International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 04 Issue 02 February 2024

Page No: 206-210

DOI: https://doi.org/10.47191/ijmscrs/v4-i02-09, Impact Factor: 7.949

Reviewing Choices of Topical Corticosteroids for Modulating Inflammatory Response in Chronic Wound Management

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ABSTRACT

Chronic wounds, characterized by prolonged inflammatory responses and impaired healing, pose a significant challenge in clinical practice. This review explores the potential of topical glucocorticosteroids in modulating inflammation and promoting wound healing in chronic wounds. We delve into the mechanisms underlying chronic inflammation, emphasizing the crucial role of proinflammatory cytokines, reactive oxygen species, and impaired cellular responses. Topical corticosteroids, known for their anti-inflammatory, anti-mitotic, and immunosuppressive properties, emerge as promising candidates to influence the transition from the inflammatory to the proliferative phase of wound healing.

The discussion encompasses the mechanisms of action of topical corticosteroids, focusing on their binding to glucocorticoid receptors, inhibition of inflammatory mediators, and potential adverse effects. We address the importance of selecting the appropriate corticosteroid based on potency, application duration, and patient-specific factors. Various formulations, such as ointments, creams, gels, and foams, are evaluated in terms of their advantages and drawbacks in wound management.

While acknowledging the recognized efficacy of topical corticosteroids in chronic wound management, we highlight concerns regarding their standalone use, such as immunosuppression and potential infection masking. Furthermore, we explore the integration of retinoids with corticosteroids as a novel approach to mitigate unwanted effects and enhance wound healing outcomes. Despite emerging studies on combination therapies, careful consideration and clinical judgment remain paramount for further development and implementation.

In conclusion, this comprehensive review provides insights into the potential of topical corticosteroids in chronic wound management. As research in this field progresses, the integration of innovative therapeutic strategies, including retinoids, holds promise for improving outcomes in the challenging realm of chronic wound care.

KEYWORDS: topical corticosteroids, chronic wound management, inflammation modulation, immunomodulation, retinoids, wound healing outcomes.

ARTICLE DETAILS

Published On:
07 February 2024

Available on:
https://ijmscr.org/

INTRODUCTION

The process of wound healing involves the reparation and the rebuilding of damaged tissue. It involves the inflammatory phase, proliferation phase and remodelling phase.[1,2] A wound that does not undergo through the normal phases of healing in a timely manner and persists for over three months is called a chronic wound.[3,4] Chronic wounds may present as a result of prolonged inflammatory response, persistent infection, formation of bacterial biofilm that impedes the ability of the dermal and epidermal cells to have normal regenerative responses.[4] Chronic wounds can manifest as a result of chronic venous insufficiency, prolonged pressure (pressure ulcers) , arterial related diseases and neuropathies. It has and still remains a challenge for clinicians, requiring multidisciplinary approach as a patient with chronic wound usually presents with an underlying illness that may

exacerbate the progression of the wound itself, leading to systemic infection and most likely their untimely demise.[4] Not only it has a high mortality and morbidity rate, but it may also decrease quality of life. It has imposed an economic burden, not only through cost of healthcare but also in terms of human capital productivity. According to Fortune Business insight, the economic burden of venous leg ulcer care reached USD 14.90 billion in the United States alone.[5] Geriatric patients are more susceptible to develop chronic wounds than their younger counterparts.[6]

Various measures have been taken to alleviate individual economic and physical burden caused by the wound itself.[6,7] Basic fundamentals in improving wound healing is to deal with the systemic disease underlying the condition (blood glucose control) and lifestyle changes, debridement of nonviable tissues, reduction of bioburden, reduce oedema (elevation and compression), optimize blood flow and using appropriate dressings. Clinicians have developed treatments to help regulate the molecular and cellular deficiencies, may it be pharmacological or non-pharmacological.[6,7] Clinicians also have utilized non pharmacological measures in the treatment of chronic wounds, such as negative wound pressure therapy, hyperbaric oxygen therapy, biophysical therapy and surgical debridement if necessary. Wound practicians use appropriate dressings to provide a moist environment and assist in removing excessive exudate to help the regeneration process. Chronic wounds demonstrates a abnormally high level of proinflammatory cytokines, proteases and reactive oxygen species (ROS).[7] Inflammatory by products can affect the nociceptors and reduce pain threshold, this can cause a patient to feel excessive pain. The use of topical corticosteroid can be beneficial in reducing the inflammatory response may be a logical step to help reduce such response. Low doses of topical corticosteroids can help reduce exudates, relieve pain and help to supress the excessive granulation of tissue. A low dose and gradual release of topical corticosteroids combined with antimicrobials and antifungal on chronic wounds can help managing the inflammatory phase and can promote the progression of the inflammatory phase to the proliferation phase.[8]

Mechanisms of inflammation in chronic wounds

The normal phases of wound healing involves haemostasis phase, inflammation phase, proliferation phase and ends in a long remodelling phase. Haemostasis occurs right after initial injury, platelets are an integral part of this process. Platelets arrives at the injury site and sticks itself to the collagen of the endothelium.[8] Circulating fibrinogens is transformed into fibrins, forming a thrombus that helps to stop bleeding. The activation of the fibrinogens into fibrins attracts neutrophils and macrophages as well as transforming growth factors beta (TGF-ß) that is released by degranulating platelets and platelet derived growth factor (PDGF).[8,9] It functions to degrade the extracellular matrix to prepare for wound healing. Transforming growth factors beta (TGF-ß) helps the release of cytokines from macrophages and increase fibroblast and smooth muscle cell migration. Neutrophils also function as debridement and infection control.[9] Macrophages help phagocytose bacteria and debris then in turn take in fibroblasts and growth factors for the extracellular matrix (ECM) which then activates the proliferative phase.[9]

In a chronic wound, wound healing stops at the inflammatory phase.[9] Repeated tissue hypoxia, trauma, infection with the underlying systemic problems, poses a vicious cycle of inflammation thus preventing the progression of the inflammatory phase to the proliferation phase.[9] In a molecular level, there is a high level of pro inflammatory cytokines, reactive oxygen species (ROS) and senescent cells, persistent infection and defective stem cells. Excessive neutrophil infiltration is the key to this chronic inflammation. Tissue hypoxia and the inflammatory environment produces reactive oxygen species (ROS) destroys the extracellular matrix (ECM) and cell membranes in contradiction to the fact that in low concentrations reactive oxygen species (ROS) helps to fight against microorganism.[9] Neutrophils and macrophages also release proteases like etalase and matrix metalloproteinase (MMP) that degrade growth factors, tumor necrosis factor beta (TNF-ß), platelet derived growth factor (PDGF) and pro inflammatory cytokines Interleukin-1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α). The inflammatory cytokines increases matrix metalloproteinase (MMP) as well as tissue inhibitors of matrix metalloproteinase (TIMP). This further exacerbates the degradation of the extracellular matrix (ECM), impairs cell migration and collagen synthesis. In conclusion, there is an imbalance of inappropriate inflammation and host response that causes the hindrance of re-epithelialization of the wounds.[9,10]

Role of topical corticosteroids in inflammation modulation

Topical corticosteroids have been widely used in medicine, mainly in dermatotherapy. It has anti-inflammatory, anti-mitotic and immunosuppressive properties and thus it is commonly used in the treatment of various dermatologic conditions. The anti-inflammatory properties of topical corticosteroids are due to their ability to bind to the glucocorticoid receptor (GR or GC-R) in the cytoplasm, inhibition of the release of phospholipase A2, and a direct inhibitory effect on deoxyribonucleic acid (DNA) and inflammatory transcription factors of cells. Thus, the use of topical corticosteroid is supposed to be a logical approach to treat chronic inflammation. However, it is good to note the adverse effects that comes with prolonged usage of topical corticosteroids such as skin atrophy, striae, rosacea and other systemic effects.[10]

After haemostasis event, there is an apparent vasodilatation that ensures macrophages and neutrophils to infiltrate the wound area and defend against microbial infiltration. During

this process, pro-inflammatory mediators are produced. The use of topical corticosteroids controls the amount of infiltration of the pro-inflammatory mediators in the wound region.[10] However, the prolonged or excessive use of topical corticosteroid has its side effects, weaken the immune system, barrier function and inhibit wound healing instead. This side effect is known as cacostasis (allostasis).[10] To counteract this excessive inflammatory properties of the corticosteroid, Jozic and colleagues (2017) proposed the future use of mineralocorticoid receptor antagonists or reverse agonists for efficient wound healing.[11-13]

Topical corticosteroids binds to glucocorticoid receptor in deoxyribonucleic acid (DNA) to form a glucocorticoid-receptor complex (GR or GC-R) to give off its effects. When there is an inflammatory stimulus (e.g the presence of TNF), it will remain in the cytoplasm and exert its biological anti-inflammatory properties unbound. Corticosteroids synthesizes lipocortin, and inhibiting phospholipid A2, therefore inhibiting the release of leukotrienes and prostaglandins that help reduce inflammation.[13]

Selection of topical corticosteroid

The potency of topical corticosteroid translates as the required dosage used to attain the desired therapeutic effect, and it is based on its vasoconstriction ability in the cutaneous area.[13] Specific considerations must be used during application to obtain the desired anti-inflammatory effect and minimize the adverse effects. Patient characteristics such as age, lesion location, lesion type and severity should be accounted for. Corticosteroids can be classified into various classes based on their potency: class I (ultra high potency), II (high potency), III (medium potency), IV (medium potency), V (lower mild potency), VI (mild potency), and VII (least potency). Class I includes clobestasol, halobetasol; class II includes betamethasone, desoximetasone, fluocinonide; class III includes betamethasone, triamcinolone; class IV includes desoximetasone, fluocinolone, flurandrenolide, class V includes fluticasone, class VI includes desonide, and class VII includes dexamethasone, hydrocortisone and methylprednisolone.[13,14]

Recommended use of medium to high potency topical corticosteroids are mainly for areas with thicker skin like he sole of foot, leg and palm, and in cases of severe dermatoses. Clinicians should not apply medium to high potency topical corticosteroids more than 12 weeks at maximum to prevent adverse cutaneous and systemic effects. Recommended use low potency corticosteroids are for areas with thinner skin such as eyelids and outer ears due to the epidermal nature, for paediatric skin, and for cases in need of longer duration of usage with knowledge of its minimal adverse effect.[14]

Clinicians can find topical corticosteroids in different formulations with each advantages and drawbacks.[14] The formulation is analogy for the drug transportation mode to facilitate contact, increase absorption into the skin layer and therefore provide effective process. We acknowledge formulations as follows: ointments, creams, lotions, gels, foams and solutions.

Ointments are a petroleum based formulation that functions as a lubricant for skin types with smooth and non-hairy surface, dryness, and hyperkeratotic appearance.[14,15] Ointments have less add-ons and consequently has lesser allergens, and also more absorptive than creams.[14,15] The downside is that it is occlusive so it leaves a residue upon cleaning, potentially leads to maceration and folliculitis when applied on hairy skins.[15] Creams and lotions are a water and oil based formulation which are less occlusive than ointment, but often has add-ons like alcohol substance that may potentially lead to allergic reactions in certain sensitive groups.[15] They possess a drying property and do well for highly exudative wounds. Gels are water based formulation, it has a good drying effect but often stings if applied to exposed tissues. One notable advantage is it can be applied to hairy skin areas without the inconvenience of the greasiness unlike ointments and creams. Foams spreads very easily on skin, but it is very costly. Solutions is ideal for hairy areas like the scalp, has lesser add-ons than creams however it still potentially cause allergic reactions in sensitive groups (for example: shampoos).[15]

Like all medications, topical corticosteroids have their own adverse side effects, may it be cutaneous or systemic.[15,16] Their side effects depend on the potency and the length of usage, therefore it is best to account for the appropriate use of the topical corticosteroids based on the clinical characteristics of the patients. Reports showed cutaneous adverse effects like striae, skin atrophy, telangiectasia, perioral dermatitis, rosacea and allergic reactions occur. Skin atrophy happens due to the antimitotic effect of topical corticosteroids, results in the thinning of epidermis and increased resorption of the dermis.

Systemic side effects occur in conditions with hypothalamic-pituitary axis suppression, and case reports showed cases of glaucoma, Cushing syndrome and hyperglycemia as a result of topical corticosteroids. Systemic side effects are rarerely due to its absorption unless in cases where topical corticosteroids used within areas with thin epidermis.[16,17]

Efficacy and safety of topical corticosteroid use in chronic wound management

The use of topical corticosteroids as a single modality treatment is not a common practice for chronic wound management.[17] Clinicians believed that the immunosuppressive properties of topical corticosteroids potentially faciltate more bacterial and even opportunistic fungal infection.[17,18] Clinicians also agreed that the vasoconstriction effect of corticosteroids may mask the on-going infection process. We mentioned earlier that the antimitotic effect of the corticosteroids may result in thinning of the epidermis and increased resorption of the dermis, thus causing skin atrophy.[18] Topical corticosteroids also prevent the migration and proliferation of keratinocytes, as

discovered by a research in which medium potency corticosteroids applied in animal wound inhibiting wound closure more obvious than the low potency corticosteroids did.[18] The use of topical corticosteroids on wound beds for long periods of time in high doses can have the same effects as their systemic counterparts.[18] And the prolonged use of topical antibiotics can cause bacterial resistance that might worsen the condition of the wound bed.[18,19]

The use of retinoids partially reverses the effects of topical corticosteroids. This can mitigate the unwanted effects of corticosteroids on tumour growth factor beta (TGF-ß), Insulin growth factor 1 (IGF-1) and collagen deposition. Studies agreed that vitamin A has the ability to stimulate epithelial growth, generation of capillaries, fibroblast deposition and collagen synthesis, which in turn can enhance the wound healing process. Retinoids also has antimicrobial properties by preventing the growth and proliferation of bacteria.[19]

Future Perspectives

The use of topical corticosteroids on wound beds have not been a common practice for the treatment of chronic wounds, although there was an emerging case of the use of topical combination therapy involving corticosteroids with antimicrobials. However, emerging studies combining the use of retinoids with topical corticosteroids have been suggested yet has never been experimentally tested in human beings. With that in mind, we believe that the use of such treatment should have so many considerations and a good clinical judgement to be the foundation for further development.

CONCLUSION

In conclusion, topical glucocorticosteroids emerge as a promising avenue for modulating inflammation in chronic wounds. Their anti-inflammatory, anti-mitotic, and immunosuppressive properties make them potential candidates for influencing the transition from the inflammatory to the proliferative phase of wound healing. Through the binding to glucocorticoid receptors, topical corticosteroids control the release of inflammatory mediators, thereby regulating the inflammatory response. However, caution must be exercised in their usage, considering potential adverse effects such as skin atrophy and systemic repercussions associated with prolonged use.

The selection of an appropriate topical corticosteroid is crucial, with considerations for potency, application duration, and patient-specific factors. The formulation of these agents also plays a significant role, and clinicians should tailor their choices based on the characteristics of the wound and the surrounding skin. While the efficacy of topical corticosteroids in chronic wound management is recognized, their use as a standalone treatment remains uncommon due to concerns about immunosuppression and potential masking of infections. The integration of retinoids with topical corticosteroids presents a novel approach that merits further exploration, holding promise for enhanced wound healing outcomes. As research in this field progresses, careful consideration and clinical judgment will be essential for the development and implementation of innovative therapeutic strategies in chronic wound management.

REFERENCES

I. Gould L, Abadir P, Brem H, Carter M, Conner-Kerr T, Davidson J, et al. Chronic Wound Repair and Healing in Older Adults: Current Status and Future Research. Journal of the American Geriatrics Society [Internet]. 2015 Mar;63(3):427–38. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4582412/

II. Järbrink K, Ni G, Sönnergren H, Schmidtchen A, Pang C, Bajpai R, et al. The humanistic and economic burden of chronic wounds: a protocol for a systematic review. Systematic Reviews [Internet]. 2017 Jan 24;6(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5259833/

III. Zhao R, Liang H, Clarke E, Jackson C, Xue M. Inflammation in Chronic Wounds. International Journal of Molecular Sciences. 2016 Dec 11;17(12):2085. https://doi.org/10.3390/ijms17122085

IV. Thorne CH, Chung KC, Gosain AK, Gurtner GC, Mehrara BJ, Rubin JP et al. Grabb and Smith's plastic surgery: Seventh edition. Wolters Kluwer Health Adis (ESP), 2013.

V. Chronic wound care market size, share & covid-19 impact analysis, by type (diabetic ulcers, pressure ulcers, venous leg ulcers, and others), by product (advanced wound dressings, wound care devices, active therapy, and others), by end user (Hospitals & wound clinics and homecare settings & others), and Regional Forecast, 2023-2030 [Internet]. Fortune Business Insight; 2023 [cited 2023 Sept 6]. Available from: https://www.fortunebusinessinsights.com/amp/industry-reports/chronic-wound-care-market-100222

VI. Frykberg RG, Banks J. Challenges in the Treatment of Chronic Wounds. Advances in Wound Care [Internet]. 2015 Sep;4(9):560–82. https://doi.org/10.1089/wound.2015.0635

VII. Nirenjen, Narayanan J, T. Tamilanban, Vetriselvan Subramaniyan, V. Chitra, Neeraj Kumar Fuloria, et al. Exploring the contribution of pro-inflammatory cytokines to impaired wound healing in diabetes. Frontiers in Immunology [Internet]. 2023 Jul 27 [cited 2023 Sep 26];14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10414543/

VIII. Zhao R, Liang H, Clarke E, Jackson C, Xue M. Inflammation in Chronic Wounds. International Journal of Molecular Sciences [Internet]. 2016 Dec 11;17(12):2085. https://doi.org/10.3390/ijms17122085

IX. Mahmoudi M, Gould L. Opportunities and Challenges of the Management of Chronic Wounds: A Multidisciplinary Viewpoint. Chronic Wound Care Management and Research [Internet]. 2020 Jul;Volume 7:27–36. https://doi.org/10.1089/wound.2015.0635

X. Gabros S, Zito PM. Topical Corticosteroids Treasure Island (FL): StatPearls Publishing [Internet]. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532940/

XI. Bosanquet D, Rangaraj A, Richards A, Riddell A, Saravolac V, Harding K. Topical steroids for chronic wounds displaying abnormal inflammation. The Annals of The Royal College of Surgeons of England [Internet]. 2013 May;95(4):291–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4132506/

XII. Stress Signals, Mediated by Membranous Glucocorticoid Receptor, Activate PLC/PKC/GSK-3β/β-catenin Pathway to Inhibit Wound Closure. Journal of Investigative Dermatology [Internet]. 2017 May 1 [cited 2023 Aug 28];137(5):1144–54. Available from: https://reader.elsevier.com/reader/sd/pii/S0022202X16328032?token=3EB145C6B20C8DEDD9CBD731FC2350F40E54C2716DBD2E7AED8CFF464FF40F9759F5126EC4AFAD01B47C6B61AE85E222

XIII. Slominski AT, Zmijewski MA. Glucocorticoids Inhibit Wound Healing: Novel Mechanism of Action. Journal of Investigative Dermatology [Internet]. 2017 May;137(5):1012–15

XIV. Stacey SK, McEleney M. Topical Corticosteroids: Choice and Application. Am Fam Physician [Internet]. 2021 Mar 15;103(6):337-343. PMID: 33719380.

XV. Douglas WS, Simpson NB. Guidelines for the management of chronic venous leg ulceration. Report of a multidisciplinary workshop. British Journal of Dermatology [Internet]. 1995 Mar [cited 2023 Aug 7];132(3):446–52. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2133.1995.tb08681.x

XVI. Marks JG, Cano C, Leitzel K, Lipton A. Inhibition of Wound Healing by Topical Steroids. The Journal of Dermatologic Surgery and Oncology[Internet]. 1983 Oct;9(10):819–21.

XVII. Wicke C, Halliday B, Allen D, Roche NS, Scheuenstuhl H, Spencer MM, et al. Effects of steroids and retinoids on wound healing. Archives of Surgery (Chicago, Ill: 1960) [Internet]. 2000 Nov 1;135(11):1265–70. Available from: https://pubmed.ncbi.nlm.nih.gov/11074878/

XVIII. Hewish J. Guidelines for the effective diagnosis and management of local wound bed infection and bacterial colonisation. Oxford Health. NHS Foundation Trust, 2016

XIX. Oluwole DO, Coleman L, Buchanan W, Chen T, La Ragione RM, Liu LX. Antibiotics-Free Compounds for Chronic Wound Healing. Pharmaceutics. 2022 May 9;14(5):1021. https://doi.org/10.3390/pharmaceutics14051021