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SYSTEMATIC REVIEW: PHARMACOLOGICAL MANAGEMENT OF CHRONIC KIDNEY DISEASE PATIENTS WITH NEUROPATHIC PAIN UNDER HAEMODIALYSIS

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Abstract: **Neuropathic pain is pain arising from a disease or lesion that affects the somatosensory system. In Indonesia, neuropathic pain is found in 31.6% with almost 75% of cases experiencing chronic pain and disrupting the patient's daily activities and quality of life. Neuropathic pain is an important comorbid factor in impaired renal function or chronic renal failure with hemodialysis. Objective to determine the pharmacological management of overall opioids use and the use of different types of opioids including acetaminophen, anti-inflammatory drugs (NSAIDs), adjuvants, and opioids in patients with chronic kidney disease under hemodialysis.Systematic review with inclusion and exclusion criteria through search engines obtained 114 journals that were reviewed. 8 journals were used as main references in writing this review. The data obtained are in the form of qualitative and quantitative data which are then arranged systematically and according to each topic discussed so that a conclusion is obtained that represents the entire content of the review. We observed that opioids such as morphine and codeine were associated with a significantly higher risk of altered mental status in patients receiving hemodialysis. There is no evidence that at equivalent analgesic efficacy weak opioids carry a lower risk of addiction than low-dose strong opioids. Safe opioid that are recommended such as transdermal fentanyl patch, methadone, buprenorphine are opioid groups which are said to be relatively safe. Gabapentin and pregabalin are the two most common anticonvulsants used and SNRIs are renally cleared except for duloxetine. Pharmacological management of neuropathic pain in chronic kidney disease with hemodialysis that can vary between type of opioids consumed and the effectiveness of the opioids used.**

Keywords: **neuropathic pain, chronic kidney disease, hemodialysis.**

1. INTRODUCTION

Pain is an unpleasant sensory and emotional experience due to tissue damage, both actual and potential. Pain is the most common reason why patients come to seek medical help. The feeling of pain is a warning that there is tissue damage it can provide a warning to avoid danger that can be life threatening. Based on the mechanism, pain divided into nociceptive pain, neuropathic pain, and mixed pain.[1] Neuropathic pain is pain arising from a disease or lesion affecting the somatosensory system. In simple terms, this type of pain occurs when nerves in the central nervous system are injured or damaged. Neuropathic pain may coexist with other types of pain such as nociceptive pain or pain due to damage to non-

nerve tissue (somatic or viscera). Generally, neuropathic pain will be chronic with moderate to severe pain intensity, so it will interfere with the patient's daily activities and quality of life.[2]

Neuropathic pain is suspected if there are spontaneous pain symptoms such as a feeling of jerking, needling, slicing, burning, tearing, cold, electrocution, or tingling sensation. Neuropathic pain is one of the manifestations of peripheral neuropathy in addition to a significant reduction in touch, vibration, leg proprioception, and the presence of kinesthesias. The onset of these symptoms is due to the presence of lesions on nerve cells in the form of apoptosis and inhibition of nerve regeneration. The pathomechanism that underlies the emergence of neuropathic pain is thought to be reflected in the symptoms and signs it causes, which serve as guidelines for determining more rational pain therapy. Neuropathic pain is an important comorbidity factor in several diseases, one of which is in patients with impaired renal function or chronic renal failure.[3]

Renal failure is a clinical condition characterized by irreversible decline in renal function to a degree and requires renal replacement therapy, which remains in the form of hemodialysis or kidney transplantation. Kidney Disease Outcome Quality Initiative (KDOQI) recommend initiation of hemodialysis if there are conditions such as extracellular fluid overload that is difficult to control and / or hypertension, hyperkalemia, metabolic acidosis, hyperphosphatemia, anemia, decreased functional capacity or quality of life without a clear cause, weight loss or malnutrition, and neurological disorders, pleurisy or pericarditis. Healthy kidney tissue will take over the tasks and work of diseased kidney tissue. When the structure of the damaged kidney tissue reaches 77-85%, the compensatory power is no longer sufficient, resulting in uremia syndrome or a buildup of substances that cannot be excreted by the diseased kidney. Symptoms of uremia syndrome in the neurological system include apathy, depression, precoma, and neuropathic pain.[4]

The prevalence of neuropathic pain that has been reported in several countries has varied greatly from 0.8% to 17.9%. Since many chronic pain conditions are classified as neuropathic pain, the prevalence varies according to the specific situation. Research in the city of Bandung, Indonesia shows the prevalence of diagnosed cases of neuropathic pain is 31.6%, with most of the patients showing moderate to severe pain intensity and nearly 75% of cases experiencing chronic pain.[3] In addition, there were studies conducted in 13 major cities in Indonesia to collect data on the clinical characteristics of neuropathic pain patients. A higher prevalence of neuropathic pain was reported in patients aged 41 to 60 years, more in men, and in respondents with low educational levels.[5]

Seeing how important neuropathic pain affects the quality of public health and there is not much research data in Indonesia, the authors are interested in raising the topic of pharmacological management of neuropathic pain in chronic renal failure patients with hemodialysis management. This research is expected to be the basis for the development of further analytical research.

2. MATERIALS AND METHODS

Protocol and Registration

A comprehensive summary in the form of a systematic review regarding the pharmacological recommendation on neuropathic pain in chronic kidney disease under hemodialysis. The protocols used in this study are The Center for Review and Dissemination and The Joanna Briggs Institute Guideline as a guide in evaluating the quality of the collected studies. Systematic review assessment uses the PRISMA checklist to determine the completion of studies that have been found and adjusted to the objectives set.[6]

Eligibility Criteria

The strategy used in finding articles is the PICOS framework which consists of:

1. Population is the population or problem that will be analyzed based on this systematic review topic.
2. Intervention is an action in the form of therapy given to cases in accordance with this systematic review topic.
3. Comparation is another action or intervention that is used as a comparison. If none of these are applicable, the control group in the selected study is used.
4. Outcome is the result or outcome obtained in previous studies in accordance with the topic of this systematic review.
5. Study design is a research design used by selected articles for further review.

Further description of the PICOS framework used in this systematic review can be seen in table 1

Table 1: PICOS framework criteria for systematic review the characteristics of neuropathic pain in chronic kidney disease under hemodialysis

PICOS *framework*	Inclusion Criteria	Exclusion Criteria
Population	A study of chronic kidney disease stage 5 with hemodialysis >> 18 years old	A study with a population that is kidney disease but not under hemodialysis (CKD under stage 3 and 4, acute kidney injury) <<18 years old Acute pain or pain related to dialysis
Intervention	Studies evaluating treatment interventions in the form of opioid for neuropathic pain and its complementary (anticonvulsant used, acetaminophen used, NSAIDs used)	There were no exclusion criteria
Comparison	The comparison intervention groups used were non-opioid for neuropathic pain and apart form its complementary	There were no exclusion criteria
Outcome	Studies that describe the pharmacological use to be observed	Studies that do not address the pharmacological use to be observed
Study design	Randomized control trial, original research	Case control, animal studies, literature review

In addition, the eligibility criteria are also used through the publication year of the articles used, namely 2010-2020 as inclusion criteria with national and international journals.

Information Sources

Literature searches conducted during October 2020 to January 2021 against literature obtained from previous researchers or secondary data in the form of national and international journals using the database such as PubMed, Science Direct, and Google Scholar.

Literature Tracing Strategy

Literature search is carried out by keywords and using filters in the form of MeSH (Medical Subject Headings) and text words so that it can make it easier to find the literature to be used. The filters used were: neuropathic pain, chronic kidney disease OR CKD, and hemodialysis.

Study Selection

Based on the results of a literature search through the database that was previously mentioned using keywords and filters, 114 articles were obtained. Furthermore, a selection was carried out in the form of screening based on the title and abstract so that there were 29 articles. A total of 29 articles were then analyzed thoroughly using inclusion and exclusion criteria so that there were 8 articles that could be used in this systematic review.

Data Collection Process

The checklist sheet obtained from PRISMA was used by researchers to evaluate the literature used and extract data from articles which were then typed according to the thesis guide. Furthermore, the data collection process carried out is as follows:

1. Use of guides in the form of The Center for Review and Dissemination and the Joanna Briggs Institute and the PRISMA Checklist.

2. Use of keywords and filters in the form of MeSH to find literature in the database

3. Determination of the database used in this study is PubMed and Google Scholar

4. The determination of the eligibility criteria is carried out using the PICOS framework and criteria in the form of inclusion and exclusion.

5. The study selection process was carried out by reading the entire article according to the PRISMA flow.

6. Taking into account the possibility of bias results with the JBI Critical appraisal, then the appropriate article will be analyzed and synthesized in this systematic review.

Types of Data and Variables

Based on the topics used in this systematic review, it should have data on several variables as follows:

1. Research characteristics data in the form of the type of study used, location, research year, number of patients, hemodialysis duration, age

2. The type of intervention used as therapy.

3. Limitations faced by researchers in conducting analysis or research processes.

Risk Assessment of Bias in Individual Studies

The risk assessment can be carried out using the JBI Critical Appraisal in analyzing the methodology used by the study that will be used in the preparation of this systematic review. A critical appraisal (CA) was conducted to assess a study as having a score of at least 50% meeting the CA criteria. The risk of bias in this systematic review uses an evaluation of research methods in each study consisting of:

1. Theory: the explanation in the form of a theory presented is inappropriate, out of date, and lacks credibility

2. Design and research instruments: designs that do not fit the research objectives and instruments that are invalid or reliable

3. Variables: unsuitable research that do not address the characteristic to be observed

4. Analysis: use of the type of analysis that is not in accordance with the standards of analysis

Summary Measures

The intervention given regarding the pharmacological management of neuropathic pain in the population of kidney disease under hemodialysis was the main variable evaluated in this systematic review. The results of the literature search used were based on JBI CA and PRISMA which were then presented in the form of characteristics, neuropathic pain treatment, and result of the study based on the interventions that had been given.

Synthesis of Results

The result synthesis used in this systematic review is a descriptive method, namely an explanation in the form of a narrative description in describing the results obtained. The narrative explanation used aims to gather evidence about the pharmacological management of neuropathic pain in chronic kidney disease under haemodialysis and develop a coherent and systematic textual narrative. The data were evaluated by review questions namely background, theoretical framework, research objectives, research content, research design, sample size, sampling method, sample description, validity and reliability, instruments used, statistical analysis, and analysis of results.

Additional Analysis

The analysis used in this systematic review is descriptive analysis by narrating the findings of scientific articles. This study did not use any other additional analysis techniques, the researcher only summarized the results in the literature then analyzed descriptively with a description in the form of a narrative explanation.

3. RESULTS

Literature Selection

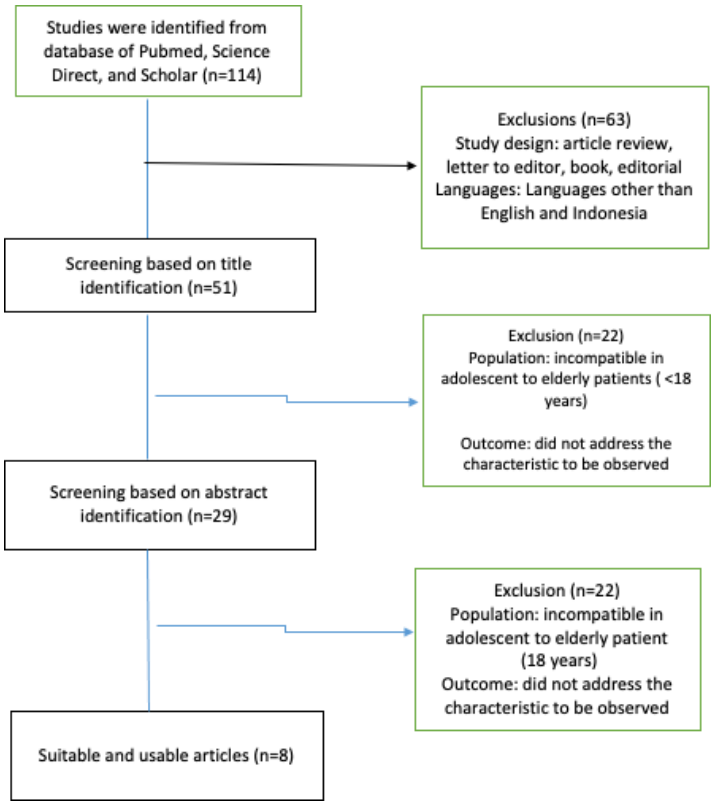

Figure 1: Literature Search Flow Diagram Characteristics Of Neuropathic Pain In Chronic Kidney Disease Under Haemodialysis

Study Characteristic

The characteristics of the articles used are 8 study articles (table 1) taken from the period 2010 to 2020. The population in the study of the articles used in this systematic review is a population originating from 6 countries. The number of patients varied with the duration of hemodialysis from 6 months to 42 months. Patient ages ranged from 18 years to 90 years (adolescents to elderly).

Table 2: Characteristic of Study Used

Reference	Drug	Location	Year Research	Duration of hemodialysis (mean)	Total Patients	Age	Results
Han et al. (2015)	High dose 100 and 500mcg/hr of transdermal fentanyl patches	Amerika	2012	>24 months	191	18-80 years old	fentanyl patch may be a safe option in individuals on HD while requiring long acting opioids for pain control
Heleniak et al. (2017)	NSAIDs	Poland	2014	NR	84	18-55 years old	Patients with CKD often takes NSAIDs especially people undergoing hemodialysis

Toth et al. (2010)		Canada	2005-2008	12 months	146	18-70 years old	The results of this open-label assessment of PGB substitution for GBP suggest that PGB may provide additional pain relief and possible improvement in quality of life above that received by GBP use in patients with NeP
Kimmel et al. (2016)	Opioids	Amerika	2010	NR	153.758	20-65 years old	opioid drug prescription is associated with increased risk of death dialysis discontinuation and hospitalization in dialysis patients
Ishida et al. (2016)	Opioids	Amerika	2011	NR	140899	18-65 years old	Opioids were associated with adverse outcomes inpatients on hemodialysis, and this risk was present even at lower dosing
Otsuki et at (2016)	Pregabalin	Jepang	2014-2015	> 6months	35	20-85 years old	Pregabalin can be effective treatment for peripheral neuropathic pain in patients under hemodialysis
Tessa et al. (2019)	Opioids, Nsaid	Amerika	2008-2017	NR	46246	21-54 years old	prescription opioids was associated with a higher risk of death and hospitalization compared with other pain medications, particularly with higher doses and at lower eGFR
Ka Man et al (2019)	NSAIDs	Taiwan	1998-2013	1998	3383	18-80 years old	NSAID use was associated with an increased risk of mortality in the patients with end-stage renal disease

Based on the table above, opioids as stated from 3 articles shows that prescription of opioids has a higher risk of death and hospitalization compare to other pain medications. There are 2 articles stated about the pregabalin are safe and one article about the safety of the transdermal fentanyl pathches. The other two articles refer about the risk of Nsaids and how people take NSAID for pain relieve.

Risk of Bias from Entire Study

The risk of bias from the review results on several research articles can occur so it is necessary to identify it so that there is no cross-study bias. In the articles that were selected for analysis, most of the studies were cross-sectional and prospective cohorts, some articles found the risk of bias such as some characteristics, for example, the patient's educational level was limited to patient admission and could not be fully confirmed, or the characteristics of deep pain location. Several studies were assessed using a questionnaire so that they are prone to information bias. In addition, other confounding variables are also not well paid attention to, and the solutions for these confounding variables are not explained so that they will participate and influence the research results.

4. DISCUSSION

Summary of Evidence

This systematic review is a summary of the outcomes for pharmacology management in chronic kidney disease patients with neuropathic pain under hemodialysis. This review discusses about the risk and safety of opioids and other medications used by hemodialysis patients who suffers with pain. In addition, the results of data collection from several studies indicate that the most commonly used treatments for neuropathic pain include anticonvulsants, anti-inflammatory, anti-depressant and analgesics (opioids).

Neuropathic pain in patients with chronic renal failure or better known as uremic neuropathy is a distal symmetric sensorimotor polyneuropathy caused by uremic toxins and usually affecting the lower limbs. The severity of the neuropathic pain correlates strongly with the severity and insufficiency of the kidneys. The mechanism of neuropathic pain in patients with chronic renal failure is unclear, but is associated with length-dependent axonal degradation and loss of focal myelin sheath. This condition is considered to be a demyelinating process leading to axonal degeneration involving the posterior column spine. Accumulation of uremic toxins such as guanidine, myoinositol, and parathyroid hormone associated with free radical activity or oxidative stress causes motor, sensory and autonomic nerve damage which has implications for uremic neuropathy.[7]

These neurotoxic compounds deplete the energy supply in the axons by inhibiting nerve fiber enzymes which are required for the maintenance of energy production. Although all parts of the nerve will be equally affected by a toxic attack, the long axons will degenerate first because the longer the axons the greater the metabolic load the pericaryon will bear. Lack of energy in axons will greatly affect Ranvier's nodes because these nodes require more energy for impulse conduction and axonal transport. In toxic neuropathy, damage to the tip of the axon is more severe or in the distal aspect of the neuron and can result from metabolic failure of the pericaryon. Lack of energy in the axons may be very influential on Ranvier's nodes, because these nodes require more energy for impulse conduction and axonal transport. The re-supply of enzymes from the nerve bodies may not meet the demand for growing axons, causing a critical decrease in the distal area leading to local energy blocks and pathological changes.[8]

Nielsen theorizes that uremic neuropathy is associated with impaired nerve axon membrane function and inhibition of ATPase which activates Na + / K + by toxic factors in uremic serum. Membrane dysfunction occurs in the perineurium which serves as a diffusion barrier between interstitial fluid and nerves, or in the endoneurium which acts as a barrier between blood and nerves. As a result, uremic toxins can enter the endoneural space at one site and cause direct nerve damage as well as changes in water and electrolytes to either expansion or retraction of the surrounding space.[9] There is also a hypothesis which states the role of electrolytes in this process. Hyperkalemia and hyperphosphatemia lead to chronic uremic depolarization of nerves. This occurs because potassium disrupts the normal ionic gradient and activates the calcium-mediated axonal death process. Studies investigating the nature of the axonal membrane by measuring nerve excitability in chronic renal failure patients before, during and after hemodialysis have shown motor and sensory axons in patients with uremic neuropathy depolarize before dialysis, and hyperkalemia which is primarily responsible for uremic depolarization contributing to the development of uremic neuropathy.[10]

During recent decades, hemodialysis has proved to be a succesful life sustaining therapy, and its effectiveness is judged largely by patient survival. Although hemodialysis therapy sustains life, underlying systemic disease, such painful syndromes, and neuropathies sometimes persist. The earliest symptoms usually reflect sensory dysfunction, resulting in paraesthesia, pain, and numbness mainly confined to the lower limbs, characteristically exhibiting a pattern of distal ‘‘stocking’’ sensory loss.[11]

Providing treatment in the form of opioids based on available epidemiological data states that most drugs in this category cause worsening and an increased risk of complications, especially in patients on hemodialysis. A previous study of 150,000 patients in the United States who underwent hemodialysis with prolonged opioid therapy for neuropathic pain showed associations with mortality, dialysis discontinuity, and in-hospital care.[12] Recommendations that are given consistently suggest not to use morphine and codeine, which will be metabolized by the body and produce active metabolites that accumulate so that it can impose kidney performance, especially in chronic renal failure which aggravates the patient's condition.[13] We observed that opioids were associated with a significantly higher risk of altered mental status, fall, and fracture in patients receiving haemodialysis, even at lower dosing and for agents recommended by guidelines. There is no evidence that at equivalent analgesic efficacy weak opioids carry a lower risk of addiction than low-dose strong opioids.[13,14,15]

However, there are safe opioids that are recommended such as fentanyl and methadone are opioid groups which are said to be relatively safe, this is because these drugs are converted into inactive metabolites but still need monitoring by health practitioners in their handling. Transdermal fentanyl patch (fentanyl citrate) was a safe option on hemodialysis patient with a long-acting opioid for pain control by different studies.[16] Besides fentanyl citrate, there is buprenorphine which is also safe in severe renal dysfunction without dose adjustment make it well suited for chronic pain management in elderly and kidney impaired individuals including those requiring HD. Buprenorphine is a potent semisynthetic opioid. It is a partial m receptor agonist and a k receptor antagonist. Different studies also have stated that fentanyl, methadone, and buprenorphine may be potentially useful opioids which have stable analgesic affect during hemodialysis.[17]

The American Society of Nephrology recommended that all patient with hypertension, heart failure or CKD including hemodialysis patients to avoid using NSAID, in their ‘Choosing Wisely” campaign published in 2012. NSAID have been shown to negatively impact residual renal function and dialysis patient thus dialysis patient can be a greater risk of harm from NSAID use.[18] In a different research, the results showed that the use of diclofenac, celecoxib, and etoricoxib were associated with a higher risk of mortality.[19] The American Geriatric Society recommends that the chronic use of all oral NSAIDs, including high-dose aspirin be avoided, especially in the elderly, 75 years.[20]

The two most commonly used anticonvulsants are gabapentin and pregabalin, which bind to the alpha -2-delta subunit of voltage gated calcium channels, resulting in an increase of gamma-aminobutyric acid (GABA) without direct activity on GABA itself. Dosing in CKD is reduced based on creatinine clearance to avoid dangerous accumulation by affecting glomerular blood flow, filtration rate, tubular secretion and reabsorption, and renal bioactivation and metabolism. Once a patient with ESRD begins HD, supplemental doses are recommended following each dialysis session as both gabapentin and pregabalin are readily dialyzed.[18,21] As a whole, all SNRIs are renally cleared and have associated dosing adjustment in CKD but it is said that duloxetine should be avoided in patients with creatinine clearance <30 mL/min, primarily due to a 2-fold higher area under the curve in those with ESRD.[18]

Limitation

Based on the research, the dominant cross sectional study has limitations on the limited research sample. This was followed by a prospective cohort study which had limited follow-up and follow-up to assess definite characteristics. This systematic review found the risk of bias as a limitation of various studies. The biases found from this study include selection bias and information bias. In addition, the risk of bias can also be found from the literature search due to the limited number of studies regarding the pharmacology management chronic kidney disease patients with neuropathic pain under haemodialysis.

5. CONCLUSION

Based on the results and discussion, it can be concluded as follows:

1. Analgesics play an important role in pain management but they should not be the sole focus of treatment, especiallyfor patients with chronic pain where the somatosensory component of the pain tends to assume greater importance

2. The pharmacologic management of pain for patients with CKD with hemodialysis requires careful selection of analgesics with close attention to efficacy and safety,

6. RECOMMENDATION

Suggestions that can be given through this paper are the need for counseling and providing further information to health workers and health services regarding neuropathic pain in chronic kidney failure patients with hemodialysis management so that they can choose the right treatment according to pain management and avoid various side effects which may result from inadequate or exaggerated to optimize safe and effective management of pain for our patients.

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