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THE EFFECT OF KETOPROFEN LYSINE SALT ON BLOOD MORPHOLOGY, BIOCHEMICAL BLOOD PARAMETERS AND SUPEROXIDE DISMUTHASE ACTIVITY IN RAT'S KIDNEY

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ABSTRACT

Ketoprofen lysine salt (KLS) is a new nonsteroidal antiinflammatory drug (NSAID) of better solubility and better tolerability than older NSAIDs. It is metabolized in the liver and eliminated from the organism with urine. Like all NSAIDs KLS has possible side effects on the gastrointestinal tract, cardiovascular system and the kidney.
The aim of the study was to measure the effect of KLS on blood morphology, biochemical blood parameters and superoxide dismuthase (SOD) activity in rat's kidney.
The project of the experiment was accepted by the Local Ethical Committee (70/2021). A total of 12 young female Wistar rats were used. They were randomly divided into 2 groups: controls receiving 0,9% NaCl by gavage and study group receiving KLS by gavage at the dose of 12.8 mg/kg b.w. for 5 consecutive days. On day 6 the animals were decapitated. Their blood and kidneys were obtained. Blood morphology and serum creatinine were measured. The neutrophil - lymphocytes ratio (NLR), platelet-lymphocytes ratio (PLR) and monocytes-lymphocytes ratio (MLR) were calculated. The SOD activity was measured in the kidneys with an Elisa kit.
There was no significant differences among the groups in blood morphology (except for neutophil and eosinophil count, which were significantly elevated in the group exposed to KLS), creatinine concentration nor SOD activity. However there were significant differences in NLR it was much higher in the KLS group. NLR is considered to be a good prognostic parameter used in monitoring inflammatory and neoplastic diseases.
Conclusions:
1 KLS does not significantly affect the activity of SOD in the kidneys suggesting the it does not produce much oxidative stress.
2. NLR is a new interesting and cheap marker of inflammatory processes.
Keywords: ketoprofen lysine salt, superoxide dismuthase, oxidative stress, kidney.

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INTRODUCTION

Ketoprofen lysine salt (KLS) is available in the form of oral granules under the brand name Ketonal Sprint in two doses- 25 mg and 50 mg. The drug should be used for short-term treatment of acute pain that is mild or moderate. Ketonal Sprint should be used to treat toothache, headaches, pains related to strain and sprain, or painful menstruation. KLS is approved for use only in patients over the age of 16 [1].

The most common side effects of the medicine primarily involve the gastrointestinal tract (vomiting, nausea, abdominal pain, constipation, bloating, gastritis), but sometimes it can also cause headache, dizziness, drowsiness, itching or rash. Much rarer potential side effects include bronchial asthma, allergic reactions, or much more serious complications involving the gastrointestinal system, such as bleeding or perforation. It may also lead to skin inflammation, hepatitis, or even lead to kidney failure or nephrotic syndrome. Due to its combination with lysine, KLS demonstrates reduced gastroduodenal toxicity compared to other nonsteroidal anti-inflammatory drugs (NSAIDs), as it has a much shorter contact time with the gastrointestinal mucosa compared to other medicines from this group and shows greater solubility [1,2].

Ketoprofen is one of the NSAIDs that exhibits non-selective activity on both cyclooxygenase enzymes (COX-1 and COX-2) and is derived from propionic acid. It shows three main directions of action- analgesic, anti-inflammatory and antipyretic (without disrupting thermoregulation processes). It is also used in the treatment of rheumatic diseases due to its antirheumatic properties. These effects result mainly from the inhibition of COX-1 and COX-2, however ketoprofen may also indirectly affect other inflammatory mediators (such as kinins) and inhibit the penetration of leukotrienes (LTs) to the site of inflammation. Additionally, it is highly probable that it affects supraspinal cholinergic pathways and descending cholinergic pathways, which is responsible for central analgesic effect. It also inhibits elastase produced by neutrophils at the site of ongoing inflammation [1-3].

The above-mentioned cyclooxygenases are isoenzymes involved in the synthesis of prostaglandins (PGs). COX-1 is considered a constitutive isoenzyme involved in the production of PGs E2, I2 and thromboxane (TX) A2, which protect the kidneys and stomach from damage. It is also located in the vascular endothelium and platelets, regulating their function. COX-2 is an inducible enzyme and produces PGs responsible for pain and swelling during inflammation and increased vascular permeability. Inflammatory stimuli, such as cytokines and endotoxins, contribute to the action of COX-2. Furthermore, COX-2 is believed to play a role in labor and ovulation, as it is present in fetal membranes and the uterine muscle. In the central nervous system (CNS), kidneys, testes and bronchial epithelium, COX-2 also plays a constitutive role [3-5].

The effect on the hypothalamus of the thermoregulation center occurs only when the body temperature is elevated, therefore higher than the physiological one, which results in an antipyretic effect. The anti-inflammatory effect is also associated with a decrease in the threshold of pain receptors excitability and increased sensitivity to pro-inflammatory factors during inflammation [6].

KLS used for receptor pain, both inflammatory, visceral and somatic, shows effective action. It is also used for toothaches, headaches, and to alleviate post-traumatic pain. Moreover it is recommended in combination with other drugs for cancer pain (including pain caused by bone metastases), when postoperative pain occurs, or for acute pain [2].

In combination with acetylsalicylic acid, in doses used for anti-aggregation, it does not cause adverse interactions. When used cautiously without exceeding the maximum recommended daily doses (200mg), it has a slight gastric toxicity character [2].

The term oxidative stress refers to the disturbance of the balance between the formation of reactive oxygen species (ROS)- also called free radicals- during oxidative reactions, and antioxidant processes occurring within the body [11]. Sometimes during cellular respiration, the oxygen molecule does not undergo four-electron reduction, but reduction occurs with only one, two or three electrons- results of that process is formation of ROS. Therefore, free radicals are molecules that have at least one unpaired electron located on the outer electron shell. They tend to accept or donate electrons, which make them highly reactive [12].

Apart from the possibility of their formation in the respiratory chain, which is responsible for approximately 90% of free radicals, they can also be generated under the influence of physical factors (UV radiation, elevated temperature) or as a result of autoxidation of biologically active compounds (e.g. hemoglobin-HGB), but also as a result of immune reactions [11,12].

Free radicals are formed after UV irradiation or exposure to anticancer drugs (e.g., cisplatin). They are present in cigarette smoke and are also used during drying laundry and sterilization with hypochlorous acid. The body produces them to eliminate xenobiotics, and they are even formed during the metabolism of arachidonic acid [13].

Free radicals mediate important cell functions, such as differentiation, growth, apoptosis and proliferation, and any disruption of these processes changes the balance of free radical formation in their favor, which leads to cytotoxicity. The negative effects of free radicals include: damage to proteins, carbohydrates, nucleotides and lipids [11]. It is believed that oxidative stress may be responsible for the progression of many diseases, such as Parkinson's disease, Alzheimer's disease or neurodegeneration and is also associated with aging [13].

In order to counteract the processes of cell destruction by free radicals, organisms have developed defense mechanisms. These include the isolation of areas susceptible to the generation of free radicals, which are by-products of the processes occurring there, but also many metabolic mechanisms involving: substances quenching reactive molecules (vitamin E, carotenoids), heat shock proteins (proteases), antioxidant enzymes (superoxide dismutase- SOD, glutamine peroxidase- GPx, S-aminotransferases, catalases- CTs and others) and non-enzymatic substances (transferrin, ceruloplasmin and others) [11].

The three most important antioxidant enzymes are superoxide dismutase (SOD), glutamine peroxidase (GPx) and catalase (CT) [11]. Enzymatic antioxidants are

significantly more effective than non-enzymatic ones because they catalyze important reactions aimed at eliminating free radicals [12].

SOD catalyzes the reaction during which molecular oxygen and hydrogen peroxide are formed from the superoxide anion radical, while GPx is a catalyst for the formation of oxidized glutathione and water from hydroperoxide and hydrogen peroxide. CT does not directly catalyze the transformation of free radicals, but prevents the conversion of hydrogen peroxide into hydroxyl radical. It can act as a peroxidase and catalase, depending on the environment [12].

There are four different SODs depending on the metal in the active site, there can be: copper-zinc SOD (Cu,Zn-SOD), iron (Fe-SOD), nickel (Ni-SOD) or manganese (Mn-SOD). Their levels decrease with ageing, so they are used as an antioxidant and anti-aging ingredient in cosmetics to prevent age-related skin changes. Moreover, they also support wound healing. It has also been discovered that Cu, Zn-SOD and Mn-SOD may be inhibitors of inflammation [14].

AIM OF THE STUDY

The aim of the study was to investigate the effect of KLS on blood morphology, serum creatinine level and SOD activity in the kidneys of female rats.

MATERIALS AND METHODS

The experiment was conducted at the Center for Experimental Medicine (CEM) of the Medical University of Lublin. The experiment was approved by the Local Ethics Committee in Lublin, and the consent was issued on November 8, 2021 (number 70/2021).

12 young, healthy, non-pregnant female ratswere used. They were bred in the CEM. Their body weight at the beginning of the study was 190-205g. The strain of animals used in the study originated from Charles River Laboratories (Cologne, Germany). At the beginning of the experiment, the animals were 7 weeks old. In order to tame the animals and accustom them to contact with people, handling was conducted for a period of 7 days. The temperature of 21-22℃ and relative air humidity of 55-60% were constantly maintained during the experiment in the CEM room, which was monitored throughout the study. The daily cycle for the animals was maintained- it was dark for 12 hours and the room was lit for another 12 hours. Three experimental animals were kept in one cage. Drinking water and feed were freely and easily accessible at all times to the rats. The water given to the animals was sterilized by UV, and the feed given to the animals was purchased from Altromin International (Lage, Germany). The 0.9% saline solution used in the experiment was manufactured by B. Braun Melsungen AG (Hasse, Germany). The KLS preparation used in the study was Ketonal Sprint in granule form (Sandoz GmbH, Vienna, Austria). In order to ensure proper administration of the test product, it was administered via a gastric tube.

The control group consisted of animals receiving a dose of 5 ml/kg of body weight of 0.9% saline solution for 5 days, while the treatment group was administered KLS at a dose of 12.8 mg/kg of body weight also for 5 days. The doses were calculated based on therapeutic doses for humans, taking into account the body weights of the animals used in the trial. After the study was completed (5 days), the animals used in the study were killed by decapitation using a guillotine.

Venous blood was collected for further analysis, which was performed at the veterinary laboratory Vet Diagnostyka in Lublin.

The next step involved calculating the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) based on the obtained results, which were analyzed using statistical software.

The activity of SOD in the kidneys was determined using Cloud Clone ELISA kits (Rat SOD ELISA Kit 96T) according to the manufacturer's instructions.

The obtained research results were analyzed using the Statistica software, access to which was provided by the Medical University of Lublin. The results were statistically analyzed using the t-student test. The mean, standard deviation and basic statistics were calculated, the control group was compared to the treatment group, $p<0.05$ was considered statistically significant.

RESULTS

The results were shown in Table 1.

Tab.1

Results.

	Controls (n=6)	Study group (ketoprofen lysine salt 12.8 mg/kg b.w.) (n=6)	p<0.05
white blood cells (WBC) [10^3/uL] Mean±SD	9.670±3.566	12.61±2.211	
eosinophils (EOS) [10^3/uL] Mean±SD	0.1000±0.02739	0.3000±0.1088	*
neutrophils (NEU) [10^3/uL] Mean±SD	0.8900±0.2706	3.118±1.363	*
lymphocytes (LYM) [10^3/uL]Mean±SD	8.198±3.193	8.430±1.012	
monoctes (MON) [10^3/uL] Mean±SD	0.4617±0.1286	0.7017±0.4403	
Erythrocytes [10^6/uL] (ERY) Mean±SD	7.860±0.2532	7.575±0.6470	
hemoglobin (HGB) [g/dL]Mean±SD	15.87±0.4761	15.33±1.221	
Platelets (PLT) [10^3/uL]Mean±SD	933.5±180.7	1184±206.6	
Creatinine [mg/dL] Mean±SD	0.2150±0.02588	0.2217±0.03656	
neutrophil to lymphocyte ratio (NLR) Mean±SD	0.1202±0.04201	0.3742±0.1570	*
platelet to lymphocyte ratio (PLR) Mean±SD	138.9±84.03	142.0±31.05	
monocyte to lymphocyte ratio (MLR) Mean±SD	0.04723±0.04283	0.07433±0.05565	
superoxide dismutase (SOD) [ng/mL]Mean±SD	3.395±0.3192	4.390±0.8182	

DISCUSSION

One of the possible side effects of KLS is gastrointestinal bleeding. Blood loss may increase the likelihood of anemia caused by iron deficiency. These bleedings may not depend on the duration of use, and special caution in the use of the drug should be considered in patients using higher than recommended doses, as well as in patients who have suffered from gastric or duodenal ulcer [1,15]. In the conducted experiment, KLS was administered short-term (for 5 days) at doses adjusted to the animals' body mass based on therapeutic human doses, so the doses were not exceeded in relation to the maximum dose, and the animals used in the study were healthy. For this reason, no significant differences were observed in hemoglobin (HGB) concentration and number of erythrocytes between the control and treatment groups. No bleeding from the upper and lower gastrointestinal tract was observed.

NSAIDs can induce the production of ROS, which in excess can lead to oxidative stress. Controlled synthesis of free radicals can support tissue repair processes and wound healing, but their excessive amount can disrupt the body's physiology, and as a result, can lead to the suppression of the mechanisms that defend the body against oxidative stress. Erythrocytes (ERT) generate free radicals even in the physiological process of respiration, so as a result of the action of KLS more of them than usual may be created, because the drug may intensify this process. Free radicals are able to denature proteins. The protein is hemoglobin contained in erythrocytes [15,16]. In our experiment no changes in HGB concentration and numbers of ERT were observed, which may result from the use of a therapeutic dose of the preparation in accordance with the manufacturer's recommendation (according to the characteristics of the medicinal product).

The blocking effect of KLS on COX-1 and COX-2 resulting from the mechanism of action inhibits the synthesis of TX, thereby impairing platelet (PLT) function.

The incidence of thrombocytopenia associated with KLS use is unknown, but it is listed as an adverse effect in the characteristics of the medicinal product [1,15]. Nevertheless, our experiment did not show a decrease in the number of PLT after KLS, which may be due to short-term use and administration of safe doses.

Due to the lack of sufficient counter-effects of vasoconstrictor angiotensin II and vasopressin in the form of PGs, acute renal failure may occur in individuals taking NSAIDs. Inhibition of PGs synthesis, which results from the mechanism of action of KLS, can significantly reduce the lumen of the blood vessels in the kidney and, consequently, blood flow through the kidney. Moreover, PGs inhibition combined with high concentrations of KLS in the kidney may reduce blood flow in the renal papilla and medulla, leading to ischemia, and, subsequently, organ damage [17]. Administration of high doses of NSAIDs may result in acute renal failure within a few hours, which is usually reversible upon drug discontinuation, while chronic use (over 3 years) may contribute to irreversible damage. The tests that allow for detecting abnormalities in kidney function include urine analysis (pH, composition, volume, osmolality) and blood serum analysis (creatinine, eGFR). To observe differences in creatinine concentration, there must be a reduction in eGFR by 50-70%, and an elevated creatinine concentration is not always a marker of kidney pathology, as it may even result from dehydration [17]. Since KLS was administered for a short period of time in the experiment, in doses calculated based on the animals' body mass and healthy rats were used in the study, no significant differences were observed in the mean creatinine concentration between the both groups. In order to analyze the effect of KLS in terms of toxicity to the kidney, it would be necessary to assess all parameters that help detect kidney abnormalities and perform a histopathological evaluation after the study, as creatinine concentration alone does not allow for reliable assessment of kidney function. However, due to limited finances, it was not possible to conduct the full range of tests required to evaluate kidney function.

Free radicals can induce oxidative stress in the kidney, which leads to damage to its cells. Two of the probable reasons for the occurrence of oxidative stress in the kidney may be the formation of an excess intermediate product or binding to molecules in the cell when using KLS [17]. SOD, through its enzymatic activity, catalyzes the conversion of the superoxide anion radical and contributes to maintaining balance and eliminates the toxic effect of ROS in the kidney. In this study, SOD after KLS administration showed greater activity compared to the control group, however, the difference between groups was not statistically significant. During chronic kidney disease, the accompanying chronic inflammation could significantly affect kidney function- it is possible that study on animals with the described condition and administration of KLS could demonstrate differences on SOD activity compared to individuals not receiving the drug [18].

Ruszel et al. in one of their studies from 2024 described the immunomodulatory effect of KLS and ketoprofen on the brain in female rats. The results presented in their work regarding the concentration of creatinine, numbers of white blood cells (WBC), ERT, PLT and HGB concentration in the blood of rats in the control group taking 0.9% NaCl and taking KLS are similar to those presented in our study, as no statistically significant differences were observed there either. Therefore, the results obtained in our study are consistent with those of Ruszel et al. [19].

Another study by Ruszel et al. published in 2024 compared the effect of ketoprofen and KLS on the nutritional status of female rats after exposure to alcohol the day before, intended to replicate the intake of NSAIDs the next day after alcohol intoxication. As in our study, no significant differences were found between the group receiving 0.9% NaCl and the group exposed to KLS in terms of creatinine concentration, numbers of WBC, ERT, PLT and concentration of HGB [20].

In 2015, Cimini et al. studied the effect of KLS on the gastric mucosa using an in vitro model of ethanol-damaged gastric mucosa and this NSAID was shown to have protective effect. However, many processes that occur in a living organism do not occur in an in vitro model, so such a study on a cell line is not able to fully demonstrate whether KLS truly has a protective effect on the stomach following ethanol-induced damage [21]. Ruszel et al. tested the hypothesis of the gastroprotective effect of KLS after the previous exposure to ethanol in female rats. Histopathologically examined stomachs of rats in all groups except the control group (0.9% NaCl) showed inflammation of the gastric mucosa, which did not confirm the protective effect due to the combination with lysine [22].

A comparative experiment of KLS and the acid form of ketoprofen on the kidneys and gastrointestinal tract conducted on beagle dogs by Novelli et al. showed fewer side effects resulting from the use of lysine salt form compared to the classic form of ketoprofen. All tests conducted on dogs subjected to a two-phase study provided evidence for the superiority of KLS over ketoprofen, both when taking into account the effect on the kidneys and the gastrointestinal tract. According to the authors, differences in adverse effects should be attributed to better tolerability of KLS rather than a difference in the mechanism of action between KLS and ketoprofen. The authors attribute the antioxidant effects to L-lysine (LYS) [23].

A study conducted on mice with a lipopolysaccharide induction model, which aimed to assess the protection of LYS on acute lung injury resulting from sepsis, was conducted in 2019 in China. In the experiment, animals were divided into groups- sham, control (having acute lung injury) and two study groups, one taking 5 mg/kg body weight of LYS and the other taking twice as much LYS for 45 days. Both study groups also had acute lung injury, due to the induction of inflammation in mice. During the study, the activity of antioxidant enzymes, including SOD, as well as the numbers of neutrophills (NEU), lymphocyes (LYM) and the total numbers of cells in the bronchoalveolar lavage fluid were determined. In the case of the control group, all cellular parameters were increased, and in the study groups they were reduced, including the group taking more LYS showed a greater effect of reducing these parameters. Acute lung injury decreased antioxidant enzymes activity, which increased with LYS administration. Therefore, LYS contained in KLS may support fight inflammation and increase the activity of antioxidant enzymes [24].

In the results obtained in our study, no statistically significant differences in SOD activity in the kidney were observed between the groups, although the study was conducted only for 5 days. Perhaps when using

KLS for a longer period of time the result would be different, due to LYS, which is contained in the drug. Additionally, the use of healthy animals in our experiment could have influenced the results of the study, because the study on mice with the polysaccharide induction model allowed for the assessment of the antioxidant capacity of LYS in disease subjects [24]. However, it is not known whether LYS acts in the same way with ketoprofen, so further studies could focus on the evaluation of ketoprofen, KLS and LYS in healthy and diseased animals in the short and long term with measurements of SOD activity and other antioxidant enzymes.

In 2021, the results of a study conducted by Kuczyńska et al. were published, examining whether KLS has gastroprotective effect on the stomach after ethanol intoxication in male rats. In this study, the gastric mucosa was assessed histopathologically, and blood morphology and serum were also analyzed. The percentage of NEU in the rats' blood was elevated after KLS administration compared to the group receiving 0.9% NaCl, however, the difference was not statistically significant. Likewise, no statistically significant differences were found in the percentage content of NEU, eosinophills (EOS), LYM, monocytes (MON) or in the concentrations of HGB and ERT and in the numbers of PLT and WBC between the two groups. The experiment of ours also showed no differences statistically significant in HGB and ERT concentration and numbers of PLT and WBC. We took into account absolute numbers, instead of percentages of NEU, LYM, EOS, MON and observed statistically significant differences between the numbers of NEU and EOS between groups. Increased numbers of these parameters were observed in the group taking KLS, the remaining results were consistent with Kuczyńska's findings [25]. An increased number of EOS is most commonly associated with allergic diseases or parasitic infections, but they also play a role in viral infections. In response to substances produced during inflammation, EOS migrate toward the affected area, which may explain their increased numbers during KLS administration [26]. NEU are produced at the earliest stage during inflammation in the body, so their number could increase in response to the administration of KLS, which can induce the formation of free radicals causing inflammation [27].

Kuczyńska et al. in 2023 investigated the effect of KLS and ketoprofen on the kidneys, liver and nervous system in male rats after prior administration of ethanol to induce alcohol intoxication. During this study, behavioral tests were performed along with histopathological analysis of the kidneys, liver and brain. Histopathological evaluation of the kidneys did not reveal any changes or signs of inflammation in either group, which explains why our study did not show any statistically significant differences in SOD activity between the control and KLS-exposed groups [28].

The neutrophil-to-lymphocyte ratio (NLR) is the ratio of neutrophils (which increase during inflammation) to lymphocytes (which decrease during inflammation). It is a cheap and easy-to-measure factor that can be used as a marker of postoperative complications or to determine patient prognosis. In the article by Fuss et al. from 2022, the association of NLR with the possibility of predicting complications in patients with colon cancer was examined. NEU and LYM were measured within a month before surgery, values below 3 were considered low, and those above 3 were considered high. A correlation was found between high NLR and the occurrence of complications. However, no cut-off value has yet been established for NLR that would allow for prediction of postoperative complications risk in colorectal cancer patients. NLR has also been considered as a factor for assessing the safety of hospital discharge [29]. In 2016, Kuźniar-Placek described the relationship between NLR and cardiovascular diseases. This factor was recognised as helpful in predicting potential complications and even survival rate of patients suffering from cardiovascular conditions. Using NLR, it is possible to determine the inflammation occurring in the body, which may contribute to the pathogenesis of, among others, hypertension [30].

Wójcik et al. in a study conducted in 2018 tried to determine the prognostic value of the PLR in patients with small-cell lung cancer. PLR is the ratio of PLT to LYM. The baseline PLR greater than 210 has been shown to worsen patient prognosis, but it has not been considered a major prognostic factor for survival rate in small-cell lung cancer [31].

Both NLR and PLR have already been considered in the diagnosis of prostate cancer. However, a 2021 study by Zhamping et al., conducted in China, focused on the use of monocyte to lymphocyte (MLR) ratio for the diagnosis of prostate cancer. Blood samples were collected from patients and healthy volunteers taking part in the study and the numbers of NEU, PLT, MON and LYM were determined, from which PLR, NLR and MLR were calculated. The values of the calculated markers were significantly higher in patients with prostate cancer compared to healthy volunteers. Nevertheless, prostate-specific antigen (PSA) remains the most important diagnostic indicator for this type of cancer, but in this study the author showed that together with MLR the diagnostic value is higher and it is a valuable auxiliary indicator used in the diagnosis of prostate cancer. However its usefulness requires further studies. Zhamping pointed out that the highest diagnostic value of prostate cancer occurred when taking into account 3 factors- NLR, MLR and PSA, which in the future could result in a reduction of the number of unnecessary biopsies performed due to the PSA level alone. The author also mentioned the use of NSAIDs as a prophylaxis of prostate cancer due to the relationship of this disease with inflammation [32].

The study conducted on patients with psoriatic arthritis and ankylosing spondylitis by Wiąk-Walerowicz et al. aimed to check whether NLR, PLR and MLR correlate with the duration of remission in these patients. These parameters were examined before and after 6, 12 and 18 months of treatment with TNF-α inhibitors. PLR and NLR were significantly higher at month 12 of therapy, and at 18 only PLR in psoriatic arthritis, and their increased values were associated with a shorter duration of remission. In the case of the second disease, no correlation was observed [33].

The low cost, ease of determination, and demonstrated relevance of PLR, MLR and NLR in many cancer-related studies make them valuable and useful indicators of inflammation. These markers sometimes help with diagnosis, or serve to predict prognosis or postoperative complications in various diseases, and their utility has been demonstrated in multiple studies. However, due to the insufficient number of studies focused on a specific type of disease, with a small number of participants, they are not yet clinically significant. It would be worthwhile to direct future experiments to the relationship between NLR, PLR and MLR in neoplastic diseases and other diseases accompanied by

inflammation [29-33]. In our study, a statistically significant difference in the NLR value was demonstrated between the control group and the group after KLS administration, and its value was higher in the treatment group. No statistically significant differences were observed in values of PLR and MLR. Marseglia et al. investigated the effect of KLS on upper respiratory tract infections in a group of adolescents with an average age of 13.4 years. The study showed effective and well-tolerated treatment in this group of patients [34]. In 2025, an article by Italian researchers was published regarding the use of KLS and ketoprofen in treatment of pain in children. The studies presented there include, for example, a comparison of KLS suppositories with paracetamol used rectally after various urological procedures in hospitalized children. It defined KLS as acting faster, longer and more effectively than paracetamol. Among the studies presented in the article, there were also selected studies comparing KLS, paracetamol and placebo used orally, in single doses for acute pharyngitis and tonsillitis. No differences in the safety and effectiveness of the compared drugs were shown. Suppositories with KLS and niflumic acid were also compared in children with acute otitis media, where KLS also proved to be more effective and acted faster. Other studies in the review also showed that KLS is more effective or there are no differences between the preparation used. According to the authors, KLS is safe and effective in treating children over the age of 6. On the other hand, they point out that all studies, except for one, were conducted in Italy, and some of them contain imprecise data or lack of placebo group, which may affect the reliability of the results [35]. In Poland KLS is available as a granulate preparation, which can only be used by patients over 16 years of age [1]. Perhaps if the studies on the effectiveness and, above all, safety of KLS were in-depth and there were more of them, it would be a viable alternative for treating fever and pain in patients under 16 or even 12 years of age.

Entering the keyword 'ketoprofen lysine salt' into the PubMed search engine, 46 results were found (checked on May 8, 2025). This is a very small number of results, especially considering that the keyword 'ketoprofen' alone returned over 5,000 results. The limited data available on this drug should serve as an incentive for further investigation into its effects, safety, potential side effects, and any properties that might favor the lysine salt formulation over ketoprofen, other NSAIDs, or even the broader group of analgesic medications.

CONCLUSIONS

KLS does not significantly affect SOD activity in the kidney. It does not induce oxidative stress in the kidney.

NLR, MLR and PLR are new promising and cheap parameters that can be helpful in assessing the activity of inflammatory and neoplastic diseases, because they are calculated from basic blood parameters.

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