Efficacy of topical mupirocin versus 2% mupirocin in novel Cogen-S base in chronic skin ulcers: a pilot study

Key words:

- *Chronic skin ulcer*
- *Cogen-S*
- *Collagen*
- *Efficacy*
- *2% Mupirocin*
- *Wound healing*

Aim: To compare the efficacy and safety of topical Mupimet (2% mupirocin in a novel Cogen-S base) against mupirocin alone in the management of skin ulcers. **Methods**: We conducted a randomised controlled trial (RCT) with patients suffering from skin ulcers of Wagner grading 1 or 2 for over 4 weeks. Both the medications were applied topically twice daily for 12 weeks. Ulcer area, wound size and wound infection score were assessed on a five-point scale. During this study period, treatment-emergent adverse reactions were not observed either by the investigators or by the patients. The results were expressed as mean± standard deviation values to imply the wound size of the foot ulcer from the baseline to the week 12. **Results**: We recruited 50 patients, with 21 patients treated with mupirocin 2% and 24 patients treated with Mupimet ointment (five were lost to follow-up). We observed that the ulcer area was significantly reduced in the test groups (2% mupirocin in novel Cogen-S base) at 10 weeks, whereas the control group demonstrated a decrease in the wound size of over a period of 12 weeks. Statisical comparison using a t-test between two groups was conducted and showed statistical significance between the two groups in the study. When compared with the control value after 12 weeks, the test value is highly significant ($p \leq 0.05$ control and $p \leq 0.05$ test). **Conclusion**: The wound healing effect of topical Mupimet (in Cogen-S base) with the antimicrobial effect of mupirocin toward the overall management of skin ulcers. The acceleration of wound healing is higher in combined form than mupirocin alone.

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Ulcers can be defined as wounds with a "full-thickness depth" and a "slow healing tendency". Chronic ulcers are a leading cause of morbidity and mortality, affecting the quality of life of patients and while imposing a major burden on the health-care system (Järbrink et al, 2017). Chronic ulcers or wounds can be describes as breaks in the skin of greater than six weeks or with frequent recurrence. Venous dysfunction, diabetes mellitus, infections, peripheral neuropathy, pressure, trauma, malignancy, smoking and atherosclerosis are the major predisposing factors behind chronic skin ulcers. Furthermore, the lower limb is most commonly affected (Agale et al, 2013). Skin ulcers provide a favourable environment for bacterial propagation, and numerous microorganisms may be isolated from an ulcer. Infection and replication of bacteria in the wound site can delay the wound healing process (Keyvan Khezri et al, 2019). Treatment methods for chronic skin ulcers depend on the type of wound, these include topical and systemic antibiotics, surgical debridement, skin grafting, compression stockings and dressings.

Topical agents are the products designed to stay in contact with the wound surface for a longer period of time. Mupirocin, fusidic acid, neomycin, gentamicin, bacitracin and polymyxin B combination, and metronidazole are widely used for skin ulceration with

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Table 1. Inclusion and exclusion criteria.

iInclusion criteria	
1	Men or women aged between 18 and 65 years
2	Grade 1 or Grade 2 ulcer according to Wagner grading system, with at least 4 weeks duration
3	Subject is able to give written informed consent before the study start and to comply with the study requirements
Exclusion criteria	
1	Known connective tissue or malignant disease
2	Treatment with corticosteroids
3	Immunosuppressive agents, radiation therapy, or anticancer chemotherapy
4	Topical application of any advanced wound care on the wound (growth factor, antiseptics, antibiotics or debriders) within 30 days
5	Patients with hypersensitivity to gel and collagen
6	Immunocompromising disorders such as HIV/Aids
7	Patient with cardiovascular disease or intermittent claudication or stroke
8	Pregnant and breast feeding women

inflammation (Frank et al, 2005). The use of topical antimicrobial agents can decrease the risk of infection during wound healing.

Mupirocin is a natural crotonic acid derivative extracted from *Pseudomonas fluorescens* that acts by reversible inhibition of isoleucyl-tRNA synthetase (Nandimath et al, 2018). It is used for the treatment of small areas of skin infection and has been found to be effective, especially against methicillin-resistant *Staphylococcus aureus* (MRSA; Poovelikunnel et al, 2015).

Collagen, a major component of the extracellular matrix, plays a key role in each phase of wound healing process due to its chemotactic role. It also attracts cells such as fibroblasts and keratinocytes to the wound bed (Olczyk et al, 2014), which encourages debridement, angiogenesis and reepithelialisation. Collagen has been used widely within wound care and in multiple forms for different reasons. The multiple forms of collagen lend themselves to a variety of wound presentations, making it popular among wound specialists.

Aims

In this study, we compared efficacy of topical mupirocin (2% Mupirocin alone, leading commercial brand) versus topical Mupimet (2% Mupirocin combined with Cogen-S; Manufacturer-Fourrts, India, Laboratories Pvt.Limited, Chennai) in the treatment of chronic skin ulcers at our hospital. Cogen-S is a biodegradable sterile collagen granules with mupirocin 2% w/w that may prevent the adverse effects of long-term systemic antimicrobial therapy and enhance the acceleration of the wound healing process while also reducing the time of exposure to topical antimicrobials.

Materials and methods

We conducted a randomised controlled trial (RCT) with patients suffering from skin ulcers of Wagner grading 1 or 2 persisting for over four weeks. This study was approved by the Institutional Ethics Committee of Hycare Super Specialty Hospital in Chennai (Project No: 012/HSSH- EC/2021) and the approved protocol was implemented as per the regulatory guidelines. The subjects were screened based on the inclusion and exclusion criteria as summarised in ***Table 1***. The protocol was explained to all the subjects in both groups. The patients signed the informed consent and were randomly assigned to control (2% Mupirocin alone, T Bact) or test group (Mupimet, 2% Mupirocin combined with Cogen-S)

Both the medications were applied topically twice daily for 12 weeks in a quantity sufficient to cover the whole ulcer and up to 1cm beyond the ulcer edge.

Application of the topical ointments were first administered in the Outpatient Department, while subsequent application were carried out unsupervised by the patient or carer. Both ointments were dispensed from their original collapsible tube packs. At day 0, 10 weeks and 12 week ulcer area, wound size and wound infection score were determined by grading the following parameters: Erythema, Edema, Pain, Exudate and Pus. Cumulative Wound Evaluation Score (CWES) and Average Wound Evaluation Sore = (CWES/5)(0=Absent, 1= Mild,

Table 2. Comparison of demographic features of two groups under study.			
Parameters	**Test n=24**	**Control n=21**	**p-value**
Gender (%)			
Male	20 (83.3%)	16 (76.2)	
Female	4 (16.7%)	5 (23.8)	
Age	Range 40–79	Range 20–89	0.895
Mean	56.6	56.1	
Standard deviation	9.8	12.4	
Body mass index (BMI)			0.804
Mean	23.7	24.0	
Standard deviation	2.6	3.0	

The p-value of the comparison between the groups is done with a t-test, which showed that there was no statistical significance between the two groups in the study

Table 3. Ulcer grade based on Wagner Classification.		
Wagner grade for ulcer(%)	**Test**	**Control**
Grade 1	17 (70.83)	18 (85.71)
Grade 2	7 (29.16)	3 (14.28)

2= Moderate, 3= Severe). Participants in both the groups were permitted to receive systemic treatment for concomitant diseases provided these were not antimicrobials.

Statistical analysis was performed using a Student's t-test — $p<0.05$ is considered statistically significant

Results

Of 50 subjects recruited to the study, 21 patients were treated with mupirocin 2% (control) and 24 patients treated with Mupimet ointment (Test), with five subjects lost to follow-up, one subject from the test group and four from the control group, these were due to complications relating to the COVID-19 pandemic. *Table 2* represents a comparison of demographic features of two groups under study. A comparison of the *p*-value between the groups with a Student's t-test showed no statistical significance between the two groups under study. *Table 3* shows the grade of ulcer based on Wagner classification in the test and control group as a percentage. Wound evaluation score with time period between the study groups is depicted in *Table 4* the results were expressed as mean ± standard deviation of the foot ulcer wound evaluation from the baseline to week 12. For both the test and control values when compared with the baseline $p\leq0.05$ at 10 and 12 weeks, however, the test group was observed to be more significant than control group values. *Table 5* presents the alteration in ulcer size with time between study groups in the test and control group. The ulcer area was significantly reduced in the test group following 10 weeks of treatment. We observed that the ulcer area was significantly reduced in the test groups

Table 4. Wound Evaluation score with time between the study groups.				
Parameter	**Control group**	**p-value**	Test Group	p-value
Wound evaluation score at baseline Mean±SD	2.35 ± 0.08		2.49 ± 0.02	
Wound evaluation score at 10 weeks Mean±SD	1.75 ± 0.06	2.55E—20	0.24 ± 0.07	6.52E—29
Wound evaluation score at 12 weeks Mean±SD	0.21 ± 0.03	7.40E—31	0.058 ± 0.05	4.03E—32

Note: p<0.05 for both test and control when compared with the baseline for 10 and 12 weeks but test group is observed to be more significant than control group

Table 5. Change in ulcer size with time between study groups.				
Parameters	**Control group n= 21**	***p*-value**	**Test group n=24**	***p*-value**
Size at baseline (cm^2)	4.31 ±2.24		4.32 ± 2.11	
Size at 10 weeks (cm^2)	2.14±0.08	6.99E-11	1.09 ± 0.63	5.09928E-09
Size at 12 weeks (cm^2)	1.13 ±0.72	2.47484E-07	0.038±0.043	3E-73

As p< 0.05 it is statistically significant that there is difference between initial wound size and final would size with respective to test and control.
Inference: Though both the test value and control value is statistically significant, Test value is highly significant after 12 weeks when compared with control value of wound size after 12 weeks

(Mupimet, 2% mupirocin in novel Cogen-S base) at 10 weeks, whereas the control group demonstrated a decrease in the wound size of over a period of 12 weeks. It could be inferred that both the test value and control value are statistically significant. However, the test value was highly significant in a period of 12 weeks when compared with the control value at 12 weeks. ***Figure 1a–b*** shows the wound healing in control and test group over 12 weeks. The control group showed a delay in wound healing when compared with the control group. During the study period, treatment-emergent adverse reactions were not observed either by the investigators or by the patients.

Discussion

Surgical wounds, burns, trauma and various chronic skin ulcers can injure the skin and weaken its protective mechanisms. Complex macromolecules constituting the ECM include fibrous components (such as collagens and elastins) and glycoprotein components (such as fibronectin, proteoglycans and laminins). These molecules interact to drive the process of tissue function, growth and repair (Csapo et al, 2020). Many factors affect wound repair, including angiogenesis, immune response activation locally and availability of growth factors, including EGF, basic fibroblast growth factor (bFGF) and transforming growth factors.

Collagen, a key component of the extracellular matrix, plays a vital role in the regulation of the phases of wound healing either in its native, fibrillar conformation or as soluble components in the wound milieu (Mathew-Steiner, 2021). Collagen helps in wound debridement by attracting the monocytes, provides a matrix for tissue and vascular progression, attracts fibroblasts, binds with fibronectin, supports differentiation and migration of keratinocytes, and helps in the deposition of organised fibres (Xue et al, 2015). It has also been demonstrated that collagen can inactivate potentially detrimental factors, such as proteases, oxygen free radicals and excess metal ions present in chronic wound fluid, while simultaneously protecting positive factors, such as growth factors, and delivering them back to the wound (Dickinson and Gerecht, 2016).

Mupirocin, a topical antibiotic ointment, is widely used in the management of wounds infected by Gram-positive bacteria, particularly against MRSA. The major issue with the use of these topical antimicrobial agents is the risk of development of antimicrobial resistance and the significant negative impact on ulcer healing (Kale et al, 2015; Williamson et al, 2017). Perumal

Figure 1a. Wound healing completed nearly in 10 weeks - test subjects.

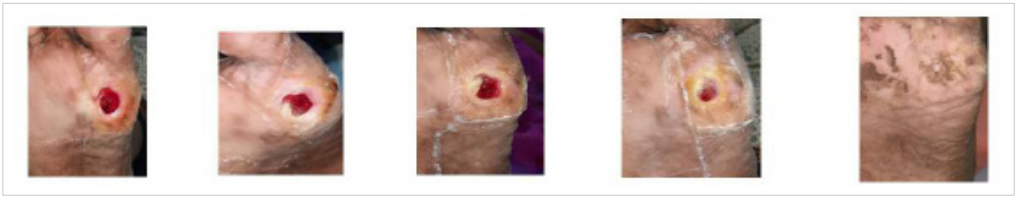

Figure 1b. Delayed wound healing observed in 12 weeks - control subjects.

(2014) reported a synergistic effect on wound healing when Mupirocin was added to the collagen granules. Hence, it was found to be an suitable biomaterial for the treatment of surface wounds, burns and foot ulcers.

According to the findings of our study, Mupimet, a combination of 2% Mupirocin with Cogen-S, is superior in terms of both ulcer size reduction and wound healing.

Conclusions

The protein collagen can directly modulate the wound microenvironment, serve as a scaffold for cellular attachment and deliver biologically active principles or antimicrobials to aid in wound healing. From our study, it could be concluded that topical application of the Mupimet ointment (2% mupirocin in a novel Cogen-S base) appears to be safe and may improve clinical and microbiological outcomes of diabetic foot infections of moderate severity when combined with standard of care. Thus, it can be inferred that Mupimet ointment (2% mupirocin in a novel Cogen-S base) can be used as a topical ointment for wound healing. WAS

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