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ORIGINAL ARTICLE

Comparative effects of topically applied diclofenac, ketoprofen, and piroxicam on interleukin-17, signal transducer and activator of transcription 3, and prostaglandin E2 levels in a rat model of collagen-induced arthritis

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ABSTRACT

Aim To evaluate and compare the effects of topically applied diclofenac, ketoprofen, and piroxicam on key inflammatory mediators, including interleukin-17 (IL-17), prostaglandin E2 (PGE2), and signal transducer and activator of transcription 3 (STAT3), in a rat model of collagen-induced arthritis (CIA).

Methods Thirty male Wistar rats were assigned to five groups: three experimental groups receiving topical diclofenac, ketoprofen, or piroxicam, respectively, a positive control group receiving a placebo patch, and a negative control group without collagen injection. CIA was induced using bovine type II collagen and incomplete Freund's adjuvant, with arthritis severity assessed through macroscopic scoring. NSAID patches were applied to the right hind paw for 6 hours daily over 5 days. Immunological parameters were quantified via enzyme-linked immunosorbent assay (ELISA). Statistical analysis included ANOVA, Kruskal-Wallis, and mixed-effects models to evaluate drug effects over time.

Results A significant difference was observed in tissue PGE levels ($F(4,25) = 4.235$; $p=0.009$; $\eta^2 = 0.404$), with diclofenac showing significantly lower values compared to the negative control and ketoprofen groups, while no significant differences were found for IL-17 or STAT3.

Conclusion Topical NSAIDs demonstrated selective anti-inflammatory effects, primarily through significant suppression of tissue PGE , confirming effective local COX pathway inhibition. The absence of significant changes in IL-17 and STAT3 suggests that short-term topical therapy mainly targets prostaglandin-mediated inflammation rather than upstream cytokine or transcriptional pathways involved in rheumatoid arthritis pathogenesis, warranting further investigation into their long-term therapeutic benefits.

Keywords: arthritis, IL-17, NSAID, PGE2, STAT3

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a diverse group of compounds that exert their therapeutic effects by competitively inhibiting cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis (1). These drugs target both COX-1, which is constitutively expressed and maintains normal homeostasis, and COX-2, which is induced in inflammatory conditions. While the primary mechanism of NSAIDs involves COX inhibition, emerging evidence suggests additional modes of action, including modulation of NF-κB and JAK3/STAT3 signalling pathways (2–4).

Topical NSAIDs have been developed to minimize systemic adverse events associated with oral administration (5). This

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route of administration offers several advantages, including localized drug action, reduced systemic exposure (0.2% to 8% of oral administration levels), and a lower risk of gastrointestinal and cardiovascular complications (6). From a pharmacokinetic perspective, topical application allows for pain reduction with lower daily doses, protection from gastric enzymes, avoidance of first-pass metabolism, and achievement of constant plasma drug concentrations (7,8).

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by joint inflammation and cartilage destruction (9,10). Its pathogenesis involves complex interactions between immune cells, cytokines, and synovial tissue. Key players in RA include fibroblast-like synoviocytes (FLS), T-lymphocytes (particularly Th17 cells), and various inflammatory mediators such as IL-17, STAT3, and PGE2 (11,12).

The pain mechanisms in RA are multifaceted, involving both peripheral and central nervous system components. Inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-17 directly alter nociceptive neuron responses, contributing to pain hypersensitivity (13). The synovial membrane serves as the primary site of pathogenesis, where complex cellular interactions and cytokine production occur.

NSAIDs remain an important component of RA management, primarily providing symptomatic relief through COX inhibition and subsequent suppression of prostaglandin synthesis (2,14). However, unlike disease-modifying antirheumatic drugs (DMARDs), NSAIDs do not alter the underlying course of the disease. Their clinical efficacy in controlling pain and inflammation nevertheless underscores the importance of further elucidating the inflammatory mechanisms involved in RA pathogenesis.

A review of the pharmaceuticals registered in Bosnia and Herzegovina on the website of the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (B&H) (www.almbih.gov.ba) revealed that no non-opioid analgesic products in transdermal patch form are currently available on the market. Furthermore, a literature search identified no studies from B&H or the broader region, addressing pain management through the topical administration of NSAIDs in patients with RA, either in preclinical or clinical settings.

The aim of this study was to assess and compare the effects of topically applied diclofenac, ketoprofen, and piroxicam on tissue concentrations of IL-17, STAT3, and PGE2 in a rat model of collagen-induced arthritis. By investigating these key immunological parameters, the study seeks to elucidate the local anti-inflammatory effects of topical NSAIDs and their potential role in modulating RA pathogenesis.

MATERIALS AND METHODS

Materials and study design

The study was conducted in June 2022 in an animal laboratory of the Medical Faculty, University of Sarajevo, and the Institute for Genetic Engineering and Biotechnology, University of Sarajevo (INGEB). It was conducted in compliance with the Guide for Care and Use of Laboratory Animals, adhering to applicable legal regulations (15) and principles for conducting experiments on laboratory animals (16), with an approval of the Ethics Committee of the Faculty of Medicine, University of Sarajevo (approval number 02-3-4-5194/20 dated 29 July 2020).

The study included 30 male Wistar rats (220-300g) from the in-house breeding. The rats were randomly divided into five groups: three experimental groups receiving topical diclofenac, ketoprofen, or piroxicam, respectively, a positive control group with a placebo patch, and a negative control group without collagen injection.

Methods

Arthritis was induced using an emulsion of bovine type II collagen (CII) and incomplete Freund's adjuvant (IFA) (Chondrex, Inc., Redmond, WA, USA), following the protocol described by Trentham et al. (1977) (17). Initial injections were administered on day 0, with a booster dose on day 7. The onset of arthritis was expected between days 10-13 and was confirmed by clinical scoring as follows: score 0 - no arthritis; score 1 - swelling and/or redness of 1 to 2 interphalangeal joints; score 2 - swelling and/or redness of 3 to 4 interphalangeal joints or 1 large joint; score 3 - swelling and/or redness of more than 4 joints; score 4 - severe arthritic changes of the entire paw.

Commercially available transdermal patches of diclofenac, ketoprofen, and piroxicam were applied to the dorsal side of the right hind paw for 6 hours daily over 5 consecutive days. Patch sizes were calculated based on human-to-rat dose conversion according to Nair and Jacob (2016) (18).

Immunological parameters were analysed at INGEB. Levels of interleukin 17 (IL-17), prostaglandin E2 (PGE2), and signal transducer and activator of transcription 3 (STAT3) were determined using enzyme-linked immunosorbent assay (ELISA) method, with samples prepared according to standardized manufacturer protocols. Specific ELISA kits were used for each parameter: Rat Prostaglandin E2 ELISA Kit (MyBioSource, Inc), Rat IL-17A SimpleStep ELISA® Kit (Abcam, ab214028), and Rat STAT3 Total SimpleStep ELISA Kit (Abcam, Ab176655). The PGE2 assay utilized polyclonal anti-PGE2 antibody and PGE2-HRP conjugate, with colour intensity inversely proportional to PGE2 concentration. The IL-17A kit, with a sensitivity of 1.1 pg/mL, employed a sandwich ELISA technique. STAT3 determination involved anti-tag antibody-coated wells and a specific antibody cocktail. For all assays, final measurements were performed spectrophotometrically at 450 nm, with signal intensity proportional to the amount of bound analyte. This comprehensive approach enabled accurate quantification of key inflammatory mediators in the rat model of collagen-induced arthritis, providing crucial data for assessing the effects of topically applied NSAIDs.

Statistical analysis

Normality and homogeneity of variances were assessed using QQ-plots, the Shapiro–Wilk test, and Levene's test. Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, or median (Q1–Q3) for non-normally distributed data, where Q1 and Q3 represent the first and third quartiles, respectively, defining the interquartile range (IQR). For normally distributed variables, between-group comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) post-hoc test. Non-normally distributed data were analysed using the Kruskal–Wallis test followed by Dunn's post-hoc test. Time-dependent effects were evaluated using mixed-effects ANOVA with repeated measures. Categorical and ordinal variables were analysed using Fisher's exact test or the Fisher–Freeman–Halton exact test, as appropriate.

Effect size for ANOVA was reported using eta-squared (η^2), which represents the proportion of total variance in the depen-

Table 1. Body weight of rats before collagen administration

Variable	Group						p^*
	Total (N = 30)	Ketoprofen (N = 6)	Diclofenac (N = 6)	Piroxicam (N = 6)	Positive-control (N = 6)	Negative-control (N = 6)	
Body weight Median (IQR) (g)	250 (238–270)	265 (252–270)	248 (238–261)	270 (254–286)	255 (239–271)	240 (231–249)	0.256

* Kruskal–Wallis test collects rank.

Table 2. Arthritis score values in groups by day

Group	Median (Q1–Q3) score value by the day									p^*
	10	11	12	13	14	15	16	17	18	
Ketoprofen	2.00 (2.00–2.50)	3.00 (2.25–3.75)	4.00 (3.25–4.00)	4.00 (4.00–4.75)	5.50 (4.25–7.50)	9.50 (8.25–10.00)	12.00 (10.50–12.00)	12.00 (11.25–12.00)	14.00 (13.25–14.00)	<0.001
Diclofenac	4.50 (4.00–5.00)	6.00 (5.25–6.00)	6.00 (6.00–6.75)	6.50 (6.00–7.75)	7.00 (6.25–7.75)	8.50 (8.00–9.75)	11.50 (10.25–12.00)	12.00 (12.00–12.75)	13.00 (12.25–13.75)	<0.001
Piroxicam	3.50 (2.00–5.00)	6.00 (6.00–6.00)	6.00 (6.00–6.75)	7.00 (7.00–7.75)	8.00 (7.25–8.75)	9.50 (8.25–10.00)	10.50 (10.00–11.00)	12.00 (12.00–12.75)	14.00 (13.25–14.00)	<0.001
Positive control	5.00 (4.25–5.00)	6.00 (5.25–6.75)	6.00 (5.25–6.75)	7.00 (6.00–8.00)	7.00 (6.00–8.00)	9.00 (8.00–10.00)	10.50 (10.00–11.75)	12.00 (12.00–12.00)	13.00 (12.00–14.00)	<0.001
Negative control	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	

* Kruskal–Wallis test collects rank.

dent variable explained by the independent variable. Effect size estimates were also used to describe the magnitude and direction of differences between group means, where the sign indicates the direction of the effect relative to the comparator group. All statistical tests were two-tailed, and the significance level was set at $\alpha = 0.05$. Where applicable, corrections for multiple comparisons were applied.

RESULTS

The study included 30 Wistar rats, with an average body weight of 255 grams. The lowest recorded weight at the beginning of the experiment was 210 grams, and the highest was 310 grams. The lowest median body weight was recorded within the negative control (240 g), and the highest within the piroxicam-exposed group (270 g). No statistically significant difference was recorded between the 5 groups (p = 0.256) in body weight before the beginning of the experiment (Table 1).

The lowest value of the arthritis induction score in the groups on day 10 was 1, and the highest was 6. On day 14, these values were 4 and 10, and on day 18 of the experiment, these values were 12 and 14 (Table 2).

All individuals in all groups had a statistically significant difference in the induced arthritis score (p < 0.001) from day 10 to the end of the experiment. In the negative control group, no changes in the induced arthritis score were recorded during the experiment. The lowest median (Q1-Q3) value on day 10 was recorded in the ketoprofen group, 2.00 (2.00-3.50), and the highest in the positive control, 5.00 (4.25-5.00). The lowest median (Q1-Q3) value on day 14 was recorded in the ketoprofen group, 5.50 (4.25-7.50), and the highest in the piroxicam group, 8.00 (7.25-8.75). On day 18, the median (Q1-Q3) values in the positive control and diclofenac groups were equal, 13.00 (12.00-14.00), and a higher value, 14.00 (13.25-14.00) was recorded in the piroxicam and ketoprofen groups.

Arthritis score values did not differ significantly between the experimental groups on day 10 (p = 0.088), day 14 (p = 0.209) and day 18 (p = 0.609).

Immunological parameters in all groups were compared using a one-way ANOVA test. The lowest mean PGE2 values were recorded in the diclofenac-treated group, 1.472 (± 0.141) ng/dL. The values recorded in the piroxicam-treated group were 1.726 (± 0.189) ng/dL, in the positive control 1.729 (± 0.222) ng/dL, and the values recorded in the ketoprofen-treated group were 1.777 (± 0.115) ng/dL. The highest values were in the negative control, 1.876 (± 0.197) ng/dL (Table 3).

A statistically significant difference between the groups was found: F(4,25)=4.235 (p = 0.009) with $\eta^2 = 0.404$ in PGE2 values.

Table 3. Tissue immunological parameter values

Immunological parameter	Median (Q1–Q3)					F(4,25)	p
	Ketoprofen (N = 6)	Diclofenac (N = 6)	Piroxicam (N = 6)	Positive control (N = 6)	Negative control (N = 6)		
PGE2 (ng/ml)	1.777 (± 0.115)	1.472 (± 0.141)	1.726 (± 0.189)	1.729 (± 0.222)	1.876 (± 0.197)	4.2	0.009
IL-17 (pg/ml)	0.121 (± 0.026)	0.117 (± 0.026)	0.094 (± 0.043)	0.119 (± 0.020)	0.092 (± 0.023)	1.5	0.23
STAT3 (μg/ml)	0.212 (± 0.083)	0.143 (± 0.055)	0.157 (± 0.037)	0.191 (±0.043)	0.151 (± 0.039)	1.8	0.17

* One-way ANOVA test.

Table 4. Tukey's honestly significant difference (HSD) test for prostaglandin E2 (PGE2)

Group	Negative control		Positive control		Piroxicam		Diclofenac	
	Effect size (ng/ml)	p	Effect size (ng/ml)	p	Effect size (ng/ml)	p	Effect size (ng/ml)	p
Ketoprofen	0.098	0.870	−0.048	0.989	−0.051	0.987	−0.305	0.046
Diclofenac	0.403	0.005	0.257	0.121	0.254	0.128		
Piroxicam	0.149	0.598	0.003	1.000				
Positive control	0.147	0.614						

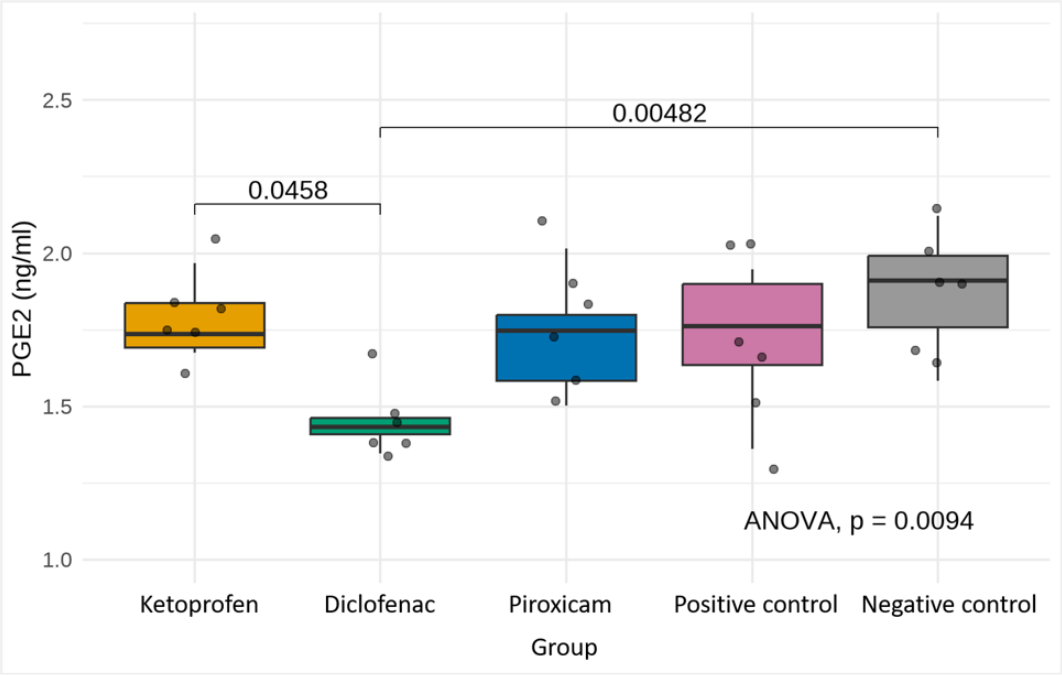

Figure 1. Tissue prostaglandin E2 (PGE2) values

Post-hoc analysis of mean values revealed a statistically significant difference (p= 0.005) in PGE2 values in the group treated with diclofenac compared with the negative control, with an effect size of -0.403 ng/dL. Also, a statistically significant difference (p=0.046) with a lower effect size of -0.305 ng/dL was recorded in the comparison of the group treated with diclofenac and the group treated with ketoprofen (Table 4).

No statistically significant differences in PGE2 values were recorded between the other groups (Figure 1). The lowest mean IL-17 values were recorded in the negative control, 0.092 (± 0.023) pg/dL. In the piroxicam-treated group, the recorded mean values were 0.094 (±0.043) pg/dL. In the diclofenac-treated group, the mean IL-17 concentration was 0.117 (± 0.026) pg/dL, and in the positive control, the concentration was 0.119 (± 0.020) pg/dL. The highest mean IL-17 values were in the ketoprofen-treated group (0.121 (± 0.026) pg/dL.

No statistically significant differences between the groups were found: $F(4,25) = 1.493$ ($p = 0.234$) with $\eta^2 = 0.193$ in IL-17 values. Post-hoc tests for group comparisons quantified effect size s ranging from -0.029 pg/mL ($p = 0.414$) to 0.024 pg/mL ($p = 0.593$), none of which were statistically significant.

The lowest mean STAT3 values were recorded in the diclofenac-treated group, 0.143 (± 0.055) ng/dL. The mean values recorded in the negative control were 0.151 (± 0.039) ng/dL, in the piroxicam-treated group, 0.157 (± 0.037) ng/dL, and the values recorded in the positive control group were 0.191 (± 0.043) ng/dL. The highest mean values were in the ketoprofen-treated group, 0.212 (± 0.083) ng/dL. No statistically significant differences between groups were found, $F(4,25) = 1.762$ ($p = 0.168$) with η^2=0.22 in STAT3 values. Post-hoc tests for group comparisons quantified effect sizes ranging from -0.069 µg/mL ($p = 0.21$) to 0.048 µg/mL ($p = 0.556$), none of which were statistically significant.

DISCUSSION

This study aimed to investigate the effects of topically applied NSAIDs (diclofenac, ketoprofen, and piroxicam) on tissue concentrations of IL-17, STAT3, and PGE2 in a rat model of collagen-induced arthritis (CIA). The findings provide insight into the local immunopharmacological effects of these commonly used anti-inflammatory agents in experimental RA.

The statistical analysis demonstrated a significant difference in tissue PGE2 levels among the groups, confirming that NSAID treatment effectively modulates the COX pathway at the local level. A statistically significant group effect ($F(4,25) = 4.235$; $p = 0.009$) with a large effect size ($\eta^2 = 0.404$) was found, indicating that approximately 40% of the variance in PGE levels can be attributed to treatment differences. Post-hoc analysis showed that diclofenac significantly reduced PGE levels compared with the negative control, as well as compared with ketoprofen, highlighting diclofenac as the most effective agent in suppressing prostaglandin synthesis in this model.

In contrast, no statistically significant differences were observed in IL-17 or STAT3 concentrations between the groups. Although numerical variations were present, ANOVA results for IL-17 ($F(4,25) = 1.493$; $p = 0.234$; $\eta^2 = 0.193$) and STAT3 ($F(4,25) = 1.762$; $p = 0.168$; $\eta^2 = 0.22$) did not reach statistical significance, and post-hoc comparisons confirmed the absence

of meaningful intergroup differences. These findings suggest that, under the present experimental conditions, topical NSAIDs exert predominantly prostaglandin-cantered anti-inflammatory effects without substantial modulation of Th17-associated cytokine signalling or STAT3-mediated transcriptional pathways.

The significant reduction in PGE2, particularly in the diclofenac-treated group, is consistent with the well-established mechanism of NSAIDs as cyclooxygenase inhibitors. PGE2 plays a central role in RA pathogenesis by promoting vasodilation, edema formation, nociceptor sensitization, cartilage degradation, and bone resorption (19,20). The ability of topically applied NSAIDs to significantly reduce local PGE2 concentrations provides a clear mechanistic basis for their analgesic and anti-inflammatory effects in RA (21,22).

The stronger effect observed with diclofenac may reflect its pharmacodynamic potency, tissue penetration capacity, or relative COX-2 selectivity (23).

Although reductions in IL-17 and STAT3 were not statistically significant, the biological trends observed warrant cautious interpretation. IL-17 is a key cytokine in RA pathogenesis, driving neutrophil recruitment, synovial inflammation, and osteoclastogenesis (12). Similarly, STAT3 is an important transcription factor involved in cytokine signaling and fibroblast-like synoviocyte activation (FLS), key cellular mediators of joint destruction in RA (24,25). The absence of statistically significant modulation suggests that short-term topical NSAID therapy may not directly influence adaptive immune pathways or intracellular transcriptional regulators in this model. Rather, their primary effect appears confined to downstream inflammatory mediators such as prostaglandins.

These findings support the concept that classical NSAIDs, particularly when administered topically, mainly target effector inflammatory pathways rather than upstream cytokine networks (5,6). While emerging evidence suggests that NSAIDs may exert COX-independent effects, including modulation of NF-κB signalling and cytokine production, such effects have not been clearly demonstrated in the present study (3). It is possible that longer treatment duration, higher local concentrations, or alternative experimental conditions might be required to detect significant changes in IL-17 or STAT3 activity.

The differential efficacy observed in PGE suppression underscores the importance of considering individual pharmacological properties when selecting topical NSAIDs (26,27). Variations in lipid solubility, dermal penetration, and local tissue bioavailability may explain the superior performance of diclofenac compared to ketoprofen in this model (7).

Several limitations should be acknowledged. The relatively small sample size (N = 6 per group) may have limited statistical power to detect moderate differences in IL-17 and STAT3. Additionally, the acute experimental design may not fully replicate the chronic and complex immunopathology of RA. Only three inflammatory mediators were evaluated, which restricts comprehensive assessment of the broader cytokine network. Furthermore, systemic absorption of the topically applied NSAIDs was not assessed.

In conclusion, the results of this study demonstrate that topical diclofenac, ketoprofen, and piroxicam effectively reduce tissue PGE levels in a rat model of collagen-induced arthritis, with diclofenac showing the most pronounced, significant effect. However, no significant modulation of IL-17 or STAT3 was observed. These findings indicate that the therapeutic benefit of topical NSAIDs in this experimental model is primarily mediated through inhibition of prostaglandin synthesis rather than through direct modulation of Th17 or STAT3 signalling pathways, collectively suggesting that their anti-inflammatory effects are largely confined to downstream COX–PGE -mediated mechanisms with minimal impact on upstream immune signalling. Further studies are required to clarify whether prolonged treatment or combination strategies could influence upstream immune mechanisms relevant to RA pathogenesis.

FUNDING

No specific funding was received for this study.

CONFLICT OF INTERESTS

None to declare.

ETHICS STATEMENT

Research was conducted with an approval of the Ethics Committee of the Faculty of Medicine, University of Sarajevo (approval number 02-3-4-5194/20 dated 29 July 2020).

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request and with permission of the institution.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualization: S.M.K.; **Data curation:** S.M.K., E.D., N.Č., B.T.; **Formal analysis:** S.M.K., L.B.R., M.R.-T.; **Investigation:** S.M.K., L.B.R.; **Methodology:** S.M.K., L.B.R., E.D., N.Č.; **Supervision:** E.D., E.H., M.R.-T.; **Writing – original draft:** S.M.K., B.T.; **Writing – review & editing:** N.Č., E.H. All authors have read and agreed to the published version of the manuscript.

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