Check for updates

OPEN ACCESS

DOI: 10.46903/gjms/22.04.1758

ORIGINAL ARTICLE

EFFECTIVENESS OF MUPIROCIN NANOMICELLS IN THE INSULIN-BASED GEL FOR THE MANAGEMENT OF ACUTE SKIN WOUNDS: A PILOT STUDY

Maysaa Banay Zubairi[1], Manal Abdulkhaliq Ibrahim[1], Ahmed Falih Noori[2], Omar Saleh Abdulkader[3]

[1] Department of Pharmacology and Toxicology, College of Pharmacy, University of Basrah, Basrah, Iraq. [2]Ministry of Health, Basrah Health Directorate, Al Zubair General Hospital, Basrah, Iraq. [3]Department of Pharmacy, Al-Farqadein University College, Basrah, Iraq.

ABSTRACT

Background: Wound management is an extremely important clinical and societal concern. Research into the delayed healing process is progressing rapidly, as indicated by novel therapy strategies, such as nano-drug therapy, which is not conventional. Mupirocin is a commonly used antibiotic in wound healing. However, various novel delivery methods have been developed to improve patient compliance, reduce bacterial resistance, and boost mupirocin delivery. Therefore, this pilot study was conducted with the aim of evaluating the effectiveness of mupirocin nanomicelles in insulin-based gel in the management of open skin wounds in Iraqi participants.

Materials & methods: A randomized case-control, clinical trial pilot study including 40 skin-wounded patients was conducted in a private surgery clinic in Al-Zubair-Basrah, Iraq. The patients were randomly assigned to two treatment groups (20 male & 20 female patients each): mupirocin nanomicelles in insulin-based gel (2%), and mupirocin gel (2%). They were followed for 5 days. The percentage of wound contraction (% Wound Contraction) was measured and the wound areas were photographed.

Results: On day 5 of treatment, all cases treated with mupirocin nanomicelles in insulin-based gel showed complete healing (% Wound Contraction = 100) without signs of infection, compared to the mupirocin-treated group (% Wound Contraction = 90.8±1.04) with four cases of infections ($p \leq 0.001$). The majority of wounds were located in the arms.

Conclusion: The findings suggested that mupirocin nanomicelles in insulin-based gel could have applications in the future, as it can promote improved acute wound healing in various regions of the body, percentage of wound contraction, and infection-free status.

KEY WORDS: Wound healing; Mupirocin; Nanomicells; Insulin; Gel.

Cite as: Zubairi MB, Ibrahim MA, Noori AF, Abdulkader OS. Effectiveness of mupirocin nanomicells in the insulin-based gel for the management of acute skin wounds: a pilot study. Gomal J Med Sci 2024 Oct-Dec ;22(4):341-5. https://doi.org/10.46903/gjms/22.04.1758

INTRODUCTION

Infection management in wounds remains a global health challenge. As a result, infection control is important to avoid future amputations.[1] The prevalence of antibiotic-resistant *Staphylococcus aureus* has recently increased. Thus, an alternative antimicrobial delivery system or increased antibiotic potency is required. A nano-drug delivery system can reduce the minimum inhibitory concentration (MIC), consequently, increasing the antibiotic's efficacy.[2] Mupirocin (MP) is a widely used topical antibiotic for treating various bacterial skin infections due to its unique mode of action. However, its therapeutic effectiveness is impeded by its short half-life, resistance, and strong protein binding. Mupirocin's therapeutic efficacy can be enhanced by combining it with other chemicals and polymers and using a biocompatible carrier that promotes cell proliferation and viability.[3] Mupirocin-loaded nanoparticles played a major role in wound healing, as it prepared a selenium-chitosan-MP nanohybrid system, MP-loaded ROS-scavenging hydrogel, and MP-loaded nanomicelles. All showed the best antibacterial activity against MRSA. It was found that these nano-regime played a crucial role in wound contraction and epi-

Corresponding Author:

Dr. Maysaa Banay Zubairi,
Department of Pharmacology and Toxicology,
College of Pharmacy, University of Basrah
Basrah, Iraq

E-mail: maysaa.zubairi@uobasrah.edu.iq

Date Submitted: 16-07-2024
Date Revised: 26-10-2024
Date Accepted: 01-11-2024

dermis proliferation, accelerates wound healing by lowering ROS levels, and up-regulates a specific phenotype of macrophages around the wound.[3,4]

Nano-drug delivery systems effectively treat persistent bacterial infections and wound healing.[4] They are well known for delivering various active compounds to wound tissues, including growth factors, antibiotics, antioxidants, and nucleic acid, which stimulate cell proliferation, migration, angiogenesis, and collagen deposition while inhibiting microbial growth.[5] Insulin is a growth factor and peptide hormone with various physiological functions.[6] Insulin has played a more calming role in wound healing in recent years. Furthermore, topical insulin has been shown to enhance wound tensile strength and restore damaged skin integrity. [7] A novel composition containing mupirocin nano-micelles (MP-NM) and insulin-based gel has never been tested on human wounds. Therefore, this pilot study was conducted with the aim of evaluating the effectiveness of mupirocin nanomicelles in insulin-based gel in the management of open skin wounds in Iraqi participants.

MATERIALS AND METHODS

Ethical approval statements and consent to participation: The study was registered by the Ministry of Higher Education and Science Research and Faculty of Pharmacy, Basrah University, Iraq, with registration number 22/358/2024. The Local Institutional Ethical Committee of the Faculty of Pharmacy, Basrah University, Iraq, approved the study's protocol. All the patients signed informed consent forms before participating in the study.

Subjects: The case-control, non-blinded, randomized pilot study was conducted between January and May 2024, in a private surgery clinic in Al-Zubair-Basrah, Iraq. The research involved 40 skin-wounded patients (20 males and 20 females) ranging from 5 to 35 years old. The sampling method is Convenience Sampling, and the samples are all people referred to a specialist surgeon who had previously visited them and diagnosed the wounds and have full-thickness skin wounds (deep to the muscle). The random allocation of the study samples was done in this way that each patient was given a number and they were allocated in two groups using a table of random numbers.

Experimental grouping and treatment: Patients with skin wounds were randomly assigned to one of two treatment groups: Group 1 patients, received mupirocin nanomicelles (MP-NM) in insulin-based gel (2%), twice daily; and Group 2 patients were administered mupirocin (MP) gel (2%), twice daily. Participants were followed up after 5 days as wounds completely closed. The wound contraction percentage was computed by a specific equation. [8] The anatomical tissue location, type of wound, level of damage, and symptoms of infection were also evaluated. Photographs were taken throughout the treatment. The previously developed MP-NM compound in the insulin-based gel was tested on rats in an *in vivo* animal investigation. [9]

Inclusion criteria: Adult patients 18 years of age or older who were able to provide informed consent and understood the requirements of the study. Participants must have clinically proven full-thickness acute skin wounds (extending deep into the dermis or muscle layers) suitable for topical treatment. Eligible wounds should not show any signs of active infection (such as purulent discharge, intense redness, or warmth), as the focus was on evaluating wound contraction and healing rather than infection control. Patients should be generally healthy and free of underlying chronic diseases or conditions that impair normal wound healing, such as diabetes, immunodeficiency states, or connective tissue disorders. Failure to use systemic antibiotics, consent to follow up, and participants should not have a known allergy or sensitivity to mupirocin, insulin, or any of the other components used in the topical study formulation.

Exclusion criteria: The study excluded patients who had diabetes mellitus, immunocompromised conditions (cancer, radiation therapy), infected wounds, inherited healing disorders, the elderly, and those who were taking systemic antibiotics or glucocorticoids.

Statistical analysis: Statistical analyses were performed using Microsoft Office Excel (2021), and GraphPad Prism 8 computer software (GraphPad Software, Boston, USA). Standard deviation, mean, and percentage were the descriptive statistics used to analyze the study variables. The unpaired sample T-test was performed to compare the group differences at a certain time point throughout the follow-up period. Statistical significance was determined as $p < 0.05$. [10]

RESULTS

On day 5 of treatment, the MP-treated group did not show complete healing (percentage wound contraction was 90.8 ± 1.04), indicating the need for additional days. Furthermore, four patients developed infection signs such as redness, swelling, heat, pain, and purulent discharge, prompting them to switch to another treatment (systemic antibiotics, local antibiotics, and antiseptics). Compared to MP-NM insulin-based gel treatment, resulted in significant ($p \leq 0.001$) complete healing with no signs of infection, (percentage wound contraction was 100), as presented in Figs. 1 and 2; Table 1. In addition, Table 2 shows other characteristics of the patients in both groups. For patients receiving MP-NM-I or MP treatment, the majority of wounds were located in the arms (40% and 50%, respectively). All of the patients had acute wounds, and 100% of them sustained full-thickness damage.

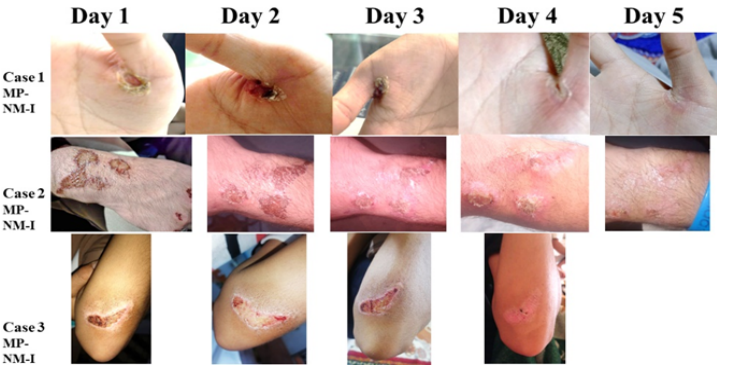

Figure 1: Morphological representation of wounds in patients treated with mupirocin nanomicells in insulin-based gels on different days. MP-NM-I: Mupirocin-Nanomicelle-Insulin

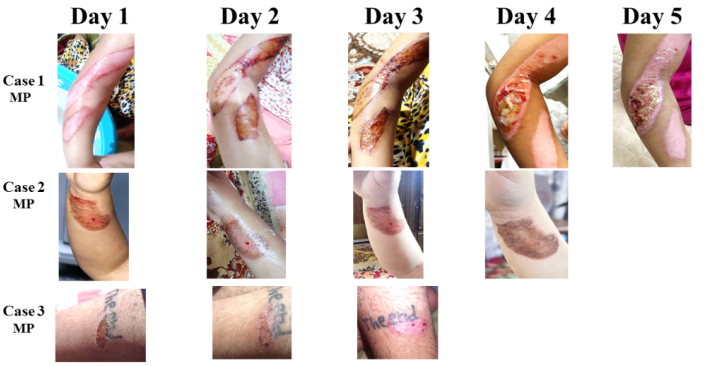

Figure 2: Morphological representation of wounds in patients treated with mupirocin gels on different days. MP: Mupirocin

Table 1: Percentage wound contraction (mean ± SD) on different time points in both groups (n = 20)

Group	Day 1	Day 2	Day 3	Day 4	Day 5
MP-NM-I	0	27±3.12*	54.7±2.24*	85±2.66*	100*
MP	0	12.2±2.48	31.4±2.93	58.2±1.55	90.8±1.04

**: Significant difference compared to MP-treated group ($p \leq 0.05$); MP-NM-I: Mupirocin-nanomicelle-insulin; MP: Mupirocin.*

Table 2: Characteristics and parameter evaluation of the two groups of patients who received mupirocin nanomicells in insulin-based gels and mupirocin.

Characteristics and parameter	MP-NM-I (n = 20) (%)	MP (n = 20) (%)
Male Female	12 8	8 12
Anatomical location Hands Arms Legs Feet	 4 8 (40%) 4 4	 2 10 (50%) 6 2
Type of wound Acute	 20	 20
Degree of damage Full-thickness	 20 (100%)	 20 (100%)
Signs of infection	Nil (0%)	4 (20%)

MP-NM-I: Mupirocin-nanomicelle-insulin; MP: Mupirocin.

DISCUSSION

This study highlights the advantages of using mupirocin nanomicelles in an insulin-based gel for treating acute skin wounds, showing that this combination not only improves wound contraction but also speeds up the healing process. By day five, the nanomicelle-insulin treatment achieved a full 100% wound contraction, with no infections noted among patients, whereas the traditional mupirocin group had a 90.8% contraction rate and four instances of infection. These results support the potential of nano-based drug delivery systems for wound care, a finding also seen in previous research that shows how these systems can accelerate healing and provide strong antibacterial benefits.[4]

Other studies on nanomicelle delivery systems show similar outcomes, particularly in enhancing drug stability, minimizing the necessary dose, and improving skin penetration, which are all critical for effective wound management.[11] For instance, Zahedi et al. found that these nanocarriers could penetrate more

deeply into tissues and retain the drug longer, potentially explaining why our study's nanomicelle group had fewer infections.[12] This improved stability and retention of the drug in wound areas are especially valuable for acute wounds, which are vulnerable to quick bacterial colonization that can disrupt healing.

Topical insulin, the main supportive agent in the tested gel, has well-established wound-healing properties. It works by binding to insulin receptors, activating the PI3K/AKT pathway, and stimulating cell movement and tissue repair.[13, 14] In this study, the insulin-enhanced wound contraction was visible from day two, progressing steadily through day five. This finding is consistent with Hrynyk and Neufeld, who showed that topical insulin speeds up healing and increases wound strength, likely due to its activation of pathways that foster new blood vessel growth and prevent inflammatory cell death.[7]

While traditional mupirocin treatments alone have been found effective for wound healing, particularly in preventing infection, they still don't reach the enhanced outcomes observed with the nanomicelle-insulin combination. Bairy et al. documented how mupirocin's antibacterial action supports wound contraction by reducing bacterial load, aligning with the contraction rate in our mupirocin-only group.[15] However, nanomicelles appear to offer superior penetration and a steady drug release, a benefit also noted by Twilley et al. in their exploration of mupirocin-loaded nanocarriers for skin regeneration.[16]

The results of this study also noted an interesting phenomenon in the nanomicelle-insulin group: the development of a white, fibrous layer over the wound from day two, leading to full fibrosis by day five. This could be due to the formula's improved absorption into wound fluids, which supports natural wound cleaning and new tissue growth.[17] A comparable result was reported by Blecher et al. with nitric oxide nanoparticles, where faster healing and higher collagen levels were recorded, further illustrating how nano-sized particles can benefit wound care formulations. [18]

Aligning with Chereddy et al. who found that nanoparticles loaded with defense peptides promoted new tissue and blood vessel growth in animal models, our findings suggest that nanomicelles in insulin gel foster the formation of new skin layers and fibroblast activity in the wound. While mupirocin alone proved effective in minimizing infections, the nano-enhanced formulation showed even greater antibacterial power due to its localized and longer-lasting effects.[19] Zubairi et al. also observed that mupirocin nanomicelles had extended antibacterial activity, which could reduce the need for frequent reapplication.[20]

LIMITATIONS

This study has several limitations worth considering. First, as a pilot study with a small sample size, the results may not apply to a broader population, so future studies with larger groups are essential for validation. Secondly, the brief five-day follow-up period does not allow for assessing longer-term healing results or possible complications. Extending the observation period would provide insights into scar development, tissue integrity, and any potential adverse effects. Furthermore, due to ethical limitations, we could not conduct histopathological analyses on human subjects to observe microscopic cellular changes. Future studies with animal models that include histopathological analyses could clarify the exact biological mechanisms at play in wound healing with nanomicelle-insulin formulations. Finally, while this research focused on acute skin wounds, it would be valuable to test this formulation on chronic or complex wounds, such as diabetic ulcers, to better understand its wider applications.

CONCLUSION

The findings of the present study were positive, indicating that this formulation (MP-NM-I) may have applications in the future. Aside from the distinct physicochemical characteristics, which included impressive nanoparticle size that promoted good penetration through skin layers, it can also enhance better acute wound healing in various parts of the body, wound contraction percentage, and infection-free status compared to MP. Also, MP-NM-I-mediated wound healing resulted in a significant improvement in inflammatory response, re-epithelialization, and fibrosis. Further clinical investigations are recommended with larger sample sizes, longer follow-up periods, and different type of wounds.

REFERENCES

1. Spichler A, Hurwitz BL, Armstrong DG, Lipsky BA. Microbiology of diabetic foot infections: from Louis Pasteur to 'crime scene investigation.' BMC Med. 2015;13:1–13. https://doi.org/10.1186/s12916-014-0232-0
2. Leid JG, Ditto AJ, Knapp A, Shah PN, Wright BD, Blust R, et al. In vitro antimicrobial studies of silver carbene complexes: activity of free and nanoparticle carbene formulations against clinical isolates of pathogenic bacteria. J Antimicrob Chemother. 2012;67(1):138–48. https://doi.org/10.1093/jac/dkr408
3. Chavan MA, Chavan MV, Shingare MD, Tayade MR. Mupirocin loaded microemulsion based gel for effective treatment of burns. Int J Pharma02. 2021;3:199–209.
4. Zare H, Rezayi M, Aryan E, Meshkat Z, Hatamluyi B, Neshani A, et al. Nanotechnology-driven advances in the treatment of diabetic wounds. Biotechnol Appl Biochem. 2021;68(6):1281–306. https://doi.org/10.1002/bab.2051
5. Rigo C, Ferroni L, Tocco I, Roman M, Munivrana I, Gardin C, et al. Active silver nanoparticles for

wound healing. Int J Mol Sci. 2013;14(3):4817–40. https://doi.org/10.3390/ijms14034817

6. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev. 1987;8(2):132–41. https://doi.org/10.1210/edrv-8-2-132
7. Hrynyk M, Neufeld RJ. Insulin and wound healing. Burns. 2014;40(8):1433–46. https://doi.org/10.1016/j.burns.2014.03.020
8. Yates CC, Whaley D, Babu R, Zhang J, Krishna P, Beckman E, et al. The effect of multifunctional polymer-based gels on wound healing in full thickness bacteria-contaminated mouse skin wound models. Biomaterials. 2007;28(27):3977–86. https://doi.org/10.1016/j.biomaterials.2007.05.008
9. Zubairi MB, Abd AH, Al-lami MS. Combinatorial treatment of mupirocin nanomicelle in insulin-based gel for wound healing in diabetic rats. Med J Babylon. 2023;20(4):721–31. https://doi.org/10.4103/MJBL.MJBL_189_23
10. Ali Z, Bhaskar SB. Basic statistical tools in research and data analysis. Indian J Anaesth. 2016;60(9):662–9. https://doi.org/10.4103/0019-5049.190623
11. Seah C, Alexander DC, Louie L, Simor A, Low DE, Longtin J, et al. MupB, a new high-level mupirocin resistance mechanism in Staphylococcus aureus. Antimicrob Agents Chemother. 2012;56(4):1916–20. https://doi.org/10.1128/AAC.05325-11
12. Zahedi P, Rezaeian I, Ranaei-Siadat SO, Jafari SH, Supaphol P. A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages. Polym Adv Technol. 2010. https://doi.org/10.1002/pat.1625
13. Liu Y, Petreaca M, Martins-Green M. Cell and molecular mechanisms of insulin-induced angiogenesis. J Cell Mol Med. 2009;13(11-12):4492–504. https://doi.org/10.1111/j.1582-4934.2008.00555.x
14. Hermann C, Assmus B, Urbich C, Zeiher AM, Dimmeler S. Insulin-mediated stimulation of protein kinase Akt: A potent survival signaling cascade for endothelial cells. Arterioscler Thromb Vasc Biol. 2000;20(2):402–9. https://doi.org/10.1161/01.ATV.20.2.402
15. Bairy KL, Nayak V, Kumar S, Adiga S, Holla A, Kumar P, et al. Comparative effect of Sodium fusidate, Framycetin and Calcium mupirocin on experimentally induced burn wound healing. Int J Pharm Sci Bio. 2010;1(2):100–2.
16. Twilley D, Reva O, Meyer D, Lall N. Mupirocin promotes wound healing by stimulating growth factor production and proliferation of human keratinocytes. Front Pharmacol. 2022;13:862112. https://doi.org/10.3389/fphar.2022.862112
17. Shanley LJ, McCaig CD, Forrester JV, Zhao M. Insulin, not leptin, promotes in vitro cell migration to heal monolayer wounds in human corneal epithelium. Invest Ophthalmol Vis Sci. 2004;45(4):1088–94. https://doi.org/10.1167/iovs.03-1064
18. Blecher K, Martinez LR, Tuckman-Vernon C, Nacharaju P, Schairer D, Chouake J, et al. Nitric oxide-releasing nanoparticles accelerate wound healing in NOD-SCID mice. Nanomedicine. 2012;8(8):1364–71. https://doi.org/10.1016/j.nano.2012.02.014
19. Chereddy KK, Her CH, Comune M, Moia C, Lopes A, Porporato PE, et al. PLGA nanoparticles loaded with host defense peptide LL37 promote wound healing. J Control Release. 2014;194:138–47. https://doi.org/10.1016/j.jconrel.2014.08.016
20. Zubairi MB, Abd AH, Al-Lami MS. Formulation and Characterization of Mupirocin Nanomicelles in Insulin-Based Gel for Dermatological Application. J Pharm Bioallied Sci. 2023;15(Suppl 2):S1178–81. https://doi.org/10.4103/jpbs.jpbs_172_23

CONFLICT OF INTEREST
Authors declare no conflict of interest.
GRANT SUPPORT AND FINANCIAL DISCLOSURE
None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	MBZ, MAI
Acquisition, Analysis or Interpretation of Data:	MBZ, MAI, AFN, OSA
Manuscript Writing & Approval:	MBZ, MAI, AFN, OSA

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.