the local anesthetic is combined with fluid restriction, leading to a decrease in the infusion rate, a reduction in the concentration of the local anesthetic in the infusion, or a discontinuation of the epidural infusion altogether. The hypotension also limits the administration of adjunctive analgesics, such as nonsteroidal anti-inflammatory drugs, which have the potential to further impair renal and splanchnic perfusion.

Recently, the use of paravertebral catheters (PVCs) in patients undergoing lung transplantation has been evaluated. Paravertebral blocks have been associated with a lower risk of hypotension, pulmonary complications, nausea and vomiting, and urinary retention in patients undergoing nontransplant thoracotomies, and there are less contraindications for placing PVCs than epidural catheters. A recent Cochrane review evaluating PVCs and TEA concluded that PVCs were as effective as TEA for analgesia in open thoracic procedures, with a reduction in both major and minor complication rates.

An advantage of PVCs in lung transplantation is that for SLT, a PVC can be placed unilaterally, preserving the function of the contralateral intercostal nerves and muscles. Hutchins et al. prospectively evaluated the use of PVCs in patients undergoing lung transplantation for the management of post-transplant analgesia in a total of 35 patients undergoing
SLT and double-lung transplantation from October 2013 to December 2014. The PVCs were placed postoperatively under ultrasound guidance and were activated with a 0.2% ropivacaine infusion, and the patients were evaluated at 5 separate time points for a total of 120 hours. The outcomes assessed were pain scores, opioid usage, catheter-related adverse events (such as infectious and neurologic), and nausea and vomiting. The authors found that the median time for extubation was 543 minutes, the maximum pain score ranged between 5 and 7, and the minimum pain score ranged from 2 to 4 using the visual analog scale; there were no adverse events; and these results were similar to those seen with TEA. Lenz et al. retrospectively compared the outcomes of 44 lung transplant patients between 2005 and 2012 based on their type of postoperative pain regimen. Prior to 2009, postoperative pain was managed with either TEA or systemic opioids. After 2009, postoperative pain was managed by a surgically implanted PVC, attached to a ball containing local anesthetic. With a surgeon-placed PVC, bleeding complications are not a concern, catheterization is faster, and the failure rate is less than with TEA. The authors found that patients with PVCs were extubated more quickly (though that may be due to the addition of remifentanil in anesthetic management more than the presence of the block), had low reintubation rates similar to that with TEA, required less opioid administration than those patients in the systemic analgesic group but more than in the TEA group, and had no complications from the catheter insertion.

As the perioperative care of patients undergoing lung transplantation is advancing, the management of postoperative pain needs to advance as well. Although these studies seem promising, randomized controlled trials evaluating the timing and the type of regional anesthesia technique still are required to obtain the optimal analgesic regime to improve the outcomes in this population of critically ill patients.

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References