

IN-DEPTH REVIEW

Topical Zinc May Augment Post-Operative Wound Healing, Including Following Mohs Micrographic Surgery: A Review of the Literature

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ABSTRACT

Background: Zinc, an essential mineral, has been extensively studied in the field of dermatology for the treatment of a plethora of skin conditions. However, minimal literature exists regarding its use for the enhanced healing of wounds after surgery, including following Mohs micrographic surgery (MMS).

Objective: Evaluate the available literature regarding the utilization of zinc for enhanced healing of post-surgical wounds in humans.

Methods: A systematic review of studies evaluating the use of zinc for post-surgical management was conducted via an electronic literature search of the PubMed database. Clinical trials were searched using ClinicalTrials.gov.

Results: Topical zinc formulations may decrease healing time and post-operative infection rates, including following MMS of the lower extremity.

Limitations: Currently, there are a limited number of studies available on this topic, with lack of a standard comparable outcome measure.

Conclusion: Topical zinc oxide may be a beneficial treatment option for post-surgical wound healing, including after MMS. Further studies are needed to better define the efficacy of zinc for post-operative wound healing and the optimal treatment regimen.

INTRODUCTION

The use of zinc has been studied for the treatment of many dermatologic conditions including warts, inflammatory dermatoses like acne vulgaris and rosacea, and

pigmentary disorders like melasma and neoplasms.¹ Zinc supplementation also reduces the risk of bacterial, viral, and fungal infections.²⁻⁴ Its efficacy has been demonstrated in the setting of cutaneous healing following burn injuries⁵⁻⁷ and as a protectant against UV radiation in the form of

topical zinc oxide. Additionally, zinc deficiency is associated with impaired wound healing and existing evidence supports the use of topical zinc oxide and oral zinc sulfate for the healing of leg ulcers.⁸⁻¹²

Zinc is required for optimal activity of numerous enzymes and serves a critical role in the development and proper functioning of the immune system.¹³ It contributes to protein structure and the regulation of gene expression.⁸ It also influences gene transcription at several levels through histone deacetylation reactions and zinc-finger motifs.

This essential mineral is found in some foods, including beef, poultry, seafood, and grains.⁸ Oral formulations are also available as zinc gluconate, zinc sulfate, and zinc acetate.¹⁴ Furthermore, zinc can be administered as an intravenous zinc chloride solution, generally as an addition to total parenteral nutrition.¹⁵

Currently, minimal literature exists regarding the use of zinc for the healing of post-surgical wounds in humans, especially after dermatologic surgery. However, the efficacy of zinc for post-operative healing has been well documented in animal studies. Studies with zinc-deficient rats demonstrated delayed epithelialization of wounds as well as a decrease in tensile strength of the resultant scars.^{16,17} Zinc has also been shown to be beneficial for zinc-sufficient rats with a significant increase in re-epithelialization of surgical sites treated with topical zinc.^{18,19} Bovine studies demonstrated similar results with a substantially decreased rate of skin regeneration following surgery in zinc deficient subjects as well as enhanced re-epithelialization of partial-thickness wounds in nutritionally balanced subjects treated with topical zinc oxide.^{20,21}

The purpose of this review is to evaluate the

currently available literature regarding the utilization of zinc for enhanced post-surgical wound healing, including after Mohs Micrographic Surgery (MMS).

METHODS

A systematic review of studies describing the use of zinc for post-surgical management was performed. We conducted an electronic literature search of PubMed database on zinc and post-surgical management twice—in May and June 2020. Additionally, clinical trials were searched using ClinicalTrials.gov.

RESULTS

Our search yielded eight studies that have been performed on human subjects. Two of these studies focused on the use of zinc oxide compression dressings for postoperative defects following lower extremity MMS.^{22,23}

Efficacy of Zinc for Post-Operative Healing
In 2006, a randomized, double-blind, placebo-controlled study compared the use of 3% zinc oxide mesh with placebo mesh on the healing of acute open wounds following pilonidal cyst excision.²⁴ The 3% zinc oxide mesh provided sustained release of bioavailable zinc to the wound at noncytotoxic levels.²⁵⁻²⁷ The results of this study demonstrated a trend toward decreased average healing time compared with placebo (54 days vs 62 days;) and a statistically significant decrease in the occurrence of *Staphylococcus aureus* in wounds ($p < 0.05$). As a result, significantly fewer zinc-oxide treated patients were prescribed systemic antibiotics post-operatively ($p = 0.005$).²⁴ Importantly, there were no local or systemic adverse effects observed in the zinc oxide group.²⁴

Administration of oral zinc sulfate has been shown to enhance the rate of wound healing in venous leg ulcers,^{11,12} sickle-cell ulcers,²⁸ and pressure ulcers.²⁹ One study investigated the effects of oral zinc sulfate in the healing of surgical wounds caused by the removal of pilonidal-sinus tracts.³⁰ Average wound volume was 32.3 ml in the control group and 54.4 ml in the treatment group. Ten participants ingested 220 mg of zinc sulfate daily while ten controls did not. The healing rate was significantly increased in the zinc-medicated group, with wound closure occurring almost three times faster than the control group ($p < 0.02$).³⁰ Aesthetics also differed between the two groups as it was noted that the wounds in the zinc-medicated group appeared cleaner, pinker, and healthier with less purulent exudate when compared to the wounds in the control group.³⁰ No toxic side effects were noted during the 61 days in which the patients were followed.³⁰

A similar study failed to produce the same results.³¹ The authors speculate that varying results were seen because oral zinc sulfate may not play a significant role in wound healing, or possibly, that neither study was sufficiently controlled to account for variations among individual patients.³¹

The parenteral administration of zinc gluconate was analyzed by Faure et. al in a double-blind, randomized study of 30 patients who underwent major reconstructive surgery for the treatment of abdominal aorta atherosclerosis.³² 15 patients received a 30 mg IV drip of zinc gluconate for 3 days, while the control group received a placebo.³² No healing complications were reported in the zinc-medicated group.³² However, 4 of 15 patients in the placebo group experienced complications including delayed wound healing, lymphorrhea, and inflammation ($p = 0.00771$).³²

Weingert and Stoll compared the efficacy of topical zinc oxide ointment and potassium/calcium chloride hydrogel on the epithelialization of split thickness skin graft donor sites from which grafts were harvested for use in oral and maxillofacial surgery. Donor sites were located on the upper thigh and demonstrated complete epithelialization more rapidly when treated with zinc oxide (8.7 days vs 10.7 days).³³ Furthermore, patients in the zinc oxide group did not have any subjective complaints. In contrast, transient burning was reported in 14 patients treated with the potassium/calcium chloride hydrogel. 14 months after grafting, no aesthetic differences were noted between the two groups.³³

Efficacy of Zinc for Post-Operative Healing in Mohs Micrographic Surgery

In 2011, Stebbins et al. utilized Unna boots, a compression dressing consisting of gauze bandages soaked with zinc oxide, for postoperative MMS wound care in 10 patients.²² The defect size ranged from 3.6 to 30 cm² and wound depth varied between subcutaneous fat and muscle. This study demonstrated significant granulation tissue development in the first post-operative week of all subjects and an average time to complete epithelialization of 7.1 weeks with a range of 4 to 12 weeks.²² No subjects in this study developed excess granulation tissue or post-operative infection, and all patients reported high satisfaction with this intervention.²² The occlusion provided by the Unna boot may enhance wound healing independently or by augmenting the anti-bacterial and anti-inflammatory properties of zinc, as occluded wounds have been shown to heal four to five times more quickly than non-occluded wounds.³⁴⁻³⁷

In 2017, a retrospective cohort study compared standard post-operative wound care to zinc oxide compression dressings for

surgical sites on the legs, a particularly challenging area to manage in the post-operative period that is often complicated by delayed healing, dehiscence, hematoma, and infection.^{22,23} The average incision length was 4.35 cm in the group receiving standard dressing and 6.35 cm in the zinc-oxide treated group. Standard wound care included applying petroleum jelly to the post-operative site followed by nonadherent dressing, gauze, and paper tape. The patients who received the standard wound care were instructed to leave the dressing in place for 48 hours following initial application and then to clean the wound, apply petroleum jelly, and change the dressing on a daily basis. The patients who received the zinc oxide compression bandage did not perform any wound care at home but returned to the office weekly for a bandage change. They were instructed to return for at least two weeks or until epithelialization of the wound was achieved. At 19 days, 91.7% of patients receiving the zinc oxide compression bandage were fully healed, whereas only 65.9% of patients receiving standard wound care were healed ($p < 0.001$).²³ Furthermore, no complications occurred in the zinc oxide group; however, 6 complications were noted in the group receiving standard wound care, including infection, wound dehiscence, postoperative bleeding, pain, and excessive swelling.²³

Currently a clinical trial is in progress which will compare scar outcomes following dermatologic surgery when treated with topical zinc oxide versus petrolatum.³⁸ This split-scar study will treat half of the incision with zinc oxide and half with petrolatum. This is the first clinical trial studying the use of zinc oxide in the post-surgical setting which will analyze its results through the use of the Patient and Observer Scar Assessment Scale (POSAS) scoring system.

DISCUSSION

Zinc in the Integumentary System

Zinc is a trace element essential for many aspects of health. It serves as a cofactor for enzymes required for cellular replication, protein synthesis and repair systems as well as transcription factors.³⁹ Specifically, zinc-finger proteins are a family of over 2,000 transcription factors that interact with DNA and RNA polymerases to initiate transcription of key genes for wound healing.^{39,40} Specific zinc-finger transcription factors identified in the skin include basonuclin, an important mediator of cellular division, and c-Krox, a vital protein that controls expression of genes that encode the extracellular matrix (ECM).⁴⁰ Zinc is also involved in intracellular signaling and neurotransmission.³⁹

In the integumentary system, zinc plays a role in mitosis, migration and maturation of keratinocytes. It is found in the form of protein complexes intracellularly and in the ECM.³⁹ While zinc is found in both epidermal and dermal tissues, concentrations in the epidermis are higher, potentially reflecting the activity of zinc-dependent RNA and DNA polymerases in the mitotically active basal cells.³⁹ Furthermore, an inverse relationship is observed in the epidermis between the zinc concentration and the state of maturation and keratinization of post-mitotic cells.³⁹ For example, as keratinocytes mature and reach the corneal layer, zinc levels are lower than in the mitotically active basal layer.

The Role of Zinc in Wound Healing

Wound healing can be characterized by three phases: inflammatory phase, proliferative phase, and remodeling phase. The inflammatory phase starts within hours of tissue injury and may last 3-4 days.⁴¹ During the inflammatory phase hemostasis is achieved by platelets and a fibrin matrix

Table 1. Studies of Zinc Therapy for Post-Operative Wound Healing

Title	Study Type	Subject Information	Route of Zinc Administration	Comparison	Conclusion
Enhanced Healing of Surgical Wounds of the Lower Leg Using Weekly Zinc Oxide Compression Dressings ²²	Observational	10 patients 6 male, 4 female Age range: 72-91	Topical zinc oxide compression bandage	N/A	Average time to complete epithelialization of 7.1 weeks with a range of 4 to 12 weeks
Effect of Postoperative Dressing on Excisions Performed on the Leg: A Comparison Between Zinc Oxide Compression Dressings Versus Standard Wound Care ²³	Retrospective Cohort	80 patients 16 male, 54 female Age range: 19-89	Topical zinc oxide compression bandage	Zinc Oxide compression dressing (n=36) vs Standard dressing (n=44)	Zinc oxide compression dressings resulted in decreased incidence of delayed wound healing with fewer complications compared to standard postoperative wound dressing group (p < 0.001)
A randomized, double-blind, placebo-controlled multicenter trial evaluating topical zinc oxide for acute open wounds following pilonidal disease excision ²⁴	Randomized, double-blind placebo-controlled trial	64 patients 53 male, 11 female Age range: 17-60	Topical zinc oxide mesh	3% Zinc Oxide mesh (n=33) vs Placebo mesh (n=31)	Zinc oxide decreased the average healing time and decreased the occurrence of <i>Staphylococcus aureus</i> in wounds (p < 0.05)
Acceleration of Wound Healing in Man With Zinc Sulfate Given By Mouth ³⁰	Randomized Control Trial	20 patients 20 male, 0 female Age range: 18-40	Oral 220 mg zinc sulfate TID	Control (n=10) vs 220 mg zinc sulfate TID (n=10)	Post-surgical wounds in the zinc-medicated patients closed three times faster compared to the control group (p < 0.02)
Lack of Acceleration of Healing with Zinc Sulfate ³¹	Randomized Control Trial	20 patients Age range: 19-35	Oral 220 mg zinc sulfate TID	Control (n=10) vs 220 mg zinc sulfate TID (n=10)	No acceleration of wound healing was found in young patients with granulating wounds given oral zinc sulfate versus the control group
Parenteral Supplementation with Zinc in Surgical Patients Corrects Postoperative Serum-Zinc Drop ³²	Double-blind, randomized study	30 patients	Parenteral IV zinc gluconate	IV zinc gluconate 30 mg/day for 3 days (n=15) vs Placebo (n=15)	Clinical inspection of wounds following complicated surgery revealed that zinc supplementation was beneficial even if serum zinc was normal before intervention (p = 0.00771)
The epithelialization of split skin graft donor sites- a test model for the efficacy of topical wound therapeutic agents ³³	Prospective, clinical study	16 patients 6 male, 10 female Age range: 18-81	Topical zinc oxide ointment	Zinc Oxide ointment (n=16) vs Potassium/calcium chloride hydrogel (n=16)	More rapid epithelialization was observed in zinc oxide group
Zinc Oxide Versus Petrolatum Following Skin Surgery: A Head-to-head, Prospective, Split-scar Study ³⁸	Comparative	30 patients	Topical zinc oxide ointment	Zinc Oxide ointment (n=30) Vs Petrolatum (n=30)	Study currently in progress

which serve as the initial scaffold for infiltrating cells.^{40,41} Before the cessation of the inflammatory phase, neutrophils and macrophages phagocytize debris and debride the tissue.^{40,41} The proliferative phase of healing begins 2-10 days after injury and is characterized by mitotic activity and

migration of keratinocytes, blood vessels, and fibroblasts.⁴¹ During this phase, the keratinocytes at the leading edge of the wound proliferate and mature.⁴¹ The remodeling phase begins approximately 3 weeks following tissue injury and can last for more than one year.⁴¹ Matrix

metalloproteinases (MMPs) have the vital job of remodeling the scar.^{40,41}

Zinc and zinc-containing proteins are involved in nearly every aspect of cutaneous wound repair. Metallothioneins (MTs) bind approximately 20% of intracellular zinc and are responsible for transporting zinc to enzymes and gene-regulatory molecules important for wound healing.^{39,40} MTs can be thought of as surrogate markers for zinc. Spectrometry and immunohistochemical techniques have been utilized to demonstrate that MTs are expressed at higher rates in healing wounds than in normal skin.^{39,40} Treatment of keratinocytes in vitro with zinc chelators has been shown to inhibit upregulation of MTs and cellular proliferation.⁴⁰ Conversely, MT upregulation can be induced in vivo by exposure to zinc.⁴⁰ Collectively, these findings show that the requirement for zinc is higher in skin during times of healing and that zinc induces the expression of MTs that serve an important role in its storage and transportation.

MMPs are a diverse group of zinc-dependent enzymes that play an important role in wound healing. MMPs are up-regulated following injury and are crucial for wound debridement, cell migration, and reconstitution of the ECM.^{39,42} This has been demonstrated by the fact that synthetic MMP inhibitors result in impaired keratinocyte migration and wound contraction.^{39,43,44} MMPs with notable action in wound healing include MMP-1, MMP-9, MMP-14, and MMP-2. MMP-1 has a primary role in initiating tissue repair and epithelization.³⁹ Elevated levels have been demonstrated in 24-hour human fibroblasts and in migrating epidermal cells during the acute phase of healing.^{39,43,44} MMP-9 and MMP-14 are likely involved in keratinocyte migration while MMP-2 is persistent in fibroblasts and endothelial cells throughout

the wound healing process and is primarily involved in ECM remodeling.³⁹

Keratinocyte migration is also modulated by zinc through the expression of integrins. In healthy skin, integrins are expressed primarily in the basal layer and promote intercellular and cell to basement membrane adhesion.³⁹ Supplementary zinc during wound healing promotes induction of key integrin subunits that enhance keratinocyte motility.^{39,45}

As well as acting on specific proteins important for wound healing, zinc enhances intracellular mitogenic signaling pathways to up-regulate endogenous growth factors that can contribute to epithelialization.³⁹ Furthermore, zinc plays a significant role in inflammation reduction.⁴⁰ Alkaline phosphatase (AP) is one zinc-dependent enzyme that regulates inflammation.⁴⁰ AP is released from the surface of epithelial cells and dephosphorylates adenosine monophosphate (AMP) to make adenosine, which has anti-inflammatory action and helps to curtail the initial inflammatory phase of wound healing.⁴⁰

Practical Implications for the Utilization of Zinc in the Post-Operative Period

Most studies evaluating the efficacy of zinc in wound healing have been conducted on patients with chronic wounds. These studies have failed to show a statistically significant benefit for oral zinc supplementation, unless there is clinical evidence of low serum zinc.^{39,46} Furthermore, a recent review of dietary supplements in dermatology demonstrated that there is not enough evidence at this time to justify the use of oral zinc supplementation for the purpose of wound healing.⁴⁷ This, combined with potential adverse events associated with oral zinc supplementation, most notably gastrointestinal discomfort, may suggest that

topical zinc therapy is better suited to augment healing in the post-operative period.^{39,48}

When choosing a topical zinc formulation, it is important to consider bioavailability and potential adverse effects. Soluble salts may be irritating, while less soluble options like zinc oxide are not. Zinc oxide formulations have been used for a wide array of dermatologic manifestations for many years with an excellent safety profile, and have been shown to effectively augment wound healing.^{19,22,23,40} While it may occasionally cause burning, stinging, itching, and tingling when utilized on inflamed tissues, hypersensitivity to topical zinc oxide is rare, and a clinical picture of contact allergy should cause the physician to evaluate components of the zinc delivery method.^{39,34}

Zinc oxide hydrolyzes on the acidic skin surface to release the biologically active Zn²⁺. Agren demonstrated that zinc oxide in a rosin-based occlusive dressing applied to normal human skin lead to accumulation of zinc in the corneal layer and deeper layers after longer exposure,⁴⁹ however, zinc oxide penetration has not been proven by occlusive hydrocolloid adhesive dressings or microfine zinc oxide.^{49,50} Despite these findings, recent studies have demonstrated enhanced healing of surgical wounds with use of zinc oxide compression dressings.^{22,23}

This information, coupled with beneficial properties of compression for wound healing, may make zinc oxide compression dressings an alternative treatment option for standard wound care in the post-operative setting, particularly for high-risk regions such as lower extremities. For patients who do not require compression but would benefit from enhanced wound healing and decreased risk of infection, zinc oxide ointment may

represent a convenient and affordable alternative to commonly used petroleum jelly.

CONCLUSION

While there is a paucity of data regarding topical zinc for post-operative wound healing in the field of dermatology, studies to date have demonstrated promising results for its use in the healing of post-operative wounds.^{22-24,33} The use of zinc may be considered for patients after MMS to help facilitate wound healing and decrease risk of infection. Topical zinc may be a safe and affordable therapy in the post-operative period, with subsequent dressing, including after flaps, grafts, and secondary intention healing. We encourage further randomized studies to assess the utility of zinc formulations on wounds after MMS.

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