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Usage of Nonsteroidal Anti-inflammatory Drugs in individuals with Chronic Renal Illness

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Introduction

The use of non-steroidal anti-inflammatory drugs (NSAIDs) among individuals with chronic renal illness is a topic of significant clinical concern. Chronic kidney disease (CKD) affects millions of people worldwide, and the management of pain and inflammation in these patients often leads to the consideration of NSAIDs. However, the renal implications of NSAID use necessitate careful evaluation.

NSAIDs are commonly used for their analgesic and anti-inflammatory properties, but they can pose serious risks to kidney function, particularly in patients with pre-existing renal impairment. The mechanism by which NSAIDs affect renal function primarily involves the inhibition of cyclooxygenase (COX) enzymes, which are crucial for the production of prostaglandins that help maintain renal blood flow and glomerular filtration rate (GFR) [Perkovic et al.,2019]. In individuals with CKD, the reliance on these prostaglandins for renal hemodynamics is heightened, making them more susceptible to NSAID-induced nephrotoxicity [Perkovic et al.,2013].

Despite the recommendations for avoiding NSAIDs in CKD patients, studies indicate that a notable percentage of individuals with varying stages of CKD continue to use these medications. For instance, a study analyzing data from the National Health and Nutrition Examination Survey (NHANES) found that approximately 5% of individuals with moderate to severe CKD reported current NSAID use [Perkovic et al.,2019]. This raises concerns about the awareness of CKD patients regarding the risks associated with NSAID use and the potential for adverse renal outcomes, including acute kidney injury and progression of CKD [McCullough et al.,2012]

Furthermore, the interaction of NSAIDs with other commonly prescribed medications for CKD, such as diuretics and antihypertensives, can exacerbate renal impairment, highlighting the need for healthcare providers to closely monitor NSAID use in this population [Perkovic et al.,2011]. The balance between managing pain effectively and safeguarding renal function is a critical consideration in the treatment of patients with chronic renal illness.

While NSAIDs are widely used for pain management, their use in individuals with chronic renal illness requires careful consideration of the associated risks. Increased awareness and education about the potential nephrotoxic effects of these medications are essential for both patients and healthcare providers to ensure safe and effective pain management strategies.

Aims and Objectives

To investigate the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on the progression of chronic kidney disease (CKD).

Literature Review

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in individuals with chronic renal illness is a critical area of study due to the potential risks associated with their nephrotoxic effects. Chronic kidney disease (CKD) affects a significant portion of the population, and managing pain in these

patients often leads to the consideration of NSAIDs, which are commonly used for their analgesic and anti-inflammatory properties.

Mechanisms of Nephrotoxicity

NSAIDs exert their effects primarily through the inhibition of cyclooxygenase (COX) enzymes, which are essential for the synthesis of prostaglandins. These prostaglandins play a vital role in maintaining renal blood flow and glomerular filtration rate (GFR). In patients with CKD, the reliance on these prostaglandins is heightened, making them more susceptible to NSAID-induced renal impairment. The inhibition of prostaglandin synthesis can lead to decreased renal perfusion, resulting in acute kidney injury (AKI) and the progression of CKD [Harirforooshet al.,2014].

Prevalence of NSAID Use in CKD Patients

Despite the known risks, studies indicate that a notable percentage of individuals with CKD continue to use NSAIDs. For example, a study utilizing data from the National Health and Nutrition Examination Survey (NHANES) found that approximately 5% of individuals with moderate to severe CKD reported current NSAID use. This raises concerns about patient awareness regarding the risks associated with NSAID use and the potential for adverse renal outcomes [Levin,et al.,2013]

Clinical Implications

The interaction of NSAIDs with other medications commonly prescribed for CKD, such as diuretics and antihypertensives, can further exacerbate renal impairment. This necessitates careful monitoring and management of NSAID use in this population. Healthcare providers must weigh the benefits of pain relief against the risks of renal damage, particularly in patients with existing renal dysfunction [Harirforooshet al.,2014].

Recommendations and Guidelines

Current clinical guidelines generally recommend avoiding NSAIDs in patients with CKD, especially those with advanced stages of the disease. Alternatives for pain management, such as acetaminophen or non-pharmacological approaches, should be considered to minimize the risk of nephrotoxicity. Education and awareness among both patients and healthcare providers regarding the potential risks of NSAIDs are crucial for ensuring safe pain management strategies [Naughton, 2008].

While NSAIDs are widely used for pain management, their use in individuals with chronic renal illness requires careful consideration of the associated risks. Increased awareness and education about the nephrotoxic effects of these medications are essential for both patients and healthcare providers to optimize pain management while safeguarding renal function.

Both over-the-counter and prescribed non-steroidal anti-inflammatory drugs (NSAIDs) are widely used all over the world. Although it is commonly used for the management of inflammation and pain, several guidelines including the Kidney Disease Initiative Global Outcome (KDIGO) guidelines recommended avoidance of NSAIDs (except aspirin and acetaminophen) for most patients with chronic kidney disease (CKD) [Harirforooshet al.,2014].

The use of NSAIDs has been associated with renal function deterioration through variable mechanisms including alteration of the intraglomerular hemodynamic, nephrotic syndrome, glomerulonephritis, chronic interstitial nephritis, renal papillary necrosis, hyperkalemia, and podocyte injury [Perazella, 2009.]. This could lead to renal impairment and worsen the degree of renal dysfunction in CKD patients up to the development of end-stage renal disease (ESRD) .Persons with CKD, however, are likely unaware of their disease and may also be unaware that NSAIDs should be avoided. Additionally, those with CKD are likely to be older and have multiple comorbid conditions or symptoms that lead to increased use of NSAIDs [Hörl, 2010].

In addition, NSAIDs interact unfavorably with some commonly prescribed medications, including loop diuretics and renin-angiotensin-aldosterone system (RAAS) inhibitors. This is referred to as “triple whammy, leading to reduced effectiveness, along with increased risk of renal impairment. Although epidemiologic studies have linked NSAID use to progressive CKD, the risks of NSAIDs in patients with CKD, while supported by consensus and theoretical effect, remain less clearly established by evidence [Loboz&Shenfield]

Despite the adverse effects of NSAIDs on renal functions, the available data on its pattern among CKD patients in Egypt is minimal. This study aimed to estimate the prevalence, to identify the pattern of NSAID use, and to assess the knowledge about their adverse effects in CKD patients. This will help in setting plans to reduce NSAID use in CKD patients, and spread awareness of their potential harms in this population

Methods

300 adult patients with CKD who were admitted to the Main University Hospital participated in a cross-sectional study. Pregnant women and those with acute renal damage and end-stage renal illness were not included. Eligible patients were interviewed in order to gather clinical and demographic data. Additionally, information was obtained regarding the pattern, history of drug-drug interactions, and awareness of NSAID adverse effects.

Sample Size and Sampling Techniques

Sample size was calculated using Epi-info software version 7.2.2.6 (CDC, 2018) with a power of 80%, a confidence level of 95%, and a prevalence rate of 65.8% for NSAID use among CKD patients. The minimum required sample size was determined to be 340 patients, which was rounded up to 350. Participants were consecutively recruited from outpatient clinics and inpatient wards until the target sample size was achieved.

Data Collection

Data were collected using a structured interview questionnaire designed to gather information on participants' sociodemographic characteristics, smoking history, comorbid conditions, and the use of NSAIDs—including type, purpose, usage pattern, and source of medical advice. For patients unable to read, researchers displayed the packaging of medications to ascertain usage. Knowledge regarding the adverse effects of NSAIDs was also assessed.

Clinical measurements included blood pressure, weight, and height. Standardized serum creatinine levels were obtained from patient records. Body mass index (BMI) was calculated using the formula: weight (kg) / height (m^2) and classified into the following categories: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2.(

The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation:CKD was defined per the 2012 KDIGO guidelines, which require the presence of markers of kidney damage for over three months, including:

Markers of Kidney Damage:

Albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g)Urine sediment abnormalities

Patients in CKD stage 5 were excluded from the study, as they had already reached ESRD, and preventing NSAID use would not provide benefits regarding disease progression.

Statistical Analysis

Data were summarized using mean ± SD, medians, interquartile ranges, or frequencies and percentages as appropriate. Comparisons between variables were conducted using the t-test, Mann-Whitney test, or chi-square test based on data type. The correlation between renal function and duration of NSAID use was assessed using Pearson's correlation coefficient. Factors associated with NSAID use were identified through multiple logistic regression analysis, including all variables significantly related to NSAID use in bivariate analysis. Results were considered statistically significant at $p < 0.05$.

Adult (18+ years) CKD patients diagnosed in pre-ESRD (i.e., before dialysis or transplantation) were included in the study. Patients < 18 years of age; those who were in stage 5 CKD (ESRD), on dialysis, with previous renal transplantation, and with acute renal injury; and pregnant women were excluded from the study.The sample size was determined using Epi-info software 7.2.2.6 (CDC, 2018) based on power 80%, with confidence level of 95% and prevalence of using NSAIDs among CKD patients of 65.8% [Hughes et al.,2013]. The minimum required sample size was 300 patients. The sample was rounded to 3500 patients. Patients were consecutively included on daily basis from the outpatient clinics and the inpatient wards until the required sample was reached.

2.5 Data collection

A predesigned interview questionnaire was used to collect data from the patients about their personal characteristics (sociodemographic characteristics and smoking), history of comorbid diseases, history of selected drugs interacting with NSAIDs (For patients who were illiterate, the researchers had to show them the boxes of the drugs to know which one is taken.), and NSAID use including the type, purpose, pattern, and source of advice. In addition, knowledge about the adverse effects of NSAIDs was determined.

Concerning smoking, patients were classified into never smokers (those who have not smoked 100 cigarettes during their lifetime), current smokers (those who report smoking at least 100 cigarettes in their lifetime and who smoke cigarettes every day or some days), and former smokers (those who has smoked at least 100 cigarettes in their lifetime but does not smoke cigarettes) [Rothberg et al,2008].

Blood pressure, weight, and height were measured, and standardized serum creatinine was collected from the patients' records.

Regarding weight, patients were classified according to body mass index (BMI) [Vassalotti et al.,2007] (weight in kilograms/height in meters^2) into underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2).

Results

NSAID usage prevalence and trends

NSAID use was reported by around two-thirds (65.7%) of the study participants (Fig. 1). Patients with osteoarthritis, NSAID use were younger, female, nonsmoking, hypertensive, and more likely to take RAAS inhibitors .

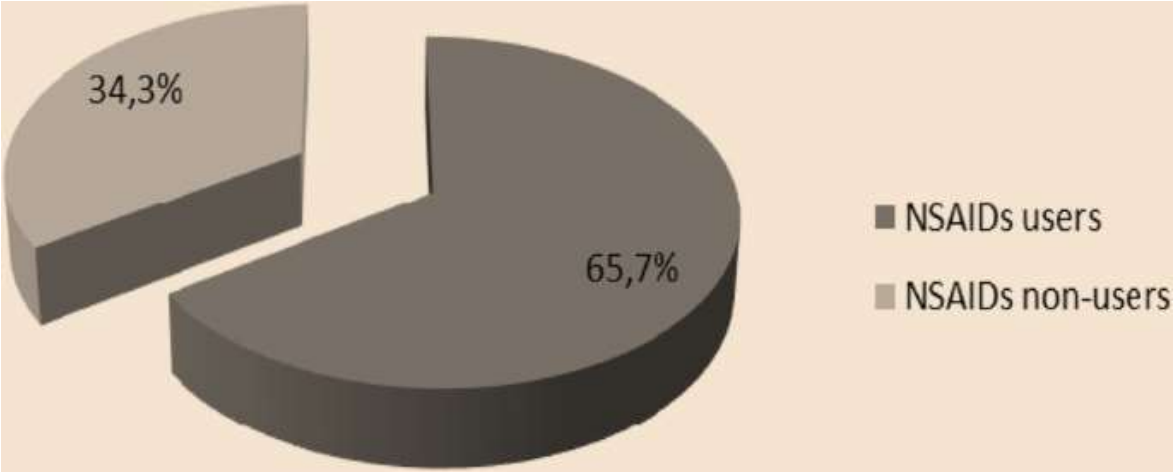

Fig.1.NSAID Prevalence usesin CKD patients

Ketoprofen was the most popular NSAID among users (50.3%), followed by meloxicam (2.3%), diclofenac (33.7%), ibuprofen (23.1%), and ketorolac (2.6%) (Table 2). Headache was cited by over two-thirds (68.7%) of patients as the primary cause for using NSAIDs, followed by joint pain (43.9%) and nonspecific pain (49.6%). In the past month, forty percent of NSAID users used them twice a week, twenty-four percent took them three times a week, and twenty-two percent took them daily. Over 80% (82.6%) of NSAID users reported a history of consistent usage, meaning they had been taking them at least twice a week for more than two months. Over 40% of NSAID users used them for more than three years, or between one and three years (46.1% and 41.7%, respectively. An inverse was present.connection ($r = -0.25$, $p < 0.001$) between the length of NSAID use and the eGFR (Fig. 2)

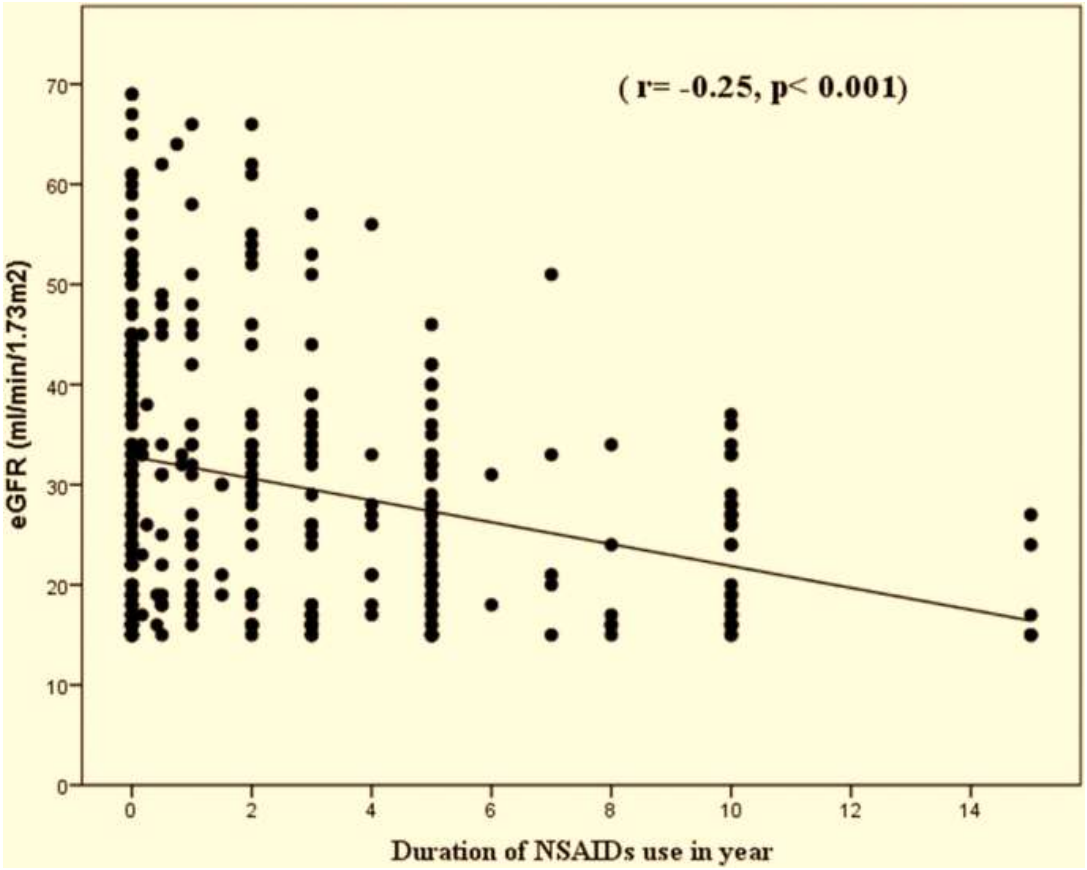

Fig. the duration of NSAID use and eGFR

25.2% of NSAID users took them on a doctor's recommendation, but the majority (76.5%) took them on their own initiative. 13.5% of respondents indicated friends and family. The percentages of pharmacists and prior prescriptions were 10.4% and 9.1%, respectively.

3.2 Awareness of the negative effects of NSAIDs Over half (53.2%) of patients with chronic kidney disease were unaware of the potential side effects of NSAIDs. Just 9.7% of respondents said that NSAIDs have no negative effects, compared to 37.1% who noted that they do. 55.4% of CKD patients who reported NSAID side effects believed that they resulted in kidney issues. According to Table 3, 45.4%, 19.2%, and 2.3% of patients, respectively, reported that NSAIDs cause issues with the gastrointestinal tract, liver, and heart.

Factors influencing CKD patients' use of NSAIDs

NSAID use among CKD patients was found to decrease considerably with increasing patient age, eGFR, and hepatitis C patients, according to a multiple logistic regression analysis of the factors influencing NSAID use among CKD patients. Conversely, patients with osteoarthritis, hypertension, and working conditions used NSAIDs at much higher rates.

Discussion

The prevalence of NSAID use was 65.7% in this cross-sectional research of 350 pre-ESRD patients who were enrolled from the Alexandria Main University hospital. The prevalence of NSAID use increased gradually as CKD progressed, reaching 2.6% in stage 2, 9.1% in stage 3a, 27% in stage 3b, and 61.3% in stage 4. The most often used medication was ketoprofen. Long-term NSAID use was also linked to a decrease in eGFR.

It has been observed that 8.9 to 69.2% of people use NSAIDs [Heleniak et al.,2017]. Differences in the legislation governing the purchase and availability of NSAIDs in various nations, as well as the lack of restrictive rules on drug use, may account for variations in NSAID use across numerous research.

patients to address their own signs and symptoms, particularly pain [Kaewpu et al,2016]. Furthermore, the quiet nature of CKD and ignorance of NSIAD consequences make it more likely that a late diagnosis would occur, leading to improper medication use. Furthermore, the prevalence of NSAID use may suggest that doctors often overlook assessing patients' renal functions when prescribing NSAIDs, particularly to high-risk patients, or they may be motivated to improve quality of life in certain comorbid conditions that justify NSAID use despite the associated risks.

The most common reason for using NSAIDs was headache, followed by joint and generalized pain,

which is in line with findings from other research [Davison et al,2014]. A number of disorders can cause discomfort in renal patients, including pathophysiological processes. Peripheral neuropathy, calciphylaxis, osteoarthritis, and osteodystrophy can all arise as a result of chronic kidney disease. Comorbid conditions such diabetic neuropathy, peripheral vascular disease, cardiovascular disease, osteoporosis/osteopenia, and inflammatory/immunological disorders are also linked to pain. Clinicians face a significant problem in treating their analgesia needs, which necessitates extra care to relieve pain without becoming harmful .

The current investigation found that many CKD patients taking NSAIDs were also taking RAAS inhibitors (23%), diuretics (8.3%), or both (6.1%). This is despite the fact that NSAIDs have been documented to block the therapeutic impact of RAAS inhibitors and diuretics (triple whammy). In the USA, Plantinga et al. identified a similar issue [Kafkia et al.,2011]. Among CKD patients with medications, they discovered 20% had prescriptions for diuretics and 16% for RAAS inhibitors for NSAIDs.

According to the current study's NSAID usage pattern, 22% of CKD patients took NSAIDs daily, 20.4% took them three times a week, and 40% took them twice a week. A sizable portion (46.1% and 41.7%, respectively) took NSAIDs for longer than three years or for one to three years. NSAID use for less than a year was limited to 12.2% of CKD patients. The NSAID use pattern varied in various research. 12.2% of people with CKD (stages 1–4) in Poland (2016) took NSAIDs occasionally, 14.8% occasionally, and 7.7% daily. More than one-third (35.6%) of CKD patients in Southern Italy (2014) received NSAID treatment for a duration of more than 90 days and about 16.5% for more than six months. According to Plantinga et al. (2011) in the USA, 64.4% of CKD patients with stages 3 or 4 and 65% of those with stages 1 or 2 had used NSAIDs for at least a year.

The current study demonstrated a strong correlation between NSAID use and eGFR, with the probabilities of NSAID use declining by 3% for every 1 ml/min/1.73 m2 increase in eGFR. This correlation aligns with the findings of other research. In order to identify potential factors linked to the progression and death of chronic kidney disease (CKD), Senevirathna et al. [2012] carried out a cohort analysis among 143 CKD patients of unclear origin. According to their report, NSAIDs were a significant individual influence.for the advancement of illness. A nationally representative sample of 19,163 newly diagnosed CKD patients was used in a cohort research conducted by Kuo and colleagues [25] to examine the potential impact of different analgesics on the course of CKD. Patients with CKD who took non-selective NSAIDs were more likely to develop stage 5 CKD. For all kinds of analgesics, there were substantial trends toward increased risk with increasing exposure dose.

The study's limitations

There are limitations to our investigation. We were unable to investigate the causal relationship between NSAID use and the advancement of CKD since the study was cross-sectional. Second, due to their relatively low nephrotoxicity and indications for pain and cardiovascular prophylaxis, respectively, the two most widely used over-the-counter analgesics, aspirin and acetaminophen, were excluded from our core criteria.

Third, people with chronic pain could overestimate or underestimate how long and how often they take NSAIDs. The high percentage of illiteracy may be the cause of this. Furthermore, we lacked information on specific dosage and frequency as well as professional recommendations. Fourth, there is a chance that CKD will be misclassified, especially for earlier stages. Lastly, the clinical history was used to gather information on concomitant conditions.

Conclusion

Since no prior research on the use of NSAIDs in kidney disease patients in Egypt is currently accessible, this study offered crucial information that would close the knowledge gap about NSAID use. It has significant ramifications as well. It highlights how crucial it is to inform doctors, other medicine prescribers, and the general public on the side effects of NSAID use, particularly their nephrotoxicity and possible interactions with RAAS inhibitors and diuretics, through workshops and training sessions.

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