

PAIN MANAGEMENT OF PATIENTS WITH CHRONIC KIDNEY DISEASE

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Pain is a complex uncomfortable sensation caused by a multitude of etiologic factors. It is divided into many different types, differing by the mechanism of origin and the presence of other subjective sensations related to pain. The phenomenon of pain is a subjective one, with various painful stimuli being described and felt differently among individual patients. Therefore, it is often hard to quantify and accurately measure. However, one thing is for certain, regardless of its etiology, type or place of origin, and it is that pain is a disabling condition affecting an individual's functional, social and biological status and should therefore be treated promptly and appropriately. Patients with chronic kidney disease (CKD), especially those with end stage renal disease, are often undertreated for pain, resulting in lower adherence to therapy and a higher incidence of anxiety and depression, ultimately leading to an overall lower quality of life. There are many factors included in the undertreatment of pain in this patient population, the main ones being inappropriate pain assessment and fear of prescribing pain medication due to renal function impairment affecting the pharmacokinetics of most commonly used analgesics. This review aims to educate all physicians working with CKD patients and provide an overview of the most commonly used pharmacological pain management strategies and their feasibility in treating this sensitive patient population, therefore hopefully making the current statistics of undertreated pain in CKD less grim than they currently are.

Key words: chronic kidney disease, end stage renal disease, opioid analgesics, pain management, quality of life

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INTRODUCTION

Chronic kidney disease (CKD) is a disease marked by persistence of structural and/or functional abnormalities of the kidney lasting for more than 3 months. While there are different methods of evaluating and quantifying the extent of functional and structural disorders, the finding most commonly used in grading and stratifying the disease in different stages of severity is the estimated glomerular filtration rate (eGFR). Using the eGFR, CKD is divided into five stages of severity, from G1 to G5 (1). Patients in the G5 group have an eGFR of less than 15 mL/min/1.73 m² (2) and are considered to have end stage renal disease (ESRD), necessitating renal replacement therapy by hemodialysis or renal transplantation. As the renal function

deteriorates in patients with CKD, especially in the G3-G5 stages, their capacity of metabolizing various medications is lowered, therefore necessitating special considerations in dosing those medications. This literature review will focus on pain management in patients with CKD and ESRD, with special emphasis on adequate dosing regimens and contraindications of various analgesic medications.

CHRONIC KIDNEY DISEASE AND PAIN

Pain in CKD patients is an often unrecognized and inadequately treated problem. It affects around 58% of patients with CKD, with about half of those experi-

encing pain rating it as moderate to severe (2). Also, in around 18% of the patients with pain, the pain is of multifactorial etiology (3), making it even more difficult to treat. While patients with CKD generally suffer from the same types of pain as the general population (musculoskeletal, neuropathic), patients with ESRD on hemodialysis suffer from pain coming from additional sources related to the procedures connected with hemodialysis, such as cannulation pain or pain caused by vascular access (3). Papers reviewing analgesic use and prescribing in patients with CKD show that despite the relatively high prevalence of pain as a symptom in this patient population, analgesic medication is often underprescribed or the less desirable therapeutic options (e.g., nonsteroidal anti-inflammatory drugs, NSAIDs) are chosen as the preferred treatment modality (4). Pain is not only a problem restricted to the patients themselves, but an issue with the ability to negatively affect treatment; ESRD patients with pain are more likely to experience irritability, insomnia, depression and decreased overall quality of life (5), which consequently lead to shortened or missed hemodialysis treatments and an increased rate of hospitalizations and emergency department visits (6).

The main causes of pain in CKD patients are related to their comorbidities, the primary renal disease itself, and the various complications of CKD (5). Among the comorbidities, the most common ones causing pain are peripheral vasculopathies and neuropathies, osteoarthritis, osteoporosis, malignancies, and ischemic heart disease. Some of the most common primary renal conditions causing pain are urinary tract infections, diabetic nephropathy, and vasculitis.

THE VARIOUS FACES OF PAIN – PAIN ETIOLOGIES AND TYPES PRESENT IN CKD PATIENTS

Pain is not a singular phenomenon, but rather a blanket term used to describe unpleasant sensations originating from various sources and caused by a plethora of different mechanisms at the micro- and macrocellular level. The following descriptions and reviews target the most common mechanisms and types of pain in CKD patients.

Renal-specific pain as a term describes the painful stimuli related primarily to the structure of the kidney. A notable example is pain in patients with autosomal dominant polycystic kidney disease, most often caused by infections or ruptures of cysts, or enlargement of the kidney itself and stretching the renal capsule (7). Other causes of renal-specific pain are dialysis-related amyloidosis (caused by deposition of β_2 amyloid

fibrils in articular and periarticular spaces, causing joint pain and limited movement in the joints) and calciphylaxis (caused by disbalance in the metabolism of calcium and phosphate, leading to vascular calcifications and subsequent ischemia) (8).

Musculoskeletal pain refers to pain caused by abnormalities in the musculoskeletal system. Several risk factors for this type of pain have been identified, with female sex, obesity, presence of comorbidities and aging being the most important ones. Muscle cramps affect 33%-85% of patients undergoing hemodialysis (9). Patients on hemodialysis are also at a greater risk of having restless leg syndrome, a disorder defined by a feeling of soreness in the legs and urge to move the legs, even during sleep. It is estimated that the prevalence of restless leg syndrome in hemodialysis patients is 2-3 times greater than in the general population (10).

Neuropathic pain is related to the abnormalities of the nerves, most commonly the peripheral ones, and can be ascribed to the two leading etiologic factors in CKD patients, i.e., diabetes mellitus (more precisely, its complication of peripheral diabetic nephropathy) and uremia (peripheral uremic nephropathy is present in more than 90% of CKD patients). These neuropathies are usually progressive and symmetric and most commonly start in lower extremities. Besides pain, peripheral neuropathies are also a contributing factor to the increased risk of pedal ulcerations and lower extremity amputations in CKD patients, together with coronary artery disease and peripheral artery disease (11). Peripheral artery disease can also cause a different type of painful sensation called ischemic pain.

Pain related to hemodialysis is a separate phenomenon caused by a variety of etiologic factors. One of the most common painful phenomena related to hemodialysis are headaches, affecting approximately 50% of patients and resolving within 72 hours of the most recent hemodialysis treatment session (12).

HOW TO ASSESS PAIN

In order to recognize and treat pain in CKD patients, various screening and measuring strategies must be utilized. While there are no specific questionnaires or inventories designed for evaluating pain in CKD patients, there are several widely used pain evaluation tools that can be applied to this patient population. Pain evaluation tools can be divided into one-dimensional, which measure only the intensity of pain, and multi-dimensional, which measure various functional, social and psychological aspects of pain. The most commonly used one-dimensional pain evaluation

tools are the numeric rating scale (NRS), which uses numbers from 0 to 10, with 0 signifying no pain and 10 signifying the worst pain imaginable, and the visual analog scale (VAS), which uses a 100-mm line to mark the intensity of pain, with 0 mm denoting no pain and 100 mm the worst pain imaginable. There is also the verbal rating scale, which uses five adjectives to describe pain (nonexistent, mild, moderate, severe and extreme) (13). Of the multi-dimensional pain evaluation tools, the brief pain inventory (BPI) and the McGill Pain Questionnaire (MPQ) are the most commonly used ones. In CKD patients, evaluating the quality of pain in addition to its intensity is of utmost importance, considering the prevalence of neuropathic pain. If neuropathic pain is suspected, one of the specially designed questionnaires for neuropathic pain evaluation can be used, with the most popular one being the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, which has a sensitivity of 82%-91% and specificity of 80%-94% (14). It should also be taken into consideration that patients experiencing pain are at a greater risk of developing depression, and proper screening for anxiety and depression should be conducted in CKD patients suffering from chronic pain. The Hospital Anxiety and Depression Scale (HADS) has been successfully used in CKD patients and has been shown as a reliable screening tool (15).

IDENTIFYING THE SOURCE OF THE PROBLEM

Despite the wide array of pain evaluation tools available, pain in CKD, as has already been stressed, is still often unrecognized and inadequately treated. There are several different problems that present a barrier to successful pain management. The first problem is inadequate assessment, which is caused by incomplete patient histories, inadequately detailed physical examinations, not using validated tools and questionnaires for evaluating pain, and not standardizing pain evaluation at a single institution in general. Pain should be assessed on every follow up visit or hemodialysis session. Another significant barrier is the fear of drug toxicity. It is well known that patients with CKD have altered metabolism of medications (16), with inappropriate dosing potentially causing either toxicity or inadequate analgesia. There are not enough data on the pharmacokinetics of analgesic medications in CKD patients, especially in those with ESRD, and more studies are necessary to provide physicians with increased confidence when prescribing and dosing analgesic agents. Also, a certain number of physicians still hold opinions that pain is an inevitable part of aging and disease, which has been refuted numerous times in the literature.

NONPHARMACOLOGICAL METHODS OF PAIN MANAGEMENT

Nonpharmacological methods of treating pain in CKD patients mostly include various physical medicine treatments. Cryotherapy can be used to reduce local inflammation and swelling, while thermotherapy can be used to alleviate muscle pain and relieve spasms. Transcutaneous electrical nerve stimulation (TENS) has been used in a variety of situations, especially in low back pain, where it has been shown to be more effective than placebo. Still, in conditions specifically related to hemodialysis and CKD, there are insufficient, if any, data to prove its effectiveness in reducing pain (17). Acupuncture has been evaluated in CKD patients, without any significant conclusions on its benefits or harms (18). Musical therapy has been shown to potentially reduce pain and anxiety during hemodialysis treatment sessions (19).

SOME CONSIDERATIONS RELATED TO PHARMACOLOGICAL TREATMENT OF PAIN

In CKD patients, there are several problems related to the pharmacokinetics of drugs; the metabolism, especially if the drug is metabolized by the kidney, can occur at a significantly lower rate if the kidney is damaged, potentially causing toxicity. Furthermore, hypoalbuminemia, often present in CKD, reduces the binding of drugs in the plasma, further increasing the 'free' fraction of the drug. Also, if the patient is undergoing hemodialysis, it means that a drug has to pass through a membrane in order to be removed from the body (20). There are two main dosing modification strategies in CKD, taking into consideration the impaired renal function. The first is interval-based, employed by increasing temporal interval between the two doses of a drug, while the dose itself remains unchanged. The second strategy is dose-based, lowering the doses of the drugs, while keeping temporal interval between the doses unchanged (21).

PHARMACOLOGICAL ANALGESIA – NON-OPIOIDS

One of the most commonly used non-opioid analgesics in general is paracetamol, which is also the most commonly used analgesic in CKD (22), being proven as effective in mild to moderate pain. In the general population, the maximum recommended daily dose of paracetamol is 4 g, taken in four 1-g doses with a 6-hour interval between the doses. In ESRD patients, it is recommended to increase the interval between doses to 8 hours (23), while several clinical studies have shown paracetamol to be effectively removed by hemodialysis (24).

Nonsteroidal anti-inflammatory drugs are often prescribed as analgesics in the general population. However, they are known to have cardiotoxic, gastronomic and nephrotoxic side effects. Furthermore, it is recommended to avoid NSAIDs for treating pain in patients with heart failure, arterial hypertension, and CKD. By inhibiting prostaglandin synthesis in the kidneys, NSAIDs indirectly cause afferent arteriolar vasoconstriction, reducing blood flow to the kidney and potentially causing acute kidney injury. They have also been shown to cause direct cytotoxicity and immune-mediated cell injury in the kidneys (25). Therefore, they should be avoided in both CKD and ESRD patients. Several clinical studies with NSAIDs were conducted in ESRD patients, but mostly with the primary goal of observing their pharmacokinetics in this patient population rather than evaluating their safety and efficacy in managing pain. Regarding the dosing, if an NSAID is indicated, it is recommended to use either naproxen (26) or indomethacin, as there are no dosing adjustments necessary in ESRD patients. Although avoiding NSAIDs is strongly recommended in patients with CKD, studies have shown that around 17% of CKD patients use NSAIDs more than several times a week. The indications for which NSAIDs are most commonly used in this population are headaches and musculoskeletal pain. Corresponding to the knowledge gained from basic science studies, the side effects of NSAIDs in CKD patients are serious and common; 40% of patients experience a decline in renal function, 37% develop peptic ulcer disease, and 18% notice oscillations in blood pressure and worsened blood pressure control (27).

When discussing non-opioid analgesic drugs, ketamine should also be mentioned and considered as a legitimate therapeutic option. Ketamine is an *N*-methyl-D-aspartate glutamate receptor antagonist with analgesic, sedative, dissociative and anesthetic properties, depending on the dose applied (28). For analgesia, doses of 0.1 mg/kg to 0.3 mg/kg are usually applied intravenously, combined with 100 mL of normal saline in a 30-minute infusion.

PHARMACOLOGICAL ANALGESIA – OPIOIDS

Although opioids are often used as the medications of choice in treating chronic pain, there is not much scientific evidence for adequate quality that would encourage their use in any chronic pain other than the one caused by malignancies. Systematic reviews have shown a moderate benefit in pain scores at most (29), which, taking into consideration the possible side effects of opioid treatment such as opioid-induced hyperalgesia and potential addiction, makes using them in any patient population, including CKD patients,

questionable at best. While there are a lot of para-medical factors related to opioid use (most notably the opioid crisis in the United States), these will not be further discussed here as this is a journal based in Europe, where access to opioids is strictly regulated in most countries and their use, in general, is several orders of magnitude less frequent than in the US. When opioids are prescribed to CKD patients, they are most often prescribed for musculoskeletal, neuropathic and post-traumatic pain. Opioid use in CKD patients is correlated to higher rates of mortality, hospitalization, and dialysis discontinuation (30). Regarding the choice of opioid agent, pharmacological studies have shown buprenorphine, methadone and fentanyl to be the safest for CKD and ESRD patients because of their pharmacokinetic properties (31). Fentanyl is a strong systemic opioid with a short half-life. It can be taken either as a transdermal patch lasting for 3 days or a rapid transmucosal formulation for acute pain in malignancy. Although it is deemed as a safer alternative to other opioids in CKD patients, it is still not recommended to any patients with severe renal, especially those on hemodialysis, as it binds with a strong affinity to plasma proteins and has a relatively large volume of distribution, making its elimination by dialysis less probable and more difficult. Buprenorphine is a full opioid agonist used mostly as a transdermal patch for analgesia. It is considered one of the safest opioids for CKD and ESRD patients, as only about 30% of it is eliminated through the kidneys. It is likely not cleared by hemodialysis, as it also has a large distribution volume and strong affinity for binding to plasma proteins. However, since most of it is metabolized and eliminated outside the kidneys, it is considered safe to use in ESRD patients in doses up to 70 mcg/h, without any need for dose adjustment based on renal function (32).

Methadone is known to be used both for treating chronic pain in patients with malignancies and for therapy of opioid addiction and withdrawal. Although it is metabolized by the liver and excreted mostly in stool, making it safe for CKD and ESRD patients, it requires dose reduction in ESRD patients due to its long half-life (33). Tramadol is going to be briefly discussed in the following section mostly due to its large availability in Europe and the low threshold that physicians have for describing it due to being a 'weak' opioid. Over 90% of tramadol is excreted by the kidneys after oral intake. In patients with moderate renal function impairment, its elimination half-life increases up to 2 times, which necessitates dosing correction and reduction even in non-ESRD patients (34). In ESRD patients, dosing needs to be strictly regulated and properly reduced, as it is estimated that less than 7% of tramadol and its metabolites are removed by hemodialysis. Therefore, it is recommended that CKD patients take a maximum of 100 mcg of tramadol *per os*

twice daily, or twice daily if they are on hemodialysis (35). Other opioids can be used in chronic pain caused by malignancies, however, all of them require specific dosing modifications and reductions and physicians should be aware of that fact when prescribing them.

PHARMACOLOGICAL ANALGESIA – NEUROPATHIC PAIN

Anticonvulsants are recommended as first-line therapy of neuropathic pain (36). Gabapentinoids are a subtype of anticonvulsants represented by gabapentin, which have a shared mechanism of action, i.e., they bind to the voltage-gated calcium channels on presynaptic neurons, inhibiting the entry of calcium ions into the neuron and therefore reducing neurotransmitter release. They are therefore especially useful in any disorders caused by inappropriate ectopic neuron discharge. Gabapentin is mostly excreted by the kidneys, therefore necessitating dosing modifications in patients with impaired renal function. However, it is also very dialyzable, owing to its weak affinity for binding to plasma proteins. The maximum daily dose for ESRD patients on hemodialysis is 300 mg, with the option of administering another dose of 200-300 mg after a hemodialysis session (37). Pregabalin, similarly to gabapentin, is also easily removed by hemodialysis, due to its low volume of distribution and basically nonexistent affinity for binding to plasma proteins. It is also excreted by the kidneys and therefore requires dosing modifications in patients with severe renal function impairment, with the maximum daily dose in patients on hemodialysis being 25-75 mg, depending on tolerability and occurrence of side effects (38). Aside from pain, gabapentinoids are also successfully used in the treatment of uremic pruritus in hemodialysis patients, with the recommended dose for that indication being 100 mg of gabapentin taken *per os* after a hemodialysis session (39).

Another type of drugs used in treating neuropathic pain are antidepressants, which act by increasing the potency and activity of the endogenous pain inhibitory pathways of the human nervous system by increasing the availability of excitatory neurotransmitters serotonin and norepinephrine in the synaptic cleft. The two classes of antidepressants shown to have the most pronounced effect on neuropathic pain are tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). However, they all have a wide array of possible side effects, with TCAs having anticholinergic, antihistaminic and anti- α 1 adrenergic action (40), while the SNRIs have significantly fewer side effects, but a high potential for toxicity in CKD patients due to their clearance being inversely proportional to the decline of renal function (41).

CONCLUSION

Pain is a complex phenomenon consisting of various etiologic entities. It is complex to understand, extremely variable and perceived subjectively. Therefore, it is difficult to properly treat in the general population, doubly so in the CKD patient population, where additional considerations must be kept in mind at all times due to a large number of analgesic drugs being metabolized or excreted really, with some of them having the potential to exacerbate the existing renal impairment. Still, adequate effort should be exerted in characterizing and evaluating a patient's pain, i.e., thorough patient history and physical examination should always be performed, and pain intensity and quality should be evaluated on a regular basis using validated, standardized forms and questionnaires. Nephrologists should be familiar with the various pharmacological modalities of pain management, their modes of action, side effects and pharmacokinetics, and should also include pain medicine specialists in the multidisciplinary treatment team. Treating pain does not only improve the patient's subjective impression, it also leads to the better overall quality of life, adherence to therapy, follow up visits and hemodialysis sessions, and reduces the rates of depression and anxiety among patients, thus indirectly improving other treatment outcomes.

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S A Ž E T A K

ZBRINJAVANJE BOLI PACIJENATA S KRONIČNOM BUBREŽNOM BOLESTI

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Bol je složen, neugodan, osjećajni fenomen uzrokovan brojnim etiološkim čimbenicima. Razlikujemo nekoliko različitih vrsta boli ovisno o mehanizmu nastanka i prisutnosti drugih subjektivnih fenomena. Doživljaj boli je subjektivan te se percepcija i intenzitet različitih bolnih podražaja individualno značajno razlikuju. Stoga je često teško kvantificirati i precizno mjeriti bol. Bez obzira na etiologiju, vrstu ili mjesto nastanka bol je onemogućavajuće stanje koje utječe na funkcionalni, društveni i biološki status te se stoga treba liječiti primjereno i pravodobno. Pacijenti s kroničnom bubrežnom bolešću (KBB), poglavito oni s bubrežnom bolešću krajnjeg stadija, često pate od neadekvatno liječene boli, što dovodi do nižeg pridržavanja terapije i veće učestalosti tjeskobe i depresije, što za posljedicu ima sveukupno značajno nižu kvalitetu života. Mnogi su čimbenici uključeni u nedovoljno liječenje boli, a najvažniji su neadekvatna procjena boli i strah od propisivanja analgetika zbog toga što poremećaj bubrežne funkcije utječe na farmakokinetičke osobine brojnih analgetika. Ovim preglednim člankom želimo naglasiti važnost kontrole boli kod pacijenata s KBB-om s obzirom na trenutno poražavajuću kontrolu boli te predstaviti najčešće korištene farmakološke modalitete liječenja boli i njihovu prikladnost u liječenju ove osjetljive populacije pacijenata, sve u svjetlu postizanja što više kvalitete života pacijenata s KBB-om prema odrednicama Svjetskog dana bubrega 2022. godine.

Ključne riječi: bubrežna bolest završnog stadija, kvaliteta života, kronična bubrežna bolest, opioidni analgetici, zbrinjavanje boli