CONFERENCE PAPER

EVALUATION OF THE HEMATOLOGICAL RESPONSE TO VARIOUS THERAPEUTIC APPROACHES IN THE MANAGEMENT OF OPEN WOUNDS: AN EXPERIMENTAL STUDY IN RODENTS

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ABSTRACT

Hematological analyses are important in veterinary and human medicine for early detection of homeostatic changes and assessment of systemic responses to injury, stress, and therapy. In this study, the hematological response of Wistar rats with surgically induced wounds was analyzed following treatment with natural and synthetic therapeutic agents.

Twenty-four healthy adult Wistar rats were randomized into six groups (n = 4): surgical control (C), gentamicin ointment (AB), Manuka honey MGO 250+ (MH1), Manuka honey MGO 550+ (MH2), chlorine dioxide (CL), and absolute control without incision and therapy (CC). After a standardized abdominal incision (except CC), treatments were applied twice daily for 7 days. On day 7, hematological parameters and peripheral blood smears were analyzed.

Significant intergroup differences were found in WBC ($p = 0.030$), lymphocytes ($p = 0.020$), RBC ($p = 0.002$), MCV and MCH ($p < 0.001$), RDW-CV and RDW-SD ($p < 0.001$). Elevated estimated marginal means were most consistent in MH1, MH2, and CC, particularly for WBC, lymphocytes, RBC, and red cell indices, suggesting a more pronounced hematological response.

Poikilocytosis was present in all groups, with annulocytes most prevalent (up to 6.01% in MH1), followed by dacryocytes and ovalocytes. The leukogram showed lymphocyte dominance in all groups, with the highest percentage in MH1 (65.75%), and the highest neutrophil percentage in AB (47.75%).

This study provides insight into potential differences in the hematological response to natural and synthetic wound treatments in an animal model, and serves as a basis for further research into the biological safety and efficacy of the therapies used.

Keywords: Chlorine dioxide, experimental wound, gentamicin, Manuka honey, poikilocytosis

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INTRODUCTION

The skin, as the body's primary protective barrier, responds to injury by initiating a cascade of complex biological processes aimed at restoring its structural integrity and reestablishing its thermoregulatory, endocrine, and sensory functions (Al-Masawa et al., 2022). Being the largest organ in mammals, the skin functions as a multilayered interface between the organism and its environment, providing critical protection to internal organs against external insults, while simultaneously playing a central role in maintaining fluid homeostasis, regulating body temperature, and supporting immunological, neurological, and metabolic activities (Percival et al., 2015; WHO, 2009; DeBoer and O'Connor, 2004).

However, wounds represent a significant disruption of this protective barrier, often accompanied by bacterial contamination. This contamination remains one of the primary causes of delayed healing and wound complications, as wounds frequently harbor diverse microorganisms—many of which are potentially pathogenic and capable of triggering purulent infections (Kožár et al., 2018; Rijal et al., 2017). The increasing prevalence of antibiotic-resistant bacteria, virulent strains, and novel pathogens has intensified the search for effective, alternative antimicrobial agents for use in both human and veterinary medicine (Chapnik and Wilkins, 2014).

Among the most promising alternatives is chlorine dioxide (ClO_2), a water-soluble gas with potent broad-spectrum antimicrobial properties. It has been widely utilized in water purification and the food industry, and is increasingly recognized in healthcare settings for its efficacy against bacteria, viruses, and fungi, combined with low cytotoxicity (Simpson et al., 1993; Sanekata et al., 2010; Wen et al., 2017; Venkatnarayanan et al., 2017; Bridges et al., 2018; Palcsó et al., 2019).

In parallel, natural substances such as manuka honey, derived from *Leptospermum scoparium*, have gained substantial attention due to their proven antibacterial, anti-inflammatory, and immunostimulatory effects (Mandal and Mandal, 2011; Ahmed et al., 2003). Manuka honey promotes wound healing through multiple mechanisms, including modulation of the local immune response, stimulation of tissue regeneration, and inhibition of microbial colonization (Yao et al., 2003).

In both human and veterinary medicine, the evaluation of hematological parameters plays a fundamental role in the early detection of pathological conditions, monitoring of therapeutic efficacy, and overall assessment of health status (Katica and Gradaščević, 2017; Katica and Delibegović, 2019). These parameters are key indicators of physiological and pathological processes, and offer insight into systemic alterations induced by local injuries or treatments (Ihedioha, 2004).

Despite the well-documented therapeutic properties of manuka honey and chlorine dioxide, current literature remains limited regarding their systemic hematological effects when applied topically to skin wounds. Most available studies focus on antimicrobial efficacy or healing outcomes, while data on hematological responses, particularly in experimental models are scarce. Furthermore, existing research primarily investigates oral or parenteral administration routes, leaving a significant gap in understanding the systemic implications of localized wound treatments.

Therefore, the aim of this study was to evaluate the hematological response to topical application of manuka honey, chlorine dioxide, and antibiotic in rats with surgically induced skin wounds. By assessing hematological parameters as systemic biomarkers, this study seeks to provide a deeper understanding of the organism's response to various wound therapies and contribute to the identification of effective alternative treatment options.

MATERIAL AND METHODS

Ethics committee approval

This study was approved by the Ethics Committee of the Veterinary Faculty of the University of

Sarajevo, who gave a positive opinion under number: 07-03-1103-2/24, from 04.12.2024.

Animal model

In the research 24 clinically healthy adult rats of both sexes, Wistar strain, aged 2-3 months, with an average weight 180-250 g were used. The rats had free access to food and water provided during the experiment, and 12-hour rotations of light and dark. The ambient temperature was maintened between 20-23^{0}C and humidity 60%±10% (Katica and Gradaščević, 2017).

General experimental procedure and study groups

The twenty-four rats were randomly divided into six groups depending on which treatment was used. The first group C (4 rats) received no therapy and served as the surgical control. The second group A (4 rats) was treated with gentamicin ointment (gentamicin Bosnalijek 1mg/g). The third group MH1 (4 rats) received Manuka honey MGO 250+ (Manuka Health, Te Awamutu, New Zealand). Fourth group MH2 (4 rats) received Manuka honey MGO 550+ (Manuka Health, Te Awamutu, New Zealand). The fifth group CLO (4 rats) was treated with chlorine dioxide (Dioxy Activ Supra), and the sixth group CC (4 rats) consisted of rats without surgical incision and without therapy, serving as the absolute control group.

Surgical procedure

Prior to the surgical intervention, all tested animals were acclimatized to the experimental conditions. General anesthesia was induced by intramuscular injection of 5 mg/kg xylazine hydrochloride 2% (2% Xylazin, CpPharma, Bergdorf, Germany) and 60 mg/kg ketamine hydrochloride (International B.V. Netherlands). Once surgical anesthesia was confirmed, the rats abdominal hair was carefully removed to ensure clear visibility and access to the surgical site. A 4 cm longitudinal incision was made through skin and subcutaneous tissue along the median abdominal line, exposing a wound surface in constant contact with the non-sterile bedding. After 24 hours, each animals received treatment depending on the group it was in. Therapies were administered twice daily for seven (7) consecutive days.

Study design

Hematological – biochemical procedures

On the seventh day of the experiment, peripheral blood samples were taken by tail vein puncture in EDTA vacutainers with a volume of 3 ml. The puncture site was previously disinfected with standard disinfectants. Analysis of hematological parameters was performed using a Mindray BC-20S automated hematology analyzer. The following parameters were determined: red blood cell count (RBC, $\times10^{12}$/L), hemoglobin concentration (HGB, g/L), hematocrit (HCT, L/L), mean corpuscular volume (MCV, fL), mean corpuscular hemoglobin (MCH, pg), mean corpuscular hemoglobin concentration (MCHC, g/L), red cell distribution width – coefficient of variation (RDW-CV) and standard deviation (RDW-SD, fL), white blood cell count (WBC, $\times10^9$/L), granulocyte count and percentage (Gran#, Gran%, $\times10^9$/L), lymphocyte count and percentage (Lym#, Lym%, $\times10^9$/L), monocyte count and percentage (Mon#, Mon%, $\times10^9$/L), and platelet count (PLT, $\times10^9$/L).

Cells of the leukocyte order were differentiated, and numerical values were expressed as percentages after 1000 such cells were analyzed. Differentiated: lymphocytes (L) (%), monocytes (M) (%), neutrophils (N) (%), basophils (B) (%) and eosinophils (E) (%).

Values are shown in percentages (Bajrić et al., 2020; Katica et al., 2019).

Quantification of poikilocytotic erythrocytes

Blood smears of peripheral blood were made, dried in air and stained by the Giemsa method. They were processed according to standard technical laboratory procedures. Poikilocytes were assessed semiquantitatively (Christopher et al., 2014).

On each original stained smear, 2000 erythrocytes were counted and characterized at a microscopic magnification of 1000 X. Poikilocytes were defined on the basis of standard morphology, and counting was limited to representative monolayer

fields in which about half of the erythrocytes touched but did not overlap. The number and type of poikilocytes was recorded and expressed as a percentage of the red blood cells. Poikilocytosis was then classified as: absent (0%), rare (0.05-0.5%), mild (>0.5-3%), moderate (>3-10%) and pronounced (>10%).

Statistical data processing

All data are presented as arithmetic means and standard deviations (SD). The normality of distribution within groups was assessed using the Shapiro-Wilk test. For variables that showed a normal distribution ($p > 0.05$), one-way analysis of variance (ANOVA) was applied to determine intergroup differences. In addition, estimated marginal means with 95% confidence intervals were calculated and visualized to better illustrate intergroup variation and deviation from the overall mean. Data analysis was done using SPSS software (version 21.0. IBM). The level of statistical significance was set at $p<0.05$.

RESULTS

Results of peripheral blood parameters

For all variables of peripheral blood parameters across all experimental groups, the results of the Shapiro-Wilk (SW) test indicated a normal distribution of data ($p > 0.05$). Therefore, the data met the assumptions for parametric statistical analysis. Table 1 presents the arithmetic means and standard deviations (Mean ± SD) for each measured parameter across all groups.

Table 1 Arithmetic means and standard deviations (Mean ± SD) of hematological parameters in all experimental groups. Data normality was assessed using the Shapiro-Wilk test (SW); p-values greater than 0.05 indicate normal distribution

	C				AB				MH1				MH2				CLO				CC			
	Mean	SD	SW test	p	Mean	SD	SW test	p	Mean	SD	SW test	p	Mean	SD	SW test	p	Mean	SD	SW test	p	Mean	SD	SW test	p
WBC $(x10n^9/L)$	2.45	0.43	0.921	0.541	3.16	0.57	0.787	0.08	3.76	0.87	0.931	0.6	3.73	0.73	0.805	0.111	2.80	0.53	0.761	0.049	4.45	1.37	0.853	0.236
Gran# $(x10n^9/L)$	1.16	0.15	0.856	0.245	1.52	0.19	0.86	0.262	1.65	0.40	0.951	0.722	1.69	0.30	0.931	0.6	1.39	0.27	0.969	0.833	1.90	0.53	0.892	0.391
Lym# $(x10n^9/L)$	1.19	0.28	0.919	0.533	1.50	0.37	0.873	0.31	1.96	0.47	0.836	0.185	1.90	0.46	0.764	0.052	1.28	0.28	0.886	0.364	2.34	0.77	0.944	0.677
Mon# $(x10n^9/L)$	0.10	0.01	0.863	0.272	0.14	0.02	0.95	0.714	0.16	0.03	0.935	0.625	0.14	0.03	0.991	0.962	0.13	0.05	0.853	0.235	0.22	0.10	0.9	0.431
Gran%	0.48	0.03	0.893	0.397	0.48	0.04	0.9	0.432	0.44	0.03	0.912	0.494	0.45	0.04	0.772	0.061	0.50	0.05	0.941	0.658	0.43	0.04	0.895	0.404
Lym%	0.48	0.03	0.898	0.42	0.47	0.04	0.923	0.555	0.52	0.03	0.873	0.31	0.51	0.04	0.812	0.126	0.46	0.05	0.952	0.727	0.52	0.04	0.886	0.366
Mon%	0.04	0.00	0.928	0.584	0.05	0.00	0.848	0.22	0.04	0.00	0.971	0.85	0.04	0.01	0.999	0.998	0.05	0.01	0.955	0.748	0.05	0.01	0.912	0.492
RBC	8.14	0.36	0.879	0.334	8.71	0.34	0.987	0.942	9.29	0.32	0.961	0.784	9.20	0.37	0.868	0.291	8.47	0.42	0.882	0.349	8.28	0.48	0.803	0.108
HGB (g/L)	148.00	9.90	0.823	0.15	148.50	4.44	0.963	0.798	156.00	5.60	0.881	0.343	152.75	5.85	0.96	0.78	158.50	27.70	0.885	0.361	145.50	7.94	0.946	0.689
HCT	0.46	0.02	0.925	0.565	0.47	0.02	0.965	0.809	0.50	0.02	0.772	0.061	0.49	0.01	0.885	0.359	0.45	0.03	0.935	0.627	0.46	0.03	0.847	0.217
MCV (fL)	56.75	0.72	0.828	0.163	53.70	1.24	0.837	0.186	54.13	0.69	0.856	0.245	53.63	1.24	0.934	0.615	53.18	0.97	0.97	0.84	55.78	0.51	0.93	0.594
MCH (pg)	18.15	0.44	0.963	0.798	17.00	0.43	0.927	0.577	16.80	0.22	0.927	0.577	16.63	0.21	0.926	0.572	16.95	0.31	0.972	0.855	17.58	0.31	0.92	0.538
MCHC (g/L)	320.25	5.56	0.994	0.975	316.75	5.50	0.908	0.473	310.75	2.22	0.801	0.103	310.00	5.23	0.859	0.256	318.50	0.58	0.729	0.024	315.50	5.57	0.957	0.759
RDW-CV	0.15	0.00	0.993	0.972	0.13	0.00	0.828	0.163	0.14	0.01	0.985	0.933	0.15	0.01	0.953	0.735	0.15	0.00	0.971	0.85	0.15	0.01	0.881	0.343
RDW-SD (fL)	33.13	0.63	0.997	0.991	27.63	0.94	0.937	0.634	29.13	1.60	0.965	0.813	30.25	2.31	0.836	0.185	30.75	1.17	0.91	0.483	32.85	1.37	0.885	0.362
PLT $(x10n^9/L)$	1039.75	154.79	0.968	0.828	990.50	117.69	0.917	0.519	1055.25	96.57	0.89	0.383	1179.00	165.92	0.978	0.891	1274.00	253.93	0.953	0.734	901.25	50.77	0.854	0.24

The analysis of variance (ANOVA) results are summarized in Table 2. Statistically significant differences among groups were observed for several parameters, including WBC ($p = 0.030$), lymphocyte count (Lym#; $p = 0.020$), RBC ($p = 0.002$), MCV ($p < 0.001$), MCH ($p < 0.001$), RDW-CV ($p = 0.001$), RDW-SD ($p < 0.001$), and PLT ($p = 0.037$). Other parameters did not show significant differences ($p > 0.05$). Table 2 shows the arithmetic means and standard deviations for each parameter across all groups.

Table 2 Analysis of variance (ANOVA of blood parameters between six groups of rats tested)

	Sum of squares	df	Mean square	F	p
WBC (x10n9/L)	10.68*	5	2.14	3.230	**0.030**
Gran# (x10n9/L)	1.32	5	0.27	2.399	0.078
Lym# (x10n9/L)	3.93*	5	0.79	3.569	**0.020**
Mon# (x10n9/L)	0.03	5	0.01	2.540	0.066
Gran%	0.01	5	0.00	2.073	0.116
Lym%	0.02	5	0.00	1.957	0.134
Mon%	0.00	5	0.00	1.305	0.306
RBC (x10n12/L)	4.55**	5	0.91	6.191	**0.002**
HGB (g/L)	512.21	5	102.44	0.607	0.696
HCT	0.01	5	0.00	2.128	0.062
MCV (fL)	39.95**	5	7.99	9.101	**0.000**
MCH (pg)	6.54**	5	1.31	11.798	**0.000**
MCHC (g/L)	342.71	5	68.54	1.297	0.077
RDW-CV	0.00**	5	0.00	7.517	**0.001**
RDW-SD (fL)	90.43**	5	18.09	8.734	**0.000**
PLT (x10n9/L)	357445.71*	5	71489.14	3.027	**0.037**

Quantification of poikilocytotic forms of erythrocytes and leukogram results (%)

Table 3 Determined poikilocytotic forms of RBCs in groups expressed in (%) from 2,000 analyzed RBCs

Types of poikilocytotic forms RBC	Group CC	Group C	Group AB	Group MH1	Group MH2	Group ClO
Ovalocytes	0.35	0.52	0.32	0.33	0.48	0.60
Dacrocytes	0.48	0.52	1.00	1.10	1.08	0.53
Anulocytes	5.00	4.53	3.85	6.01	5.66	5.47
Echinocytes	0.05	0.11	0.06	0.06	0	0.18
Stomatocytes	1.31	0.72	0.40	1.22	0.60	0.80
Drepanocytes	0	0	0	0	0	0
Schistocytes	0.15	0.16	0.18	0.13	0.10	0.18
Codocytes	0.30	0.16	1.31	0.55	0.80	1.48
Acanthocytes	0.01	0	0	0	0	0.01
Spherocytes	0.13	0.57	0.41	0.17	0.22	0.25

Table 4 Leukogram results (%)

Groups	Neutrophil	Lymphocyte	Monocyte	Basophil	Eosinophil
CC	35.25	61.5	1.25	0	1.75
C	41.0	57.00	0.25	0	1.75
AB	47.75	51	0	0	1.0
MH1	33.5	65.75	0.25	0	0.25
MH2	40.25	50.0	0	0	2.25
ClO	42.0	55.25	0.25	0	2.5

Original microscopic photos of individual poikilocytotic forms of erythrocytes from six groups of tested rats (Figure 1)

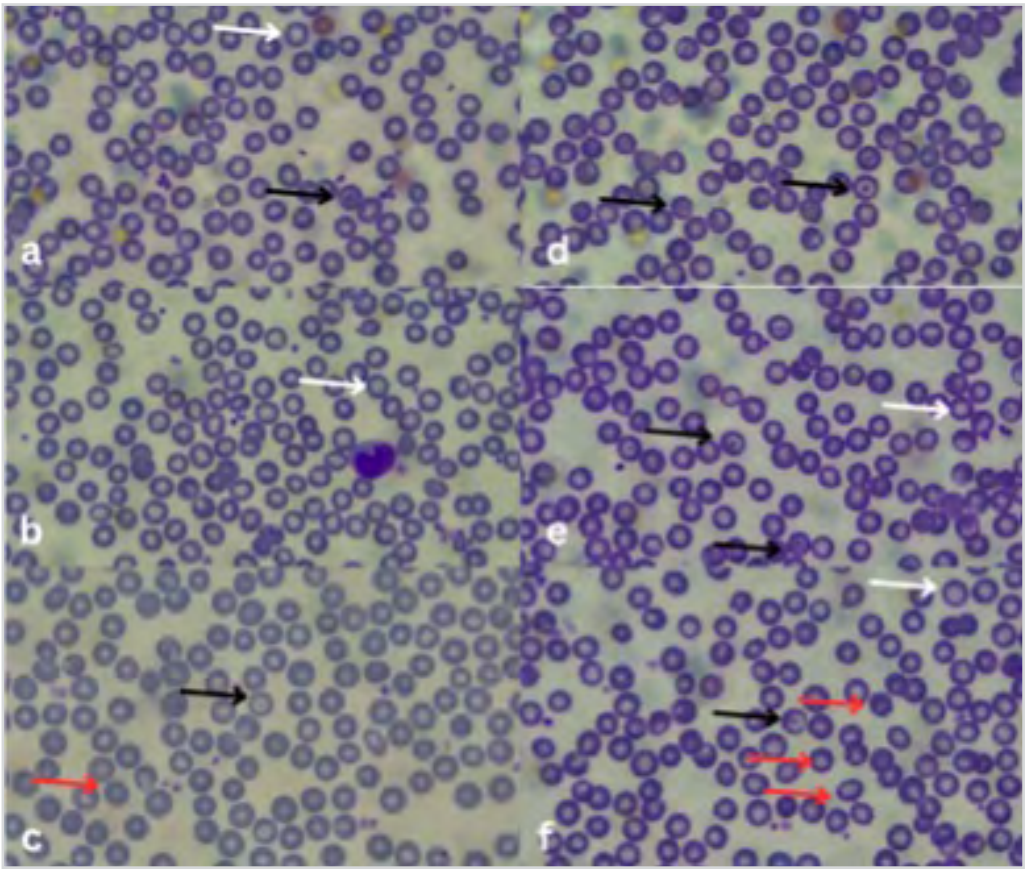

Figure 1 Poikilocytotic forms of erythrocytes a) AB group; b) CC group; c) C group; d) MH1 group; e) MH2 group and f) CLO group. Black arrows indicate target cells, white arrows anulocytes and red arrows echinocytes

DISCUSSION AND CONCLUSION

The skin, as the largest organ, protects internal organs and maintains homeostasis; however, its integrity can be compromised by wounds that often harbor diverse microorganisms. Bacterial contamination remains one of the primary causes of complications in the wound healing process, as many of these microbes can be potentially pathogenic and lead to purulent infections (Percival et al., 2015; Kožár et al., 2018; Rijal et al., 2017).

With the emergence of antibiotic-resistant bacteria, more virulent strains, and new pathogens, the need to find effective antimicrobial agents for wound treatment in veterinary medicine has become increasingly urgent (Chapnik and Wilkins, 2014).

Chlorine dioxide (ClO_2) has gained notable attention as a promising agent due to its strong antimicrobial properties against a wide range of bacteria, fungi, and viruses. Originally utilized as a gaseous, water-soluble disinfectant in water purification and the food industry, it is now increasingly considered for medical purposes. Its broad-spectrum activity combined with relatively low toxicity makes it a compelling option for healthcare applications (Sanekata et al. 2010; Wen et al. 2017; Venkatnarayanan et al. 2017; Bridges et al. 2018; Palcsó et al. 2019).

The therapeutic potential of manuka honey, particulary its role in modulating immune responses and microbial control, has been acknowledged in previous studies, which underlines its relevance in wound healing contexts (Mandal and Mandal, 2011; Ahmed et al., 2003; Yao et al., 2003).

The CC group exhibited the highest WBC (4.45×10^9/L), indicating strong systemic immune activation. In contrast, the untreated control group (C) showed the lowest WBC (2.45×10^9/L), suggesting a suppressed hematological response. The antibiotic group (AB) showed moderate elevation (3.16×10^9/L), while the manuka honey-treated groups MH1 (3.76×10^9/L) and MH2 (3.73×10^9/L) presented significantly increased values. These findings confirm the capacity of both natural and synthetic topical agents to influence systemic immune profiles.

Lymphocyte count followed a similar trend, with significantly higher values in CC (2.34×10^9/L), MH1 (1.96×10^9/L), and MH2 (1.90×10^9/L) compared to control (1.19×10^9/L), confirming immune modulation. Leukogram revealed a lymphocyte-dominant profile, especially in MH1 (65.75%) and CC (61.5%), while AB had the highest neutrophil percentage (47.75%), possibly reflecting acute antimicrobial activity induced by antibiotic treatment.

The increased RBC values in MH1 and MH2 compared to control, along with moderately altered RDW-SD values, suggest stimulated erythropoesis and red blood cell turnover. However, MCV and MCH values in these groups were lower than those in the control group, indicating microcytic and hypochromic characteristics. These findings are consistent with previous studies reporting that honey administration can modulate hematological parameters even in the absence of disease (Aliyu et al., 2012). Akinbami et al. (2013) reported that alterations in RBC, Hb, PCV, RDW, and lymphocytes can impact disease progression and prognosis. However, in their study, honey was administered orally, whereas in our model manuka honey was applied topically, possibly explaining the localized and moderate hematological changes observed.

A related study on burn injury reported significantly decreased RBC, MCV, and MCH values following thermal damage, with WBC counts varying depending on the treatment protocol. Platelet levels remained comparable to healthy controls, and neutrophils and eosinophils were largely unaffected (Kulyar et al., 2022). These results are in line with our findings, suggesting that immune modulation may be highly context-dependent and influenced by the extent of tissue injury and reparative mechanisms.

Morphological erythrocyte analysis revealed increased anulocytes in MH1 (6.01%) and MH2 (5.66%) compared to the control group (4.53%), potentially indicating regenerative erythropoiesis

or oxidative stress. Elevated frequencies of dacryocytes and codocytes in MH1, AB, and CC further support the presence of systemic stress or treatment-induced hematological adaptation. Interestingly, codocytes were most prominent in the ClO_2 group (1.48%), suggesting that chlorine dioxide may influence red cell membrane dynamics.

Chlorine dioxide (ClO_2), traditionally used as a gaseous water-soluble disinfectant in industrial and food sectors, is gaining increasing attention in healthcare due to its potent antimicrobial properties and low toxicity. It has demonstrated efficacy against bacteria, viruses, fungi, and other pathogens, and is recognized for accelerating wound healing, particularly in burn injuries (Young, 2016). In our study, ClO_2 induced moderate WBC (2.80×10^9/L) and lymphocyte (1.28×10^9/L) elevations, accompanied by an increased eosinophil count (2.5%), indicating immunological activity and systemic reactivity. In accordance with the above, our research corresponds with the study conducted by Young (2016).

Platelet count remained within the expected physiological range across all experimental groups, showing no marked thrombocytic response to treatment.

Taken together, our findings support that topical applications of manuka honey and chlorine dioxide can modulate hematological profiles and immune responses. Manuka honey demonstrated more pronounced effects on leukocyte and erythrocyte parameters, while chlorine dioxide showed relevant activity, particularly in red cell morphology and eosinophilic response. These results reinforce the therapeutic potential of both natural and synthetic topical agents in wound management. However, it is important to note that the relatively small number of animals per group and the short observation period (7 days) represent limitations of this study. These factors may have influenced the extent of the hematological changes observed and should be addressed in future research through larger sample sizes and extended monitoring.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

CONTRIBUTIONS

Conception – M.K., N.K-D.; Design – M.K., N. K-D., N.K.; Supervision – M.K., N. K-D.; Materials – M.K., N. K-D., N.K.; Data Collection and Processing – N. K-D., M.K., N.Č., N.K.; Interpretation – N. K-D, M.K., N.Č.; Literature Review – N. K-D, M.K.; Writing – N. K-D.; M.K.; Critical Review – M.K.; N. K-D

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EVALUACIJA HEMATOLOŠKOG ODGOVORA NA RAZLIČITE TERAPIJSKE PRISTUPE U LIJEČENJU OTVORENIH RANA: EKSPERIMENTALNA STUDIJA NA GLODARIMA

SAŽETAK

Hematološke analize imaju značajnu ulogu u veterinarskoj i humanoj medicini, jer omogućavaju rano otkrivanje promjena u homeostazi organizma i procjenu sistemskog odgovora na povredu, stres i terapijske intervencije.

U ovom istraživanju analiziran je hematološki odgovor Wistar štakora sa hirurški izazvanim ranama nakon tretmana prirodnim i sintetičkim terapijskim sredstvima.

Dvadeset četiri klinički zdrava odrasla Wistar štakora randomizirana su u šest grupa (n = 4): hirurška kontrola (C), gentamicin mast (AB), Manuka med MGO 250+ (MH1), Manuka med MGO 550+ (MH2), hlor dioksid (CL) i apsolutna kontrola bez incizije i terapije (CC). Nakon standardizirane abdominalne incizije (osim u grupi CC), tretmani su primjenjivani dva puta dnevno tokom 7 dana. Sedmog dana provedena je analiza hematoloških parametara i perifernih krvnih razmaza.

Značajne razlike između grupa utvrđene su za WBC ($p = 0.030$), limfocite ($p = 0.020$), RBC ($p = 0.002$), MCV i MCH ($p < 0.001$), RDW-CV i RDW-SD ($p < 0.001$). Povišene procijenjene marginalne srednje vrijednosti najčešće su zabilježene u grupama MH1, MH2 i CC, posebno za WBC, limfocite, RBC i eritrocitne indekse, što ukazuje na izraženiji hematološki odgovor.

Poikilocitoza je bila prisutna u svim grupama, s annulocitima kao najzastupljenijim oblikom (do 6,01% u MH1), zatim dakriocitima i ovalocitima. Leukogram je pokazao dominaciju limfocita u svim grupama, s najvećim procentom u MH1 (65,75%), dok je najveći procenat neutrofila zabilježen u AB (47,75%).

Ovo istraživanje pruža uvid u moguće razlike u hematološkom odgovoru na prirodne i sintetičke tretmane rana u animalnom modelu te predstavlja osnovu za dalja istraživanja biološke sigurnosti i efikasnosti primijenjenih terapija.

Ključne riječi: Gentamicin, hlor-dioksid, eksperimentalna rana, manuka med, poikilocitoza