Glogovac Kosanović et al. Scr Med. 2025 Mar-Apr;56(2):245-53. DOI:10.5937/scriptamed56-55187

ORIGINAL ARTICLE

Effectiveness and Safety of Lysozyme Chloride-Based Cream on Healing of Grade-Two Pressure Ulcers: A Pilot Study

Milkica Glogovac Kosanović,[1] Tatjana Bućma,[1, 2] Draško Prtina,[1] Aleksandar Gajić,[3] Aziz Šukalo,[4] Meliha Mehić,[4] Amna Tanović Avdić,[4] Una Glamočlija[4, 5]

Abstract

Background/Aim: Pressure ulcers develop due to prolonged periods of increased pressure on certain parts of the skin and underlying tissue. This study aimed to evaluate the efficacy and safety estimates of lysozyme-based cream in the treatment of pressure ulcers of grade two according to Yarkony-Kirk scale.

Methods: Adult patients with neurological diseases and severe functional deficits with grade-two pressure ulcers according to Yarkony-Kirk scale were included. All patients were treated with polarised light. Additionally, the patients were treated twice daily with a cream containing 20 mg/g of lysozyme chloride (lysozyme group) or with povidone-iodine dressings (control group). Visual checks of the ulcer were performed at the baseline and daily until the end of follow-up. Safety was evaluated by the presence of adverse reactions to treatment. Patients were followed for two months or less in case of withdrawal from the study, ulcer healing, or worsening. The Yarkony-Kirk scale grade was determined at the end of follow-up for each patient and one of the four categories was recorded: healed, improved, no changes or worsened.

Results: A total of 48 subjects were included, 28 (58 %) in the lysozyme and 20 (42 %) in the control group. Age, sex, pressure ulcer position and duration of follow-up were similar between groups. The percentage of healed pressure ulcers was significantly higher in the lysozyme (71 %) compared to the control (35 %) group (p = 0.005). No adverse reactions to treatments were recorded.

Conclusion: The lysozyme-based cream was found to be effective and safe in the treatment of grade-two pressure ulcers. Additional randomised, blinded, larger studies are needed to confirm these findings.

Key words: Lysozyme; Pressure ulcer; Therapy; Povidone-iodine; Light, polarised.

1. Department of Neurorehabilitation, Institute for Physical Medicine, Rehabilitation and Orthopaedic Surgery "Dr Miroslav Zotović", Banja Luka, The Republic of Srpska, Bosnia and Herzegovina.
2. Faculty of Medicine, University of Banja Luka, Banja Luka, The Republic of Srpska, Bosnia and Herzegovina.
3. Centre for Hyperbaric Medicine and Chronic Wound Treatment, Institute for Physical Medicine, Rehabilitation and Orthopaedic Surgery "Dr Miroslav Zotović", Banja Luka, The Republic of Srpska, Bosnia and Herzegovina.
4. Scientific Research Unit, Bosnalijek d.d., Sarajevo, Bosnia and Herzegovina.
5. Department of Pharmaceutical Biochemistry and Laboratory Diagnostics, Faculty of Pharmacy, University of Sarajevo, Sarajevo, Bosnia and Herzegovina.

Citation:
Glogovac Kosanović M, Bućma T, Prtina D, Gajić A, Šukalo A, Mehić M, et al. Effectiveness and safety of lysozyme chloride-based cream on healing of grade-two pressure ulcers: a pilot study. Scr Med. 2025 Mar-Apr;56(2):245-53.

Corresponding author:
UNA GLAMOČLIJA
E: UnaG@bosnalijek.ba
T: +387 33 560 688

Received: 9 December 2024
Revision received: 13 January 2025
Accepted: 13 January 2025

Introduction

Pressure ulcers develop due to prolonged periods of increased pressure on certain parts of the skin and underlying tissue.[1] It is estimated that 1–2 % of the global population suffers from difficult wounds. Pressure ulcers are among the complications of hard-to-heal wounds that can be caused by different factors[2] including diseases or injuries of the nervous system resulting

in immobilisation of patients for a prolonged time.[1, 3] Patients with neurological disease are at increased risk of developing pressure ulcers.[4] The development of pressure ulcers involves the mechanical load of the skin over bones. It can start from superficial damage to the skin or from deep tissue damage.[1] Risk factors are divided into external mechanical boundary conditions and internal susceptibility of the individual.[3] The Yarkony-Kirk scale can be used to classify pressure ulcers from grade one (a red area) to grade six (joint space involvement).[5]

Preventive measures are crucial in patients with a risk of developing pressure ulcers. Those include repositioning, skin hygiene, continence management, usage of bed linen with low friction, usage of prophylactic dressings and customised nutrition. Several care and treatment options are available to prevent the deterioration and induce the healing of already-developed pressure ulcers. Those involve pain management, support for skin healing and customised nutrition.[3] Various treatments are applied to support skin healing. Wound cleaning is performed with saline or water, surfactant-antimicrobial, or antiseptic such as povidone-iodine. It is a good practice to use cleansing solutions with antimicrobials in case of suspected or developed infection since the microbial invasion, especially if accompanied by biofilm formation, can lead to the deterioration of pressure ulcers. Appropriate wound dressings are crucial to improve healing and regeneration.[3] An improper pressure ulcer management may interfere with rehabilitation and functional recovery,[6] worsening patients' quality of life,[7, 8] prolonging the time of hospitalisation[9] and sometimes leading to surgical treatments.[10]

Despite all available knowledge and guidelines, pressure ulcers still present a significant burden and reason for high healthcare costs. The pooled estimate of incidence in observational studies published between 1997 and 2017 was 12 % (95 % CI: 10–14).[11] The data from the Global Burden of Disease (GBD) Database suggest that there is an increase in incidence rate with a decrease in mortality and disability-adjusted life-years (DALYs) for the period between 1990 and 2017 in most of the European Union countries, Australia, Canada and the United Kingdom. Despite different treatment options available, priority interventions are still not defined[12] and additional research is warranted to overcome this global problem. One option is to use the beneficial effects of lysozyme, an enzybiotic that could be utilised in the treatment of pressure ulcers. Lysozyme has antimicrobial, pro-regenerative, immunomodulatory and anti-inflammatory effects.[13] It was found to be able to inhibit bacterial biofilm formation and decrease pain.[14–16]

The aim of this study was to estimate the efficacy and safety of lysozyme chloride-based cream in the treatment of grade two pressure ulcers that will be used for planning an efficacy study with sufficient power.

Methods

Subjects

Adult patients of both sexes undergoing inpatient treatment participated in the research. This prospective, cohort, pilot study, was performed between January and December 2023. It included consecutive patients with neurological diseases and severe functional deficits (poor or completely immobile at the level of the bed) who were admitted to the department after primary treatment of diseases or injuries of the nervous system. Inclusion criteria were age older than 18 years and the presence of grade-two pressure ulcer according to the Yarkony-Kirk scale[5] in one of the predilection places (sacrum, trochanter, malleolus, heels, nape of the neck or ears). Exclusion criteria were cognitive deficit and sensitivity to components of applied therapy. Withdrawal criteria were the occurrence of adverse drug reactions or deterioration of pressure ulcers.

Methods

Before any procedure started, each subject signed a written informed consent form to participate in the trial. The Helsinki Declaration from 1975 and its amendments from 1983 were followed in all procedures. The study was approved by the relevant Ethics Committee.

The patients were divided into lysozyme and control groups, based on the investigator's decision. All patients were treated daily for ten minutes with a Bioptron®2 lamp (*Bioptron* AG, Switzerland) after cleaning the treated area with saline and hydrogen peroxide. Repositioning of each patient was performed every three hours.

Additionally, the patients in the lysozyme group were treated twice daily with a cream containing 20 mg/g of lysozyme chloride (Lysoderm® cream, *Bosnalijek* d.d., Bosnia and Herzegovina). The patients in the control group were treated with povidone-iodine dressings twice daily.

The Yarkony-Kirk scale[5] was used to determine the grade of pressure ulcers at the baseline and to monitor the ulcer changes throughout the study. Visual checks of epithelium damage, the dimensions, location and appearance of the ulcer were performed at the baseline and daily until the end of follow-up. Safety was evaluated by the presence of adverse reactions to treatment. Patients were followed for two months or less in case of withdrawal from the study or ulcer healing or worsening. The assessment of the skin morphological state included the evaluation of the existence and quantity of exudate and the tissue type on the pressure ulcer surface. As a result of visual inspection at the end of follow-up for each patient, one of the four categories was recorded: healed (there is no break in the continuity of the skin), improved (Grade I according to the Yarkony-Kirk scale), no changes (remains in the Grade II according to the Yarkony-Kirk scale), or worsened (Grades III to VI according to the Yarkony-Kirk scale).[5]

Statistical analysis

Prior to this pilot study, the sample size planning was performed. At least 20 patients per group were planned. In the analysis of the results, the usual descriptive statistics (absolute and relative numbers) were applied. Normal distribution of data was checked by visualisation of histograms, box plots and Q-Q plots. The numerical variables age and duration of follow-up did not follow a normal distribution and the Mann-Whitney U test was used to compare groups. Pearson's Chi-squared test was used to compare sex between groups. Fisher's exact test was used to compare outcomes between groups. All tests were two-sided and $p < 0.05$ was a value accepted as a statistically significant difference. The *R program*,[17] version 4.4.0, was used for the analyses and included *ggplot2, tidyverse, readxl, ggpubr, gtsummary, labeled, rstatix, coin, naniar* and *ggsci* packages.

Results

A total of 48 subjects were included in the study, 28 (58 %) in the lysozyme group and 20 (42 %) in the control group. Age, sex, pressure ulcer position and duration of follow-up were similar between groups. The median duration of follow-up in the lysozyme group was 19 days and in the control group 23 days (Table 1). There was no missing data or loss to follow-up subjects.

A statistically significant difference was observed in the percentage of different outcomes between the groups (Fisher's Exact test, $p = 0.005$). While in the lysozyme group 71 % of subjects had a healed pressure ulcer, in the control group this percentage was 35 % (Figure 1). The odds ratio of healing in the lysozyme group was 4.48 (95 % CI: 1.16–19.1) however the difference was not significant when Bonferroni correction for multiple testing was applied ($p = 0.074$).

Table 1: Characteristics of subjects included in the lysozyme and control groups

Parameter	Total N = 48[1]	Lysozyme N = 28[1]	Control N = 20[1]	p-value[2]
Sex, male*	28 (58 %)	15 (54 %)	13 (65 %)	0.400
Age, years†	66 (61–72)	66 (59–69)	66 (63–82)	0.072
Duration of follow-up, days†	19 (12–29)	19 (12–28)	23 (8–30)	0.900
Position*				0.385
Gluteal	22 (46 %)	12 (43 %)	10 (50 %)	
Sacral	10 (21 %)	7 (25 %)	3 (15 %)	
Calcaneal	6 (13 %)	5 (18 %)	1 (5 %)	
Femoral	2 (4 %)	1 (4 %)	1 (5 %)	
Hip	2 (4 %)	1 (4 %)	1 (5 %)	
Malleolar	2 (4 %)	0 (0 %)	2 (10 %)	

Foot interdigital	1 (2 %)	0 (0 %)	1 (5 %)
Plantar	1 (2 %)	0 (0 %)	1 (5 %)
Thoracal	1 (2 %)	1 (4 %)	0 (0 %)
Thoracolumbar	1 (2 %)	1 (4 %)	0 (0 %)

*n (%); †Median (interquartile range, IQR)
*Pearson's Chi-squared test; †Mann Whitney U test

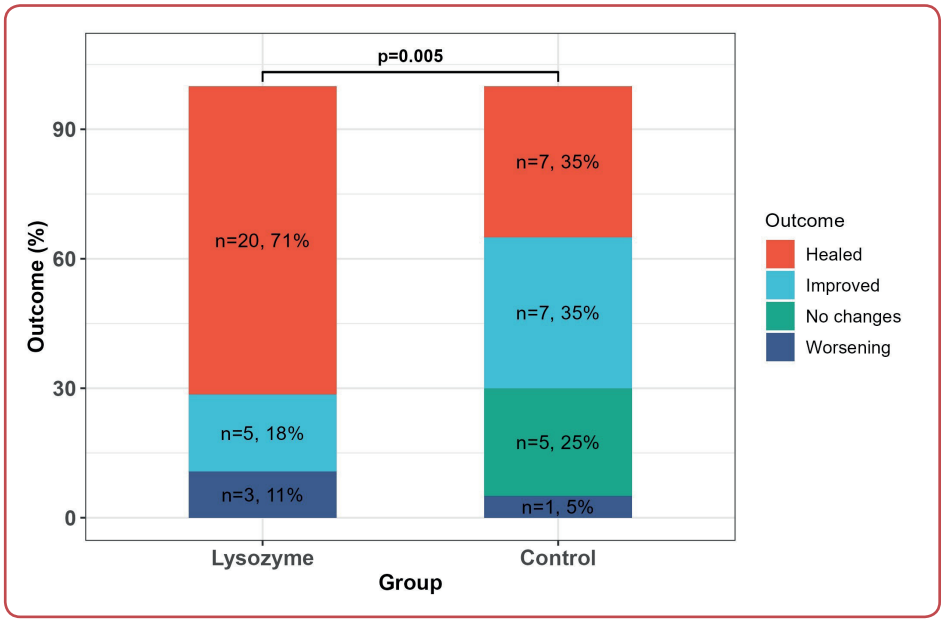

Figure 1: Treatment outcomes in lysozyme and control groups

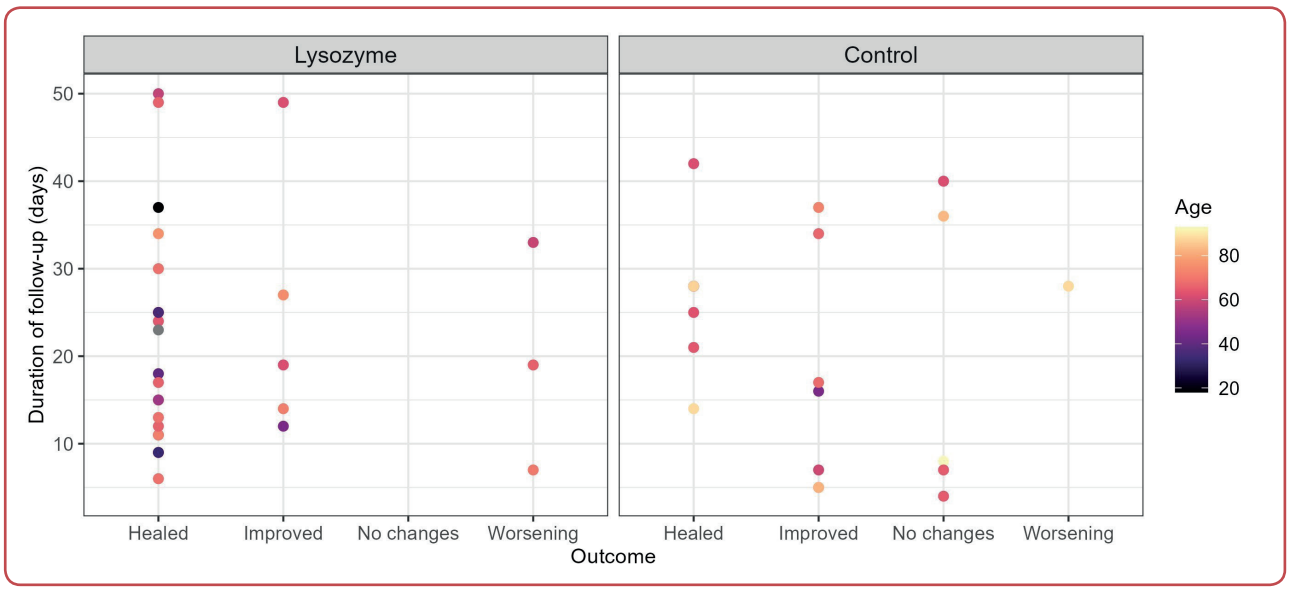

Figure 2: Characteristics of patients with different treatment outcomes in lysozyme and control groups

In patients who had healed pressure ulcers, there was no significant difference in healing time between lysozyme with a median of 18 days (IQR: 12–26) and the control group with a median of 28 days (IQR: 23–28) (U = 95, p = 0.175). The effect size was small 0.27 (95 % CI: 0.02–0.56).

Patients with the worsening pressure ulcers in the lysozyme group were followed for 7, 19 and 33 days, were 71, 66 and 59 years old and had pressure ulcers at the sacral, calcaneal and thoracal positions, respectively. In the control group, worsening of the pressure ulcer was

experienced by one patient who was followed for 28 days, was 88 years old and had a pressure ulcer at the sacral position (Figure 2).

Both treatments (lysozyme cream or povidone-iodine) were safe and no adverse reactions were recorded.

Discussion

This pilot study showed the effectiveness and safety of lysozyme-based cream in grade-two pressure ulcer treatment. The results provide information crucial for planning larger, randomised efficacy studies with adequate power. Lysozyme-based cream had better efficacy than povidone-iodine in the healing of pressure ulcers. While in the lysozyme group, 71 % of subjects had a healed ulcer by the end of the study, in the control group receiving povidone-iodine this percentage was only 35 % ($p = 0.005$). Povidone-iodine is commonly used for the irrigation of infected wounds. Intraoperative povidone-iodine irrigation decreases infection rates at surgical sites.[18] It can reduce oedema, erythema, pain, size and depth of ulcer.[19, 20] When applied to acute wounds, it increases the expression of transforming growth factor β (TGF-β) leading to increased epithelisation and neovascularisation.[19] Since pressure ulcers are often colonised by microorganisms, antimicrobial agents are commonly used in the treatment.[21] Povidone-iodine preparations showed efficacy *in vitro* against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*.[22] However, the application of povidone-iodine can have disadvantages. When the solution is not allowed to dry it can cause irritation.[23] Also, the increased concentration of serum iodide was described after the usage of povidone-iodine dressings.[24] Several other antibiotics and antiseptics are used for the treatment of pressure ulcers. Among them, lysozyme-based ointment can be used.[21] Lysozyme is a molecule with several benefits in treating pressure ulcers. It is an enzybiotic with specific biological activities that can be found in almost all living organisms.[25] In humans, lysozyme is part of innate immunity and can be found in all parts of the organism responsible for defence against pathogens.[13] Lysozyme has many activities including antimicrobial, immunomodulatory, anti-inflammatory and pro-regenerative effects.[26, 27] Elevated concentrations of lysozyme were found in fluids of infected compared to non-infected decubitus wounds, probably due to the increased number of monocytes/macrophages and neutrophils.[28] Lysozyme isolated from hen egg white (HEWL) is often used in therapeutic applications including wound healing.[29] HEWL shares a similar structure and activity with human lysozyme. The primary structure has 60 % homology while secondary domains are almost completely homologous and share very similar crystal structures.[30] HEWL was found to have inhibitory effects on methicillin-resistant *Staphylococcus aureus* (MRSA) and, when loaded into the cream, promoted wound healing and prevented wound infection in animal models.[29] Lysozyme-based ointment showed pro-regenerative and healing effects in ulcers, pressure lesions and herpetic infections.[31] Various formulations containing lysozyme were developed and found to be effective in wound healing.[32–37] Sugiyama et al treated 71 patients (88 skin regions) with lysozyme chloride-based ointment. They showed that lysozyme chloride induces anti-inflammatory reactions, proliferation of fibroblasts, acceleration of mucopolysaccharide metabolism and the formation of connective tissue. In clinical cases, the ointment with lysozyme removed necrotic mass, relieved pain, swelling and bleeding and enhanced the effectiveness of antiseptic ointments.[38] Gasior-Chrzan showed beneficial effects of lysozyme in normal saline (1 mg/mL) in the local treatment of patients with crural ulcers. The ulcerations were cleared quickly of pus, granulation tissue developed and the inflammation and pain decreased. According to Gasior-Chrzan, the beneficial effect of lysozyme on wound healing may be due to its cationic influence on the cell membranes in the epithelium and to pH change in the ulcerations.[39] According to Guidelines for the Prevention and Management of Pressure Ulcers issued by the Japanese Society of Pressure Ulcers, lysozyme is recommended for treatment of pressure ulcers with the level of evidence C1 due to limited available data.[40]

There is only one randomised study comparing iodine sugar preparation with lysozyme-based ointment to treat pressure ulcers. Similar to presented study, this study had several limitations, including a high risk of detection bias (no blinding of outcome assessment). The inclusion criteria were grades I to IV pressure ulcers. The treatment period was eight weeks. In the lysozyme ointment group 12 out of 69 (17 %) patients had wound healing during the eight weeks. This was similar to iodine sugar preparation where 15

out of 72 (21 %) patients had wound healing.[21] A lower percentage of healed patients compared to presented results could be due to the inclusion of patients with more severe grades of ulcers. The present study included only patients with grade-two pressure ulcers according to the Yarkony-Kirk scale.[5] This grade refers to the involvement of the epidermis and dermis with no subcutaneous fat observed.[5]

Although the maximum follow-up in study was two months, all patients experienced an outcome (healed, deteriorated, or excluded from the study) before that period. The median duration of follow-up in the lysozyme group was 19 days and in the control group 23 days, with no significant difference. In patients who had healed pressure ulcers, there was no significant difference in healing time between lysozyme with a median of 18 days (IQR 12–26) and control 28 days (IQR: 23–28) groups (p = 0.175). This could be due to the small sample size and power of this study which could not discriminate between healing times in the two groups although the median healing time was longer for ten days in the control compared to the lysozyme group. Similar healing time could also be due to the duration of biological processes. The time to heal pressure ulcers depends on the anatomical position and grade of the ulcer. The sacral area is among the positions with the longest healing time[41] and in presented study two out of four patients with worsening of symptoms had pressure ulcers in the sacral area. The time to heal pressure ulcers also depends on the patient's condition and applied treatments. Yoshikawa et al found that the cleaning frequency three or more times a week significantly reduces the time to pressure ulcer healing (65.3 ± 24.8 days) compared to cleaning frequency two times a week (102.6 ± 19.2 days) in older people receiving home care.[42] Kaya et al analysed the healing time of pressure ulcers in patients with spinal cord injury treated with povidone-iodine compared to hydrogel dressing. The study included 27 patients with Grade I to Grade III pressure ulcers. The mean healing time in the povidone-iodine group was 45 days similar to 48 days in the hydrogel dressing group.[43] Evaluation of time-to-healing of pressure ulcers is often not performed since many studies have short follow-up periods with a duration of eight weeks or less.[21]

To decrease the time to healing, it is important to prevent colonisation by microorganisms which postpone healing and increase ulcer severity.[21] Chen et al found that out of 88 patients, 62 (70.5 %) had wound infections with domination of Gram-negative bacteria.[44] In presented study both preparations with antimicrobial properties were used. Lysozyme is an antimicrobial protein that directly hydrolyses peptidoglycan of bacterial cell walls in Gram-positive bacteria.[45] The outer membrane of Gram-negative bacteria makes them insensitive to the direct catalytic activity of lysozyme where this protein causes lysis due to its cationic properties.[46]

All patients in presented study received treatment with polarised light.[47] Phototherapy is among the biophysical agents used for the treatment of pressure ulcers.[3] Chen et al included 88 patients with grades II to IV pressure ulcers all treated with the linear polarised polychromatic light (LPPL). Half of the patients were randomly selected for additional treatment with silver sulfadiazine cream. Out of 88 patients, 62 (70.5 %) had wound infections where Gram-negative bacteria dominated. Healing timeframes were different depending on the ulcer grade and treatment. In grade II ulcers treated only with LPPL healing time was 13.20 ± 3.76 days. When LPPL was combined with silver sulfadiazine cream, the healing time was significantly reduced to 9.76 ± 2.38 days.[44] Healing times in this study were shorter than in presented study. This could be due to different LPPL regimes of application. Chen et al treated patients with LPPL twice daily five days a week,[44] while we applied one daily treatment for the entire study duration. Also, different characteristics of patients could result in different healing times. Both studies were performed on a small number of patients and the results should be confirmed in larger studies.

This study had several limitations. No blinding or randomisation was applied that could lead to interviewer bias. The study included a small number of patients and the study was performed at a single centre, potentially leading to selection bias. The duration was too short to evaluate the time-to-heal of pressure ulcers in all patients. The data about possible confounding factors was not collected (for example presence of concomitant diseases, other therapies used, nutritional and social status of patients). The aim of this pilot study was to provide data for planning a larger, randomised, blinded, prospective, cohort study with adequate power that will provide evidence on the efficacy of lysozyme-based cream for the treatment of pressure ulcers.

Conclusion

Lysozyme chloride-based cream was found to be effective and safe in the treatment of grade-two pressure ulcers. Additional randomised, multicentric, blinded, larger studies are needed to confirm these findings.

Ethics

The study was approved by the Ethics Committee of the Institute for Physical Medicine, Rehabilitation and Orthopaedic Surgery "Dr Miroslav Zotović" (decision No: 116-31-8940/21), dated 14 July 2021.

Acknowledgement

None.

Conflicts of interest

Aziz Šukalo, Meliha Mehić, Amna Tanović Avdić and Una Glamočlija disclose the following relationships – employees of *Bosnalijek* d.d., a pharmaceutical company producing lysozyme-based cream.

Funding

The work was funded by *Bosnalijek* d.d., Sarajevo, Bosnia and Herzegovina, a pharmaceutical company producing lysozyme-based cream. *Bosnalijek* d.d. had a role in the design of the study; in the collection, analyses and interpretation of data; in the writing of the manuscript and in the decision to publish the results.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Milkica Glogovac Kosanović (MGK):
0009-0001-6076-688X
Tatjana Bućma (TB):
0000-0002-4388-4681
Draško Prtina (DP):
0009-0009-3516-0331
Aleksandar Gajić (AG):
0009-0006-1274-3209
Aziz Šukalo (AŠ):
0000-0002-9217-7473
Meliha Mehić (MM):
0000-0003-3378-6954
Amna Tanović Avdić (ATA):
0000-0003-0002-7150
Una Glamočlija (UG):
0000-0003-1206-6990

Author contributions

Conceptualisation: AŠ, MM, ATA, UG
Methodology: AŠ, MM, ATA, UG
Formal analysis: UG
Investigation: MGK, TB, DP, AG, AŠ, MM, ATA, UG
Resources: AŠ
Data curation: UG
Writing - original draft: MM, ATA, UG
Writing - review and editing: MGK, TB, DP, AG, AŠ
Visualisation: UG
Supervision: AŠ, MM, UG
Project administration: UG

References

1. Kumar S, Theis T, Tschang M, Nagaraj V, Berthiaume F. Reactive oxygen species and pressure ulcer formation after traumatic injury to spinal cord and brain. Antioxidants (Basel). 2021 Jun 24;10(7):1013. doi: 10.3390/antiox10071013.
2. De Francesco F, Ogawa R. From time to timer in wound healing through the regeneration. Adv Exp Med Biol 2024; doi: 10.1007/5584_2024_815.
3. European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel, Pan Pacific Pressure Injury Alliance; Haesler E, ed. Prevention and treatment of pressure ulcers/injuries: clinical practice guideline. The International Guideline. Schaumburg, IL: EPUAP/NPIAP/PPPIA; 2019.
4. Alito A, Portaro S, Leonardi G, Ventimiglia C, Bonanno F, Fenga D, et al.. Pressure ulcers-a longstanding problem: a 7-year neurorehabilitation unit experience of

management, care, and clinical outcomes. Diagnostics (Basel). 2023 Oct 14;13(20):3213. doi: 10.3390/diagnostics13203213.
5. Yarkony GM, Kirk PM, Carlson C, Roth EJ, Lovell L, Heinemann A, et al. Classification of pressure ulcers. Arch Dermatol. 1990 Sep;126(9):1218-9. PMID: 2101585.
6. Krishnan S, Hong I, Couture G, Tzen YT, Reistetter T. Pressure injury on poststroke admission assessment to skilled nursing facilities: risk factors, management, and impact on rehabilitation. J Am Med Dir Assoc. 2022 Oct;23(10):1718.e13-1718.e20. doi: 10.1016/j.jamda.2022.06.025.
7. Berlowitz DR, Brandeis GH, Anderson J, Du W, Brand H. Effect of pressure ulcers on the survival of long-term care residents. J Gerontol A Biol Sci Med Sci. 1997 Mar;52(2):M106-10. doi: 10.1093/gerona/52a.2.m106.
8. Reddy M, Keast D, Fowler E, Sibbald RG. Pain in pressure ulcers. Ostomy Wound Manage. 2003 Apr;49(4 Suppl):30-5. PMID: 12856291.
9. Fernando-Canavan L, Gust A, Hsueh A, Tran-Duy A, Kirk M, Brooks P, et al. Measuring the economic impact of hospital-acquired complications on an acute health service. Aust Health Rev. 2021 Mar;45(2):135-42. doi: 10.1071/AH20126.
10. Sørensen JL, Jørgensen B, Gottrup F. Surgical treatment of pressure ulcers. Am J Surg 2004;188(1A Suppl):42–51; doi: 10.1016/S0002-9610(03)00290-3.
11. Afzali Borojeny L, Albatineh AN, Hasanpour Dehkordi A, Ghanei Gheshlagh R. The incidence of pressure ulcers and its associations in different wards of the hospital: a systematic review and meta-analysis. Int J Prev Med. 2020 Oct 5;11:171. doi: 10.4103/ijpvm.IJPVM_182_19.
12. Patton D, Moore ZE, Boland F, Chaboyer WP, Latimer SL, Walker RM, et al. Dressings and topical agents for preventing pressure ulcers. Cochrane Database Syst Rev. 2024 Dec 3;12(12):CD009362. doi: 10.1002/14651858.CD009362.pub4.
13. Ragland SA, Criss AK. From bacterial killing to immune modulation: Recent insights into the functions of lysozyme. PLoS Pathog. 2017;13(9):e1006512; doi: 10.1371/journal.ppat.1006512.
14. Zhang XL, Lei Y, Xiao YB, Cao XY, Tian XY, Zhu YX, et al. Hen egg lysozyme alleviates static mechanical pain via NRF1-Parkin-TACAN signaling axis in sensory neurons. Neuroscience. 2022 Oct 15;502:52-67. doi: 10.1016/j.neuroscience.2022.08.010.
15. Bianchi C. Is Fleming's lysozyme an analgesic agent? An experimental reappraisal of clinical data. Eur J Pharmacol 1981;71(2–3):211–21; doi: 10.1016/0014-2999(81)90024-8.
16. Bianchi C. Is Fleming's lysozyme an analgesic agent? Experiments on mice. Clin Exp Pharmacol Physiol 1983;10(1):45–52; doi: 10.1111/j.1440-1681.1983.tb00170.x.
17. Anonymous. R: The R Project for Statistical Computing. n.d. [Internet] [Cited: 16-Oct-2024]. Available from: https://www.r-project.org/.
18. Saeg F, Schoenbrunner AR, Janis JE. Evidence-based wound irrigation: separating fact from fiction. Plast Reconstr Surg 2021;148(4):601e–614e; doi: 10.1097/PRS.0000000000008331.
19. Wang L, Qin W, Zhou Y, Chen B, Zhao X, Zhao H, et al. Transforming growth factor β plays an important role in enhancing wound healing by topical application of Povidone-iodine. Sci Rep. 2017 Apr 20;7(1):991. doi: 10.1038/s41598-017-01116-5.
20. Lee BY, Trainor FS, Thoden WR. Topical application of povidone-iodine in the management of decubitus and stasis ulcers. J Am Geriatr Soc 1979;27(7):302–6; doi: 10.1111/j.1532-5415.1979.tb06044.x.
21. Norman G, Dumville JC, Moore ZE, Tanner J, Christie J, Goto S. Antibiotics and antiseptics for pressure ulcers. Cochrane Database Syst Rev. 2016 Apr 4;4(4):CD011586. doi: 10.1002/14651858.CD011586.pub2.
22. Michel D, Zäch GA. Antiseptic efficacy of disinfecting solutions in suspension test in vitro against methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli in pressure sore wounds after spinal cord injury. Dermatology. 1997;195 Suppl 2:36–41; doi: 10.1159/000246028.
23. Nahlieli O, Baruchin AM, Levi D, Shapira Y, Yoffe B. Povidone-iodine related burns. Burns. 2001 Mar;27(2):185-8. doi: 10.1016/s0305-4179(00)00081-4.
24. Aronoff GR, Friedman SJ, Doedens DJ, Lavelle KJ. Increased serum iodide concentration from iodine absorption through wounds treated topically with povidone-iodine. Am J Med Sci. 1980 May-Jun;279(3):173-6. doi: 10.1097/00000441-198005000-00007.
25. Callewaert L, Michiels CW. Lysozymes in the animal kingdom. J Biosci 2010;35(1):127–60; doi: 10.1007/s12038-010-0015-5.
26. Ghosh C, Sarkar P, Issa R, Haldar J. Alternatives to conventional antibiotics in the era of antimicrobial resistance. Trends Microbiol. 2019 Apr;27(4):323-338. doi: 10.1016/j.tim.2018.12.010.
27. Khorshidian N, Khanniri E, Koushki MR, Sohrabvandi S, Yousefi M. An overview of antimicrobial activity of lysozyme and its functionality in Cheese. Front Nutr. 2022 Mar 9;9:833618. doi: 10.3389/fnut.2022.833618.
28. Hasmann A, Wehrschuetz-Sigl E, Kanzler G, Gewessler U, Hulla E, Schneider KP, et al. Novel peptidoglycan-based diagnostic devices for detection of wound infection. Diagn Microbiol Infect Dis. 2011 Sep;71(1):12-23. doi: 10.1016/j.diagmicrobio.2010.09.009.
29. Chen LL, Shi WP, Zhang TD, Zhou YQ, Zhao FZ, Ge WY, et al. Antibacterial activity of lysozyme-loaded cream against MRSA and promotion of scalded wound healing. Int J Pharm. 2022 Nov 5;627:122200. doi: 10.1016/j.ijpharm.2022.122200.
30. Sziegat F, Wirmer-Bartoschek J, Schwalbe H. Characteristics of human lysozyme and its disease-related mutants in their unfolded states. Angew Chem Int Ed Engl. 2011;50(24):5514–18; doi: 10.1002/anie.201008040.
31. Palmieri B, Boraldi F. [Topical treatment of some dystrophic and inflammatory lesions of the skin and soft tissues]. Arch Sci Med (Torino) 1977;134(4):481–5. Italian.
32. He W, Wang X, Hang T, Chen J, Wang Z, Mosselhy DA, et al. Fabrication of Cu2+-loaded phase-transited lysozyme nanofilm on bacterial cellulose: Antibacterial, anti-inflammatory, and pro-angiogenesis for bacteria-infected wound healing. Carbohydr Polym. 2023 Jun 1;309:120681. doi: 10.1016/j.carbpol.2023.120681.

33. Wang H, Huang R, Bai L, Cai Y, Lei M, Bao C, et al. Extracellular matrix-mimetic immunomodulatory hydrogel for accelerating wound healing. Adv Healthc Mater. 2023 Oct;12(27):e2301264. doi: 10.1002/adhm.202301264.
34. Gong W, He WY, Hou YY, Li YX, Hu JN. Tendon-inspired hybrid hydrogel based on polyvinyl alcohol and gallic acid-lysozyme for promoting wound closure and healing. Int J Biol Macromol. 2023 Aug 30;247:125583. doi: 10.1016/j.ijbiomac.2023.125583.
35. Meng X, Xiong H, Ji F, Gao X, Han L, Wu Z, et al. Facile surface treatment strategy to generate dense lysozyme layer on ultra-high molecular weight polyethylene enabling inhibition of bacterial biofilm formation. Colloids Surf B Biointerfaces. 2023 May;225:113243. doi: 10.1016/j.colsurfb.2023.113243.
36. Zhao M, Huang M, Li Z. Exploring the therapeutic potential of recombinant human lysozyme: a review on wound management system with antibacterial. Front Bioeng Biotechnol. 2023;11:1292149; doi: 10.3389/fbioe.2023.1292149.
37. Chen J, Xu M, Wang L, Li T, Li Z, Wang T, Li P. Converting lysozyme to hydrogel: A multifunctional wound dressing that is more than antibacterial. Colloids Surf B Biointerfaces. 2022 Nov;219:112854. doi: 10.1016/j.colsurfb.2022.112854.
38. Sugiyama N, Koyama H, Akamatsu J, et al. Treatment of skin ulcers with lysozyme chloride. Acta Dermatologica 1990;85(2):269–284.
39. Gasior-Chrzan B. [Clinical trial of lysozyme treatment of crural ulcers in humans]. Przegl Dermatol 1988;75(6):435–8. Polish.
40. The Japanese Societyof Pressure Ulcers Guideline Revision Committee; Noda Y, Sekine Y, Kaitani T, et al. JSPU Guidelines for the prevention and management of pressure ulcers (3rd edition). Jpn J PU. 2014;16(1):12–90.
41. Tahir Mahmood D, Kareem Qadir H, Mohammed Hussein M. Relationship between characteristics of the wound and healing duration among patients treated during home-visits. Arch Razi Inst. 2023;78(4):1323–32; doi: 10.32592/ARI.2023.78.4.1323.
42. Yoshikawa Y, Maeshige N, Tanaka M, Uemura M, Hiramatsu T, Fujino H, et al. Relationship between cleaning frequency and pressure ulcer healing time in older people receiving home care. J Wound Care. 2024 Jun 2;33(6):418-24. doi: 10.12968/jowc.2021.0152.
43. Kaya AZ, Turani N, Akyüz M. The effectiveness of a hydrogel dressing compared with standard management of pressure ulcers. J Wound Care 2005;14(1):42–4; doi: 10.12968/jowc.2005.14.1.26726.
44. Chen B, Liu Y, Liu Y, Xu S. Distribution characteristics of pathogens in different stages of pressure ulcers and the therapeutic effect of linear polarized polychromatic light combined with silver sulfadiazine cream. Medicine (Baltimore). 2023 Oct 20;102(42):e35772. doi: 10.1097/MD.0000000000035772.
45. Salton MR. The lysis of micro-organisms by lysozyme and related enzymes. J Gen Microbiol. 1958;18(2):481–90; doi: 10.1099/00221287-18-2-481.
46. Dožić I, Todorović T. Antimicrobial peptides of human saliva. Stomatoloski glasnik Srbije 2005;52(4):208–16.
47. Bioptron. n.d. How Bioptron Hyperlight Therapy System Works? [Internet] [Cited: 11-Oct-2024]. Available from: https://www.bioptron.com/how-it-works/bioptron-hyperlight-therapy/.