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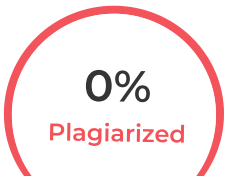

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1. Introduction Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain, fever and inflammation. NSAIDs achieve their therapeutic effect by competitively inhibiting the binding of arachidonic acid to cyclooxygenase enzyme, thus stopping the synthesis of prostaglandins - mediators of pain and inflammation (Mehta et al., 2019). Biologically active derivatives of arachidonic acid: prostaglandins E2 and F2a (PGE2 and PGF2a), thromboxane (TX) A2 and prostacyclin (PGI2) are produced by the action of cyclooxygenase (COX). This process happens as a cell membrane response to harmful factors (Quishi et al., 2022). COX exists in two isoenzyme forms - COX-1 and COX-2 (Biava et al., 2011). COX-1, as an enzyme, a constituent of almost all cells, produces prostanoids that maintain normal homeostasis. On the other hand, COX-2 is induced in inflammatory cells and highly expressed as a response to interleukin-1β (IL-1β) and other stimuli such as tumor necrosis factor-α (TNF-α) (Ueno et al., 2001; FitzGerald, 2003). The enzyme is responsible for producing mediators of inflammation. These differences are important for understanding the mechanism of action of NSAIDs, as most NSAIDs currently in use inhibit both isoenzymes, although the degree of inhibition of each is different. Side effects, especially gastrointestinal ones, are mainly related to COX-1 inhibition (Biava et al., 2011). Topical forms of NSAIDs are available for many years. Although their efficacy is ambiguous and in some parts of the world those forms are considered as placebo, some literature still confirms their efficacy in treating both acute and chronic pain (Wiffen and Xia, 2020; Derry et al., 2017). Moreover, literature suggest transdermal ketoprofen to be superior to diclofenac in achieving analgesic effect in rat models of acute inflammation (Aganović-Mušinović et al., 2021; Amagai et al., 2013). This superiority is assigned to the ketoprofen analgesic mechanism that include both COX inhibition and the inhibition of the reflex activity of the spinal cord nociceptors, thus reducing their central sensitization in the spinal cord (Atzeni et al., 2021). Even controversial in pain treatment, topical forms ensure reduced occurrence of systemic adverse effects such as peptic ulcer or bleeding in the gastrointestinal system that are common with oral application (Goi et al., 2010). It is also known that compared to systemic therapy, topical applications of NSAIDs require lower doses to achieve pain relief, and thus pose lower risk of major drug interactions (Stanos and Galluzzi, 2013). Due to these advantages, topical NSAIDs containing ketoprofen, piroxicam, ibuprofen, diclofenac and flurbiprofen are often used in the

treatment of acute (duration less than three months) and chronic (duration more than three months) musculoskeletal pain. Diclofenac is one of the most researched topical NSAIDs and its various doses were used in the studies. It has been shown that after diclofenac application directly to the painful site, its concentration in the skeletal muscle at the site of the application was 12-fold higher than in plasma, and the concentration in synovial fluid was 30% of its plasma concentration (Hagen and Baker, 2017). As data generated using animal models can predict potential of NSAID for topical application in pain treatment in clinical setting, we aimed to evaluate analgesic and anti-inflammatory effects of diclofenac and ketoprofen patch in the rat model of acute inflammation.

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2. Materials and methods 2.1. Experimental animals Wistar male rats, body weight 220-290 g were used in the experiment. They were housed at the Faculty of Medicine, University of Sarajevo, under controlled temperature (23□2 C), humidity (55□20%) and 12h/12h light/dark cycle. The animals had access to food and tap water ad libitum. All experiments were carried out in accordance with the Guide for care and use of laboratory animals (National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals, 2011). After randomization of rats into five groups with six rats, two groups were treated with diclofenac at different doses, two with ketoprofen at different doses, while a placebo patch was administered to the control group. 2.2. Drugs and patch application During the study, the following drugs were topically applied: diclofenac (140 mg/140 cm2; Voltadol® Cerotti Medicati, GlaxoSmithKline Consumer Healthcare SpA, Milan, Italy) and ketoprofen (20 mg/70 cm2; Keplat®, Hisamitsu UK Limited, London, United Kingdom). Patches were purchased as commercially available products in the European Union. Of two different doses for each of diclofenac and ketoprofen, the first dose was calculated to be equivalent to therapeutic dose based on differences in body mass between humans and rats, and the second dose was calculated as the multiplication of the first dose (3 times higher dose) as follows: Voltadol® 1 cm x 0.6 cm (group V1) and 1 cm x 1.8 cm (group V2); Keplat® 1 cm x 0.3 cm (group K1) and 1 cm x 0.9 cm (group K2). Therapeutic or placebo patch was fixed by bandage bend in the center of the dorsal surface of the right hind paw of the rat. Patches were removed three hours later, initial measurements of pain, gait, body temperature, paw temperature, color and paw volume were performed, and then one of the models of acute inflammation was applied: yeast-induced hyperalgesia and carrageenan-induced edema. The washout period between the two models was 2 weeks. 2.3. Models of acute inflammation Phase 1: To induce hyperalgesia, 0.1 mL of a 20% yeast solution (1 g of commercially purchased baker's yeast to 5 mL of physiological solution, equipping the suspension in a magnetic stirrer, Brewer´s yeast) was injected subcutaneously into the dorsal side of the hind right paw. Phase 2: The model of Winter et al. (1962) was used to induce edema: 0.1 mL of 1% carrageenan solution (λ-Carrageenan, Sigma-Aldrich, St. Louis, MO, USA) was applied to the dorsal/sub plantar region of the right hind paw. 2.4. Measurements of pain, gait, body temperature, local temperature of the paw, color and paw volume Pain intensity, gait, body

temperature, local temperature of the paw, color and paw volume (oedema ratio %) were measured at 0, 1, 3 and 5 hours after both yeast-induced hyperalgesia and carrageenan-induced edema. The intensity of the pain was measured using algesimeter according to the Randall-Selitto method (Randall and Selitto, 1957). A lower score indicated a lower pain threshold in the animal. Gait was assessed as 0 - stroke on three legs, 0.5 - significant lifting, 1 - normal stroke. Temperature was measured using Bioseb thermometer (www.bioseb.com) and recording temperature few seconds after thermometer was pressed against body back for the whole-body temperature, and against the paw for the local paw temperature. Color of the treated paw was assessed as 1 - high redness, 2 - significant redness, 3 - moderate redness, 4 - slight redness, 5 - common/normal color. Paw volume was determined by measuring the difference in the amount of fluid expelled at each measuring time point and baseline. Oedema ratio (%) was calculated using the following formula: [(Paw volume at each measuring time point – Baseline Paw Volume)/Baseline Paw Volume]x100(%). 2.5. Statistical analysis We used IBM SPSS version 20 for the descriptive and inferential statistical analysis. Shapiro-Walk test was used to test normality of distribution of continues quantitative data. For normally distributed data and homogeneity of variance (Leven´s test not significant) One-Way ANOVA test was performed to identify statistical difference between groups, and Welch's One-Way ANOVA for no homogeneity of variance (Leven´s test significant). When One-Way ANOVA or Welch's One-Way ANOVA test showed significant findings, Tukey´s or Games-Howell post hoc tests, respectively, were used to identify which groups in the sample differ. For not normally distributed quantitative data, nonparametric Kruskal-Wallis test was used to identify statistical difference between groups, and for multiple pairwise comparison test adjusted by Bonferroni correction was used to distinguish which groups in the sample significantly differ. The level of $p<0.05$ was used as statistical significance.

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· The animals had access to food and tap water ad libitum. The procedures and manipulation of the animals used in this study followed the European Communities Council ...

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Effects of topically applied diclofenac and ketoprofen ... - NCBI

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3. Results Prior to the induction of acute inflammation, no significant differences in initial measurements of pain, gait disturbance, body temperature, paw temperature, color and oedema ratio (%) were observed between control and ketoprofen or diclofenac examined groups, except in paw temperature between control and diclofenac tested groups (p=0.003), when post hoc analysis revealed significantly higher values in control compared to low dose diclofenac group [36.4 (35.75-36.63) vs 33.1 (32.9-33.75); p=0.002] after acute inflammations was induced by Brewer´s yeast. After the induction of acute inflammations by Brewer´s yeast, the mean value of pain score at the 5th hour was significantly higher in control group compared to the low dose diclofenac group (3.63±1.87 vs. 10.08±4.89; p=0.049) and in control group compared to the high dose ketoprofen group (3.63±1.87 vs. 8.67±2.90; p=0.016). There were no differences in the mean pain score at the 0, 1st and 3rd hour after induction. No difference was observed between control and treatment groups of both drugs after the induction of acute inflammations by 1% carrageenan solution. Considering the pain induced either by 20% yeast or by 1% carrageenan and its influence on walking ability, significant difference was found only at the 3rd hour after inducing inflammation by 20% Brewer´s yeast (p=0.026) between control and diclofenac groups, and post hoc analysis revealed significantly weaker walk ability in low dose compared to high dose diclofenac group (0.33±0.482 vs. 1.00 (0.88-1.00); p=0.034). Acute inflammations induced by both used models did not affect the whole-body temperature. Although in comparisons of body temperatures between control and ketoprofen groups after the acute inflammation was induced by Brewer´s yeast, significant differences in median values were found at the 3rd hour (p=0.035), and after edema was induced by carrageenan, significant differences were found at the 1st hour (p=0.016), these differences were clinically insignificant as all the values were in the normal body temperature range (Table 1). When analyzing the temperature of the treated paw, significant difference was found at the 1st hour after inflammation induction by carrageenan between control and ketoprofen tested groups (p=0.032), while used post hoc analysis revealed the local temperature to be significantly higher in control compared to low dose ketoprofen group (32.90 (32.90-33.73) vs. 34.90±0.84; p=0.048). When compared control and low diclofenac groups, except earlier mentioned significant difference in local temperature of the treated paw found at the

baseline after inflammation induction by Brewer´s yeast, significant difference was also found at the 1st hour (p=0.013), when post hoc analysis revealed the significantly higher paw temperature in the control compared to low dose diclofenac group (p=0.033), as well as in the control compared to high dose diclofenac group (p=0.030) (Table 2). At the 5th hour, after inflammation induction by carrageenan, statistical differences were found between control and diclofenac groups (p=0.000), and post hoc analysis revealed that lower mean values in the control compared to the low dose diclofenac group (p=0.000), as well as in the high compared to the low dose diclofenac group (p=0.000) (Table 2). Testing the color as the sign of acute inflammation of the area, the significant difference was found at the 3rd and 5th hour after carrageenan induced inflammation between control and ketoprofen groups (p=0.002), and post hoc analysis revealed significantly higher redness in control compared to high dose ketoprofen group (p=0.001; p=0.001) (Table 3). Significant differences in color were found between control and diclofenac groups at the 5th hour after 20% Brewer's yeast application (p=0.028) and post hoc analysis revealed significantly higher redness in low compared to high dose diclofenac group (p=0.023). Significant differences in color were also found between control and diclofenac groups at the 1st, 3rd and 5th hour after carrageenan application (p=0.033; p=0.011; p=0.015, respectively) (Table 4). Post hoc analysis at the 1st hour revealed significantly higher redness in control compared to low diclofenac group (p=0.024), and in low compared to high dose diclofenac group (p=0.024), at the 3rd hour between the same groups (p=0.028), and at the 5th hour significantly higher redness in control compared to high dose diclofenac group (p=0.015) (Table 4). Significant difference was found in mean values of oedema ratio (%) between control and ketoprofen groups at the 3rd and 5th hour after inducing inflammation by both 20% yeast (p=0.009, p=0.038, respectively), and carrageenan (p=0.006, p=0.014, respectively) (Table 5). Tukey's post hoc test revealed significantly higher oedema ratio % after inducing inflammation by 20% yeast at 3rd hour in the control compared to the low dose ketoprofen group (p=0.014), and in the control compared to high dose ketoprofen group (p=0.026), and at the 5th hour in the control compared to high dose ketoprofen group (p=0.031). Significant difference after inducing inflammation by carrageenan was found at the 3rd hour (p=0.006), and Tukey´s post-test detected significantly higher oedema ratio % in the control compared to low (p=0.026), and in the control compared to high dose ketoprofen group (p=0.007), and at the 5th hour significantly higher oedema ratio % in the control compared to high dose ketoprofen group (p=0.011). Significant difference was found in oedema ratio % between control and diclofenac groups at the 1st hour in the inflammation model induced by Brewer's yeast (p=0.005), and post hoc analysis revealed significantly higher oedema ratio % in the control compared to high dose diclofenac group (p=0.008), as well as in low compared to high dose diclofenac group (p=0.012) (Table 6). Also, significant differences were observed at the 3rd (p=0.044) and 5th hour (p=0.04) after inducing inflammation by carrageenan, and Turkey's post hoc test revealed significantly higher oedema ratio % at 3rd hour in the

control group compared to the high dose diclofenac group (p=0.043), while at 5th hour no significant difference in oedema ratio (%) between groups was confirmed (Table 6).

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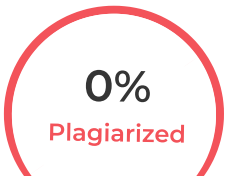

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4. Discussion We evaluated the analgesic and anti-inflammatory effects of topically applied ketoprofen and diclofenac using the rat models of yeast- and carrageenan-induced acute inflammation. While ketoprofen was proven to be effective in reducing whole body and even more potently local paw temperature, diclofenac seemed to be more effective in reducing pain and related gait disturbance, redness and oedema. We documented significantly higher pain in control group compared to the low dose diclofenac group, and in control compared to the high dose ketoprofen group, both at 5th hour after inducing inflammation by 20% Brewer’s yeast. The maximum analgesic effects for both drugs were achieved at 5th hour after inflammation induction by 20% Brewer’s yeast, suggesting better analgesic effect of diclofenac, achieved by lower dose compared to ketoprofen. Moreover, at the 3rd hour a significantly better walking ability was documented in high dose compared to low dose diclofenac group, and not in ketoprofen groups. In contrary to our findings, in a study by Amagai et al. (2013), where the effect of ketoprofen, diclofenac, and loxoprofen applied in the form of transdermal patches and gels were evaluated, ketoprofen showed the best potency and the strongest effect in gait assessment. Fukumoto et al. (2018) compared analgesic effects of the newly developed S (+)-flurbiprofen plaster, ketoprofen and loxoprofen patch. Their results suggest that only the ketoprofen in doses 1 or 2 mg/patch produced a decrease in the visual gait score but not in doses of 0.25 and 0.5 mg/patch. In our study ketoprofen achieved better antipyretic effect than diclofenac when analyzing whole body temperature as we documented significant differences in the median values at the 1st after inducing inflammation by 1% carrageenan, and at the 3rd hour after inducing inflammation by 20% Brewer’s yeast between the control and the low dose ketoprofen group. However, these differences were clinically insignificant as all the values were in the normal body temperature range. When analyzing temperature of the paw, we documented significantly higher local temperature in control compared to low dose ketoprofen group at the 1st hour after inflammation induction by carrageenan. When compared control and diclofenac groups after inflammation induction by Brewer´s yeast, due to earlier mentioned significantly higher values in control compared to low dose diclofenac group found at the baseline, the same difference found between the control and both diclofenac groups at the 1st hour cannot be considered. We can still suggest that at the 5th hour after inflammation

induction by carrageenan, diclofenac in the low dose loses its efficacy more drastically with lower mean values recorded in the control compared to the low dose diclofenac group, as well as in the high compared to the low dose diclofenac group. The documented superiority of ketoprofen may be due to its higher penetration through the skin (Bhargava et. al, 2019). Ketoprofen has been shown to be one of the best absorbed drugs and as one of the most potent NSAIDs for topical administration, while diclofenac has a lower ability to penetrate through the skin (Adachi et al., 2011). Drug formulation characterized by the ratio between lipid and aqueous solubility is the key to achieving its efficacy (Wiffen and Xia, 2020). When applied topically, the drug must be able to penetrate through the skin, subcutaneous fatty tissue, and muscle to act at the site of inflammation (da Costa et al., 2021). Testing the color, after carrageenan induced inflammation, at the 3rd and 5th hour, a significantly higher redness in control compared to high dose ketoprofen group, at the 1st and 3rd significantly higher redness in control compared to both diclofenac groups, suggesting diclofenac to be more potent than ketoprofen in the reduction of redness. These findings about the effects of diclofenac in the late accelerating phase of inflammatory response (2–6 hours post carrageenan injection) are in line with the available literature (Rao et al., 2019; Al-Majed et al., 2003; Santos et al., 2004; Tiwari et al., 2012). Anti-inflammatory activity demonstrated through the significant oedema reduction was achieved at the 3rd hour with the low dose of ketoprofen, and already at the 1st hour with high dose of diclofenac. Our results are consistent with the results shown in a study Kuznetsova et al. (2022). Ketoprofen and diclofenac efficacy in oedema reduction was demonstrated in carrageenan induced paw oedema model. Although local adverse reactions at the site of application, such as erythema and pruritus, are reported after topical application of NSAIDs, their important advantage when compared to the systemic use is the reduced number of systemic adverse reactions (Honvo et al., 2019). This is because the systemic concentration of those drugs after topical application is usually less than 5% of the concentration achieved after the oral administration (Bariguian Revel et al. 2020). Although low, those plasma concentrations are still sufficient to achieve a therapeutic effect by inhibiting cyclooxygenase 2 (Haroutiunian et al. 2010). 4.1. Limitations The limitations of this study are the small sample size, which is a feature of all preclinical research on laboratory animals, considering that the 3R principle must be respected (Lilley et al., 2021). Also, a limitation was the absence of a group of animals treated with NSAIDs per os to serve as a control.

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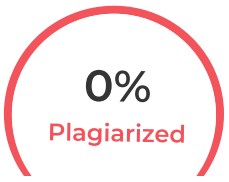

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5. Conclusions In conclusion, our results confirm the analgesic and anti-inflammatory efficacy of diclofenac and ketoprofen transdermal patches using a well-established rat models of yeast-induced paw hyperalgesia and carrageenan-induced inflammatory oedema. Such findings could lead to novel treatment approaches suggesting that diclofenac patch would be a useful formulation in clinical practice. However, new prospective double blind randomized clinical trials are necessary to evaluate analgesic and anti-inflammatory effect of topically applied NSAIDs when used in specific pain and inflammation indications.

Sources