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Efficacy of Preemptive Multimodal Opioid-free Analgesia in Kidney Transplant Recipients

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Abstract

Chronic Kidney Disease (CKD), marked by a glomerular filtration rate (GFR) of less than 60 ml/min, is a progressive condition affecting over 10% of the global population. It is expected to be among the top five chronic diseases by 2040. As CKD advances to end-stage kidney disease (ESKD), with a GFR below 15 ml/min/1.73m², patients often require renal replacement therapies, such as dialysis or kidney transplantation. ESKD increases the risk of cardiovascular diseases, frequent hospitalizations and higher mortality.

Kidney transplantation is the primary long-term treatment for ESKD, with living donor transplants offering better outcomes due to reduced ischemia and lower complication rates compared to deceased donor transplants. Effective pain management is crucial following transplantation, as traditional opioid analgesics carry risks including respiratory depression and graft failure. Therefore, a multimodal approach integrating non-opioid and regional techniques is preferred.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally avoided in kidney transplant patients due to nephrotoxicity risks. Acetaminophen is commonly used, but it requires caution in those with liver conditions. Alternatives such as lidocaine and GABA analogues provide effective pain relief with fewer opioid needs. Regional anesthesia techniques, including neuraxial blocks and fascial blocks like the Transversus Abdominis Plane (TAP) and Quadratus Lumborum (QL) blocks, offer significant benefits in pain management.

Multimodal analgesia strategies, combining these methods, enhance pain control, promote early recovery and reduce opioid reliance, though ongoing research is needed to refine these approaches and optimize patients' outcomes in kidney transplantation.

Key Words: kidney transplant**;** multimodal analgesia; opioid-free analgesia.

Introduction

Chronic kidney disease (CKD) is defined as a glomerular filtration rate of less than 60ml/min. The condition is characterized by kidney damage, and persistent albuminuria that lasts for more than three months. It is a progressive disease that affects over 10% of the population and will become one of the most common non-transmissible chronic diseases worldwide (1). The World Health Organization predicts that chronic kidney disease will be the fifth most common chronic disease by 2040. Chronic kidney disease is one of the leading causes of death in today's world (2).

However, CKD is not only a health issue, but it also poses significant social and socio-economic challenges, particularly in developing countries. Risk factors for the occurrence of CKD are diabetes mellitus, hypertension, obesity and age. End-stage chronic kidney disease (ESKD) is the last stage of renal failure, defined as a glomerular filtration rate of 15ml/kg/ 1.73m2. As CKD gets worse at this stage, patients may need to use some of the available treatments to stay alive for a long time, such as renal replacement therapy, chronic dialysis (hemodialysis or peritoneal dialysis), or a kidney transplant. But this progression also entails a significant increase in the risk of cardiovascular diseases, frequent hospitalization and increased mortality. A Scottish study revealed that at least one comorbidity affected 98.2% of patients with CKD (3). Hypertension, heart failure, diabetes and coronary heart disease, are the most common conditions in CKD patients. Estimates indicate that cardiovascular disease contributes 20 times more to excess mortality than the general population, particularly in the last two decades. That is why it is essential to promptly identify CKD, monitor it, and with increased efforts, improve prevention and treatment measures.

The only long-term treatment option for end-stage CKD is kidney transplantation, and kidney transplant surgery rates are expected to increase in the coming decades. When possible, living donor kidney transplantation has several advantages, especially when performed as a preventive strategy. Recipients have a better quality of life and a lower risk of dialysis-related complications. It also tends to allow longer graft survival due to less chance of ischemia and a lower rejection rate.

Transplant centers are developing multidisciplinary approaches to optimize outcomes and minimize the potential risks associated with surgery and hospital stays. Surgical intervention causes tissue injury, pain and a stress response influenced by a combination of endocrine, metabolic and immunological factors. This protective mechanism is associated with the risk of postoperative organ dysfunction, prolonged hospital stays, increased morbidity and mortality. The surgical approach for kidney transplant surgery is an incision in the right iliac fossa, which extends from the pubic symphysis to the iliac bone. Recently, minimally invasive techniques such as mini-incision, laparoscopic, or robotic surgery have become popular for kidney transplants. Regardless of the approach, kidney transplantation is associated with moderate to severe postoperative pain, which requires effective management. Despite advances in surgical and anesthetic techniques, pain remains an important problem for patients undergoing kidney transplantation and represents a major challenge for anesthesiologists. People are worried about the choice of analgesics because the disease process, coagulopathy, and the risk of hypotension,

which affects graft perfusion, change the pharmacokinetics and pharmacodynamics of the drugs. Inadequate pain control is associated with anxiety, delirium and delayed healing. Kidney transplant patients often have multiple comorbidities that, when combined with poorly controlled pain, can lead to cardiovascular, hemodynamic and respiratory complications that in turn impact overall graft recovery and survival. Individuals with kidney disease or poor kidney function should limit their use of analgesics due to potential harm, changes in metabolism and distribution, or slower protein binding and clearance from the body. Pain management in kidney transplant recipients is essential. Based on the available studies, it is necessary to make recommendations and choose the best pain management strategy (4). In recent years, personalized and multimodal approaches have proven to be crucial in perioperative pain management. Using a multimodal approach, along with regional pain relief techniques, is the best way to solve the problem and get rid of pain without using opioids. This allows for early mobilization and the best possible outcome after surgery. Multimodal analgesia is an approach to pain management that involves the use of different drugs and techniques in order to minimize opioid analgesia. Opioids are the traditional and standard mainstay of therapy for treating surgical pain in the immediate postoperative period. But they have an unfavorable side effect profile that includes respiratory depression, nausea, postoperative ileus, sedation, and pruritus. Furthermore, patients who use high doses of opioids in the first year after transplantation have a higher rate of death and graft failure (5).

The implementation of a multimodal approach, including non-opioid therapy and regional techniques, results in a change in pain management in patients undergoing kidney transplantation (6).

Material and Methods

The main literature search revealed heterogeneity and precluded qualitative systematic reviews or research along Dixon's suggested lines (7). Additionally, Sandelowski's method for theoretical qualitative meta-synthesis was not applicable. A narrative evaluation was conducted for the reasons listed above.
All the data used to construct this paper was found using Medline, IBMS databases, Pubmed and CINAHL Keyword searches. Kidney transplant**,** multimodal analgesia, opioid-free analgesia, were among the search terms used. We also looked up primary article references from our original search. We looked through campus and personal libraries for materials related to the research topic.

Renal Transplant Recipients and Challenges in Analgesia

Opioids are one of the most commonly used groups of analgesics. Most of the research studies that looked at how opioids affected kidney transplant outcomes and success, found that higher

opioid use during kidney transplant greatly raises the risk of cardiac arrest, ventricular arrhythmias, changes in mental status, opioid dependence, higher death rates and graft loss (8). Patients with a glomerular filtration rate of less than 50ml/min/ in 1.73m2 also produce morphine-6 glucuronidase and morphine-3 glucuronidase metabolites, which can lead to nausea and vomiting after surgery, as well as unexpected sedation effects, involuntary myoclonus, and decreased breathing. Over a 20-years period in the late 1990s, researchers identified nearly 500,000 opioid overdose deaths. The problem continues, with over 100,000 deaths identified in 2021.

Despite many publications, there is still an absence of recommendations for opioid management in these key patient populations. It is unclear whether and what the direct impact of opioids is on transplant outcomes. Patient evaluation data and the impact of highly controlled chronic opioid exposure on transplant outcomes are scarce.

A systematic review and electronic searches of 25,190 records, including 63 in the survey, assessed the impact of opioid use on transplant outcomes in 19 publications, revealing that patients receiving opioid therapy prior to transplantation. Twenty studies examined opioid minimization strategies in kidney transplant recipients, while 24 studies examined pain management strategies in living donors. In the context of kidney transplant recipients, where careful application of analgesia is critical due to the challenges presented by kidney disease, a multimodal pain management strategy aims to address the complexity of pain, and the risks associated with overuse opioids in specific patient groups (9). Patients with chronic kidney disease are more specific, which increases the challenges faced by anesthesiologists in the application of multimodal analgesia protocols and could transform pain management methods. Furthermore, recent literature and the ERAS pathway highlight the efficacy of multimodal analgesia with minimal opioid analgesia, as well as the use and advancement of newer interfacial blocks (10). In addition to optimization of analgesia, ERAS protocols encourage early mobilization, nutrition, early removal of invasive venous and arterial lines, catheters, and reduced hospital stay. During renal transplant surgery, there are number of non-opioid pain relief methods that can be used alone or together to improve pain relief while lowering or eliminating opioid exposure. We have evaluated various interventions and methods of regional anesthesia applied or potentially applied in kidney transplant surgery. We have studied the benefits and adverse effects of each technique from the perspective of the CKD patient population, providing appropriate recommendations and evidence for their safe use.

Nonsteroidal Anti-inflammatory Drugs

It is found that nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors improve analgesia in many surgical patients. Preoperative administration of these drugs has been shown to reduce 24-hours opioid consumption, as well as postoperative nausea and vomiting. It is known that these chemicals can cause more acute kidney injury by narrowing afferent blood vessels and causing acute interstitial nephritis. This is because they stop

the enzyme cyclooxygenase from working and stop prostaglandins from being made. Because they stop the prostaglandin pathway from working, there is a chance of bleeding and kidney damage. Therefore, we recommend avoiding these drugs for kidney transplant recipients due to their potential for bleeding and nephrotoxicity. As a result, the simultaneous use of NSAIDs and CNIs in kidney transplant recipients can worsen IG-hemodynamics and cause graft dysfunction. Studies on the use of NSAIDs for pain management in kidney transplantation, however, are insufficient. Nefopam, a non-opioid, non-steroidal anti-inflammatory drug, complements patient-controlled analgesia (PCA) in renal transplantation. It significantly decreased pain intensity in the first 48 hours after surgery and decreased the number of cases of sleepiness and fentanyl use.

Acetaminophen

Multimodal analgesia protocols commonly incorporate acetaminophen (paracetamol) as a fundamental component. Several meta-analyses support this, showing that patients receiving IV paracetamol or propacetamol experienced 50% less pain during the first 4 hours. But patients with end-stage chronic kidney disease are at high risk of infectious blood-borne infections, and the prevalence of chronic hepatitis in this group of patients may be higher than in the general population, complicating the routine use of acetaminophen. Its action occurs by activating descending serotonergic inhibitory pathways in the CNS. Patients with chronic liver disease should reduce the total daily dose to 2 grams.

Lidocaine

Most of the transplant centers use lidocaine as an adjuvant to opioids or as part of multimodal analgesia due to its favorable renal safety profile, which limits mild to moderate pain. Authors Abdelatif and Ibrahim investigated the efficacy of intraoperative infusions of 2% lidocaine in reducing pain in renal transplant recipients. Infusion at a rate of 10ml/h contributed to a significant reduction in pain and fentanyl consumption, as well as the need for analgesia in the first 24 hours postoperatively. During its application, it is necessary to pay attention to possible signs and symptoms of local toxicity, perioral stiffness, metallic taste, tinnitus, dizziness and slurred speech.

GABA analogues

Multimodal analgesia approaches commonly use GABA analogues (gabapentin and pregabalin). Their mechanism of action is the inhibition of calcium channels in the brain, aimed at neuropathic pain. When using them, one should be cautious to avoid potential toxicity, myoclonus, altered mental status and respiratory depression.

Ketamine

It is an NMDA receptor antagonist that causes a dissociative state and analgesia. can lead to altered mental status, hallucinations and hemodynamic changes.

Neuraxial blocks (spinal, epidural, or combined)

These blocks, which have been in use for decades, offer numerous advantages, such as a notable decrease in pain, prompt mobilization, a decreased risk of deep vein thrombosis, early bowel motility mobilization, and a shorter hospital stay. They are also useful for kidney transplant pain control, like all major abdominal procedures. Neuraxial anesthesia techniques help keep the patient's blood pressure stable and protect the graft function more effectively in people with chronic kidney disease. However, the risk of hematoma formation rises dramatically when there is coagulopathy and platelet dysfunction, which can happen to people with chronic kidney disease. Epidural block with local anesthetic, with or without adjuvant, has the dual benefit of being an intraoperative anesthetic technique and an extension of postoperative pain control. Researchers have found that low doses of intrathecal morphine (ITM) effectively provide excellent pain control. In 2022, Ja. El et al. investigated the effects of intrathecally administered morphine on postoperative pain intensity, agitation and delirium, in 296 living donor kidney transplant recipients. They showed that risk factors such as age, smoking and psychotropic drugs have a greater impact than BMI, and they even demonstrated a protective effect. Additionally, it could aid in preventing bladder discomfort following surgery, a common occurrence in CKD patients following transplantation.

Fascial Blocks

Fascial blocks, a recent advancement in regional anesthesia techniques, offer a viable substitute for traditional methods like paravertebral, epidural, or spinal blocks. The primary target of fascial blocks is the deep fascia, a thick membrane of connective tissue that surrounds and encloses muscles, nerves and other structures, including mechanoreceptors and nerve fibers. These blocks prevent direct injection into the nerve or axon, reducing the risk of serious complications such as nerve injury and neuraxial hematoma. Thus, they represent a valid alternative option for high-risk patients. Despite their increasing use even in the context of high-risk operations, there are still no recommendations for their use and management in patients at risk of bleeding. The way local anesthetics work to relieve pain after fascial blocks is by effecting neurons in the area and an effect on the whole body through vascular absorption at faraway sites. Patients with coagulopathy can still benefit from their effective pain control and minimal risk of complications.

Transversus Abdominal Plane Block (TAP)

Renal transplantation has proven these block to be effective techniques for pain control, resulting in a significant reduction in IV opioids and analgesics. Its disadvantage is insufficient coverage of visceral pain and the proximal dermatome (T6-9). In 2001, Rafi first described it. During this block, we apply a local anesthetic in the plane between the internal oblique muscle and the transverse abdominal muscle, thereby blocking the sensorimotor innervations of the anterior abdominal wall, which is innervated by the front part of the spinal segment from T7-11. A catheter can be administered once or repeatedly. This block covers the laparotomy without intraperitoneal extension, eliminating the visceral pain component, making it ideal for kidney transplant recipients. K. Mukhtar et al. first investigated the efficacy of TAP block on renal transplant recipients. Pain, postoperative morphine requirements, nausea, vomiting and sedation were significantly lower in the TAP group. Researchers Jankovich et al., Parikh BK et al., Farag et al., Gopwani SR et al. and Sing et al., looked into continuous TAP block in people who had kidney transplants and found that they had a lot less nausea and vomiting after surgery, as well as less pain and the need for opioid painkillers. In the last two decades, TAP block has become one of the main components of ERAS protocols and multimodal analgesia, but its disadvantages include limited dermatome coverage from T10-L1, lack of visceral analgesia, possible systemic toxicity, colonic hematoma, liver laceration and infections.

Quadratus Lumborum Block (QLB)

Rafael Blanco, an anesthesiologist, first described the QLB block (Quadratus lumborum block) as a variant of the TAP block in 2007. A detailed description of the QLB block emerged much later. This procedure uses the QL muscle (QLM) and pain relief in the thoracolumbar fascia (TLF) as ultrasound landmarks. The thoracolumbar fascia is a tube-shaped connective tissue made up of layers of aponeurosis and fascia that wrap around the back muscles and connects the front of the abdomen to the lower back. We have not fully elucidated the actual mechanism of QLB's analgesia. It is likely that local anesthetics spread along the TLF, and the endothoracic fascia in the paravertebral space is partially responsible for the analgesia. TLF's anatomical-histological features, specifically the surface layer with a dense network of sympathetic neurons, explain an additional mechanism of action for local anesthetics. There are high- and low-threshold mechanoreceptors and pain receptors in the fascia that are sensitive to local anesthetics. These receptors' local anesthetic blockade partially explains QLB analgesia. The most often, it occurs at the level of T7-L1 dermatomes, but it can also spread to the cranial (T4-5) and caudal (L2-3) regions. Individual anatomical variations and the site of local anesthetic administration influence the height of the block. Sindwani, along with Rahendra R. and his team, conducted research. Al showed that QLB significantly reduced opioid consumption, sedation and pain intensity in kidney transplant recipients. This block has few complications, but like other regional anesthesia techniques, it can lead to systemic toxicity of local anesthetics, infections, femoral nerve block, and quadriceps weakness. In addition, this block is a "deep block" compared to other fascial blocks of the abdominal wall, with a higher risk of hematoma

formation, especially in patients with impaired coagulation and platelets. Most of the studies have shown that QLB variations are equal, and in some cases even superior to TAP block after kidney transplant surgery, primarily due to its ability to mask visceral pain (11). However, cited disadvantages include block variation and unpredictable dermatome coverage, which vary depending on the variant and application site.

Erector Spine Plane Block (ESPB)

ESPB (erector spine plane block) is a relatively new technique in regional anesthesia and pain management. Forero first described it in 2016. It has garnered significant attention and sparked debates regarding its mechanism of action. This block provides analgesia for somatic and visceral pain. The local anesthetic diffuses through the channels in the transverse connective tissues, allowing it to reach the ventral and dorsal planes of the thoracic spinal nerves, as well as the sympathetic communications at the level of the intervertebral foramen. Lateral cutaneous branches of the intercostal nerves are also involved, contributing to the block's analgesic effect. When performed at the T9-10 level, it provides analgesia without motor block in the abdominal-pelvic region. For the first time in 2019, Temirov and his colleagues described ESPB in a 36-years-old man undergoing a kidney transplant. In a series of 28 cases, Sharipova and her colleagues demonstrated lower pain, opioid consumption, and an incidence of nausea and vomiting. In 13 patients undergoing renal transplantation, Vishwanath et al. substituted epidural catheter placement with ESPB for postoperative pain management. Paolo Capuano et al. described ESPB in pediatric kidney transplantation for the first time (12). The multimodal approach with ESPB allows optimal pain control without the need for opioids, early mobilization, and rapid recovery of bowel function without constipation and vomiting. If anticoagulant therapy, including heparin, is necessary, ESPB has proven to be a safe and effective strategy without complications, even for patients at high risk of bleeding. Toscano et al. investigated the safety of fascial blocks, especially ESPB, in patients receiving anticoagulant therapy who had coagulopathy. Its location deep in the m. erector muscle plane and superficial to the transverse processes makes the ESPB unique. Compared to other regional anesthesia techniques, this positioning reduces potential risks. Compared to epidural analgesia and paravertebral block, ESPB's distance from major blood vessels and the spinal cord reduces the risk of hypotension and hematoma. The interforaminal spread and injection of the ESPB reduces the risk of pneumothorax compared to a paravertebral block. These anatomical advantages are of particular importance in patients receiving anticoagulant and antiplatelet therapy. Onaj et al. compared QLB and ESPB in open nephrectomy. Both approaches achieved similar results on opioid consumption and pain. QLB is considered a valid option for pain management during kidney surgery, but it has certain limitations in the field of kidney transplantation. First and foremost, QLB is a deeper block with a high risk of bleeding, and secondly, the placement of the ESPB catheter in the postoperative period is more comfortable and has less of an obstacle to early mobilization.

Conclusion

The implementation of a multimodal approach, including non-opioid therapy and regional techniques, has led to a change in the management of pain in patients undergoing kidney transplantation. It is a truly multidisciplinary endeavor that includes extensive pre-transplant evaluation, intensive care during hospitalization and long-term follow-up of the transplant program. Pain management in renal transplantation remains a major challenge despite increased support for opioid minimization protocols and the ERAS pathway. Despite the available literature and evidence on the benefits, safety and efficacy of a multimodal approach to pain management in renal transplantation, there is currently no established strategy or strong procedure-specific recommendations. Also, the studies show a difference in the drug dosage, method of administration, studied group, evaluation system and different time points for pain measurement. Furthermore, there are no studies on an effective acute pain management technique for patients undergoing minimally invasive kidney transplantation, including mini-incision, open, laparoscopic, or robot-assisted kidney transplantation. Current evidence supports that the approach to pain management should be individualized and multimodal. Intravenously administered paracetamol is a well-accepted analgesic by most authors as part of multimodal analgesia. Intrathecal morphine and epidural analgesia are suitable options, and the ERAS guidelines recommend fascial blocks as new safe techniques. Avoid nonsteroidal anti-inflammatory drugs due to the risk of bleeding and renal damage and minimize the use of intravenous opioids. Future studies should further evaluate the safety and efficacy of regional methods to formulate a protocol, construct an algorithm, and develop a strategy for pain management in kidney transplant recipients. We should simplify and individualize this approach, considering available resources, patient's preferences, and anesthetist's experiences.

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