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Original Article

# Clinical Retrospective Cohort Study on the Effectiveness of Chitosan Zinc Oxide Cream for Accelerating Healing in Diabetic Ulcer Patients

**Dahrizal**[1,2]*, **Idramsyah**[2], **Septiyanti**[2]
[1]Department of Nursing, Poltekkes Kemenkes Banten, Banten, Indonesia
[2]Department of Nursing, Poltekkes Kemenkes Bengkulu, Bengkulu, Indonesia
*Corresponding author: dahrizal@poltekkesbengkulu.ac.id

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**ABSTRACT**

The evolution of wound dressings has shifted from simply covering wounds to maintaining a moist environment. Chitosan, derived from chitin, and Zinc Oxide (ZnO) are well-known for their roles in wound healing. Chitosan is used due to its natural polymer properties, and ZnO is used to promote cell growth. This study investigates the effectiveness of chitosan zinc oxide cream as a primary dressing to enhance wound healing in diabetic ulcers. This quantitative research method uses a clinical retrospective cohort design. The sample used 235 verified medical records from 2018 to 2023, namely medical records of patients with stage III-IV diabetic wounds who received a primary dressing of chitosan zinc cream every 2-3 days and there was also documentation of the results of the bates-Jensen wound assessment at the first visit and a minimum of four weeks of treatment. The analysis included univariate and bivariate analyses to correlate treatment with healing progress. The results showed significant improvement ($p<0.001$) in wound condition after treatment with chitosan zinc oxide cream, including a reduction in wound size and depth, faster removal of necrotic tissue, and increased granulation and formation of epithelial tissue. These findings highlight the efficacy of the cream in treating diabetic ulcers, although further research is needed for other types of cancerous wounds, pressure ulcers, and chronic wounds.



## INTRODUCTION

Diabetic ulcers are damage the integrity of skin tissue as a chronic complication that is threatening and frightening for people with diabetes mellitus (DM).[1] Diabetic ulcers can cause disability, amputation, and even death.[2,3] The incidence of diabetic ulcers ranges from 15-to 25% in individuals with diabetes.[4] The International Diabetes Federation (IDF) reports that approximately 40-60 million people have diabetic foot ulcers, and a global prevalence of 6.3% or approximately 33 million adults have diabetic ulcers.[5] DFU in Africa ranges from 10% to 30%, and in Southeast Asian countries, it is below 15%, in Europe is 17% (Belgium), and 52% in America.[6]

Proper wound care management is required to prevent the adverse effects of foot ulcers.[7] Although treatment advances have progressed, there is currently no cure for DFU, and if there is one, the drugs available are limited.[2] Moisture based antimicrobial dressing is a successful wound care technique, especially for diabetic foot ulcers.[8] The evolution of wound dressing from natural materials originally came from covering and hiding the wound to focus on efforts to maintain

wound moisture.[9] Moisture in wounds can be achieved by treating closed wounds until they reach the standard moisture content for various wound types.[8] Therefore, moist dressings can provide a suitable environment, prevent skin drying,[10] and promote angiogenesis in the wound area[11].

One dressing material that is useful in the wound healing process to provide a moist effect on diabetic foot ulcers is chitosan zinc oxide[12]. Chitosan has excellent potential as a wound dressing[13]. Chitosan has long been the subject of scientific interest. Although it was discovered in 1859, it was only named in 1894.[14] Chitosan is a natural polymer derived from chitin, the second most abundant polysaccharide after cellulose.[14] Chitosan stimulates inflammatory cells and releases bioactive compounds that accelerate wound healing.[13]

In addition to chitosan, zinc oxide can be used to accelerate wound healing. Zinc Oxide (ZnO) is an essential mineral for cell proliferation.[15] Zinc oxide and chitosan have been applied to diabetic wounds, ointments, gels, creams, and lotions.[11] Zinc oxide (ZnO) is more commonly used in wound care and antibacterial cream than other nanoparticles.[16] The application of topical cream can accelerate wound healing more effectively than moist gauze because it facilitates the repair process by maintaining the skin's hydration level.[11]

Chitosan and zinc oxide are widely used to support the wound-healing process. These two substances are essential for wound healing.[12] Currently, some wound care practitioners use these materials separately, which significantly increases their financing and makes the results less optimal. Thus, practitioners and researchers have attempted to combine these two ingredients. This combination aims to maximize wound healing acceleration, ease of use, and cost-effectiveness. Dressing products that combine these two materials have been developed. However, few scientific articles have discussed the efficacy of combining these two ingredients in the healing of diabetic wounds.

Previous studies have discussed the benefits of chitosan cream and ZnO on wound healing. However, in this study, researchers tried to prove the effectiveness and acceleration of diabetic wound healing, which is determined by the size of the wound, the stage of the wound, and the change in the color of the wound base. Therefore, this study aimed to explain the effectiveness of chitosan zinc oxide cream as the main dressing to accelerate the healing of diabetic ulcers.

## METHODS

This quantitative study uses the clinical retrospective cohort method to evaluate the effectiveness of chitosan zinc oxide cream for accelerating healing in diabetic ulcer patients. Data was obtained from the medical records of patients documented at the Modern Wound Care Alfacare Center Bengkulu during the period January 2018 to May 2023.

The population of this study is medical record patients with diabetic ulcers and the sample is selected based on the inclusion criteria, namely medical records of patients with stage III-IV diabetic wounds who receive primary dressing with Chitosan zinc oxide cream and secondary dressing with polyurethane foam every 2-3 days and have been cured. In addition, documentation of the results of the wound assessment The Bates Jensen Wound Assessment Tool (BWAT) scores must also be available at the time of the first visit up to a minimum of four weeks of treatment visits. Exclusion data is incomplete patient data, patients who have been interrupted from treatment or died before the wound has healed. Data samples of 235 patients' medical records were successfully collected and verified by the research team.

Data were analyzed using univariate and bivariate analyses using SPSS. Data are usually distributed using the Kolmogorov-Smirnov test (0.073). The hypotheses were tested using paired t tests. This study involved an ethical clearance process in STIKes Sapta Bakti Bengkulu with the number 052/DRMIK/KEPKSTIKesSaptabakti/2023

## RESULTS

The characteristics of respondents in this study were distributed by gender, and the type of DM, age, and duration of diabetes mellitus (DM) are shown in Tables 1 and 2.

**Table 1. Frequency Distribution of Diabetic Wound on Gender, DM Type, and Wound Stage**

| Variables | Frequency (n) | Percentage (%) |
|---|---|---|
| **Gender** | | |
| Man | 78 | 30.8 |
| Woman | 175 | 69.2 |
| **Types of DM** | | |
| IDDM | 66 | 26.1 |
| NIDDM | 167 | 73.9 |
| **Wound Stage** | | |
| Stage III | 108 | 42.7 |
| Stage IV | 145 | 57.3 |

As shown in Table 1, 67% of diabetic wound sufferers were men, 70% had type non-insulin-dependent diabetes mellitus (NIDDM), and 68% had stage IV wounds.

**Table 2. Mean Distribution of Diabetic Ulcers Based on Age, Duration of DM, Duration of Early Wound Care.**

| Characteristic | Mean | Mdn | Min-Mak | SD |
|---|---|---|---|---|
| Age (Years) | 59.51 | 58 | 35-86 | 8.968 |
| Length of Time with DM (years) | 7.91 | 8 | 1-23 | 3.865 |
| Duration of Initial Wound Treatment (weeks) | 10.32 | 10 | 1-20 | 3.617 |

Based on Table 2, the mean age of diabetic wound sufferers is 59.51 years with a standard deviation of 8.968 years, the mean duration of diabetes is 7.91 years with a standard deviation of 3.865 years, and the mean duration of initial wound care is 10.32 years with a standard deviation of 3,617 weeks.

**Table 3. Differences in Mean BWAT Scores Before and After Chitosan Zinc Oxide Cream Dressing in Diabetic Ulcers**

| Variable | Mean | SD | Min-Maks | P |
|---|---|---|---|---|
| Before | 46.9 | 6.080 | 32-65 | 0.000 |
| After | 27.45 | 3.781 | 20-37 | |

Table 3 shows that the administration of chitosan zinc cream was able to reduce the BWAT value by 19.45, from 46.9 before administration of chitosan zinc oxide, resulting in a decrease of 27.45. The results of the statistical test showed that the p-value = 0.001, indicating that Ha was accepted, suggesting a significant difference in the condition of the wound before and after administration of chitosan zinc oxide cream as a primary dressing for diabetic ulcers. These results show that chitosan and zinc oxide are effective in accelerating the healing of diabetic ulcers.

## DISCUSSION

### Characteristics of Respondents

Diabetic foot ulcers can be experienced by individuals with type I and Type II diabetes mellitus[17]. The results of this study revealed that 73.9% of diabetic ulcers occurred in patients with type II or type I DM (26.1%). This result is the same as that of previous studies, which stated that type II non-insulin-dependent DM is the most common type of DM, accounting for more than 90%.[18] The American Diabetes Association reports that 90-95% of patients with diabetes have type 2.[19]

Other research results state that the risk of wound complications in IDDM is greater than in NIDDM.[20] However, IDDM is more at risk of injury because people with IDDM have generally experienced DM since the age of 35. The incidence of insulin deficiency is absolute.[20].However, in this study, diabetic wounds were more commonly experienced by patients with NIDDM.

Research conducted in Taiwan states that type 2 DM is mostly experienced by middle-aged and elderly patients.[18] This condition is influenced by degenerative processes experienced by older people. The results of this study revealed that the mean age of patients with diabetic foot ulcers was 59.51 years. This middle age is lower compared to the results of research in Taiwan, which states that the average age of people with diabetes is 63.2%.[21] Both results of the study concluded that diabetic ulcers occur more frequently in elderly patients.

The results of this study showed that most patients with DM who experienced injuries were female. This finding is in line with the results of previous studies showing that 65% of people with diabetic wounds are women with a family history of diabetes mellitus[22]. Another study by the Taiwan Society reported that the proportion of DFU was higher in male patients (55.8%).[21]

All the diabetic wounds in this study were chronic. This finding aligns with previous research results, which stated that most chronic wounds are related to ischemia, diabetes mellitus, venous disorders, or pressure and friction.[23] Chronic ulcers are no longer present during the physiological phase of wound healing.[24,25] The results of this study showed that the average length of the injury experienced was two months. Physically, the wound should have been in the maturation or *remodelling* phase of wound healing. Acute, delayed, or chronic wounds fail to reach the normal healing stage.[23]

**Effectiveness *of Chitosan Zinc Oxide Cream***

Wound healing is a complex process involving biological and molecular activities.[25] Therefore, wound care requires a dressing that can create a good moist wound surface.[11] Maintaining the moisture on the wound surface is important. In this study, zinc oxide chitosan cream retained moisture on the wound surface. When the wound dressing is opened, it can be seen that the wound tissue does not stick to the bandage and does not cause pain to the patient, so the results of administering chitosan zinc oxide can reduce the BWAT score, resulting in a characteristic decrease in the number of necrotic tissues within four weeks of treatment. The principles of dry wound care are less effective than moist wound care. Chitosan zinc oxide can moisten surfaces.[26]

The wound-healing phase comprises hemostasis, inflammation, proliferation, and remodelling.[23,24,27] Wound healing must occur during the correct period.[23] Based on the observations of this study, the combination of chitosan and ZnO cream is effective in accelerating and overcoming inflammation in diabetic wounds. On the third day after administering chitosan and zinc oxide, signs of inflammation subsided and were no longer present. Physiologically, the inflammatory phase lasts from the beginning of the wound to 5-6 days.[24] All diabetic wounds in this study experienced pathological inflammation. Pathological inflammation occurs because of a delayed, incomplete, or uncoordinated healing process.[23]

During the inflammatory phase, inflammatory cells function optimally under moist wound conditions. Neutrophils work against bacteria. Monocytes enter the wound within 48-96 hours of injury and are activated to become macrophages at the wound site.[28] Wounds heal more optimally and quickly in moist conditions owing to growth factors, cytokines, and other factors. Immune cells, such as polymorphonuclear leukocytes, move optimally. Wound moisture was created using chitosan zinc oxide. Even three days after changing the wound dressing, the wound remained moist when the dressing was changed. Chitosan zinc cream can be used for wound healing in diabetic patients with foot ulcers using moisture care.[12]

Along with efforts to overcome pathological inflammation in diabetic ulcers, wound care management focuses on the release of necrotic tissue (debridement). Black and yellow wound tissues indicate necrotic tissue in the wound.[29] Based on international consensus, the basic color of the wound is grouped into 3, namely red, yellow, and black.[30] The debridement process must be targeted to make the yellow and black wound tissue immediately clean, and red tissue appears.

The role of chitosan zinc oxide in diabetic wound care has been proven to be effective in accelerating the preparation of the wound base through debridement autolysis. Autolysis of debridement is an attempt to clean necrotic tissue by allowing the body to release necrotic tissue [26]. The body's ability to remove necrotic tissue occurs with the help of protease enzymes that can form on moist wound surfaces.[28] Autolysis is a selective process that activates macrophages and

endogenous proteolytic enzymes.[26] They liquefy and naturally separate necrotic tissues from healthy tissues.[36]

The skin and cells can absorb ZnO nanoparticles because of their minimal size.[16] Under moist conditions, protease enzymes activate and release dead tissue and other fibrin tissue so that at an average time of 2-4 weeks, red tissue color is seen on the wound surface with a scale measuring a decrease in BWAT score and a reduction in the amount of necrotic tissue in the wound during the use of chitosan zinc oxide. When necrotic tissue is autolyzed, the treatment technique is combined with mechanical debridement in the form of conservative sharp wound debridement (CSWD).[30]

Along with technological advances, the innovation of dressing materials has led to the optimization of active ingredients that interact with cells and specific chemicals in wounds, thereby overcoming certain problems in chronic wounds that are difficult to heal.[9] The primary function of chitosan zinc oxide as a primer dressing with its active ingredients and acceleration of the release of dead tissue (autolysis debridement) proved helpful during the proliferation phase.

This study showed a decrease in BWAT score at the wound stage. Most of the injuries in this study were in stages III and IV, where damage to the skin tissue reached the hypodermis layer and even visible bones, muscles, and tendons. After the administration of the chitosan zinc oxide cream, there was a decrease in the wound stage. Stage of wound This proves that the chitosan zinc cream can effectively support the tissue proliferation process.

The proliferation phase involves angiogenesis, collagen synthesis, and epithelialization. Indicators in this phase were observed in the BWAT assessments at the number of epithelial lines. Chitosan zinc oxide cream, with its active ingredients, can retain moisture in the wounds. Thus, the active material can treat angiogenesis and support the formation of granulation tissue, and macrophages can be optimal for treating moist wounds and facilitating epidermal basal cell migration and angiogenesis.[9] When the wound is red, the process of new blood vessel formation (angiogenesis) occurs optimally with the administration of chitosan zinc cream, allowing the epithelium to form.

Chitosan zinc oxide cream is clinically beneficial for reducing wound size.[16] Ideally, physiological proliferation lasts for 21 days or three weeks. In this study, patients experienced injuries for an average of 10.32 weeks prior to treatment. All wounds were chronic, with pathological infusions and infections. After treatment with chitosan and zinc oxide cream as the primary dressing, the wound exhibited complete epithelialization, with an average treatment duration of 85.10 days, or a maximum of 3 months. This evaluation was shorter than the average length of injuries experienced before treatment.

Chitosan zinc oxide cream can retain moisture in wounds. In addition, this material can reduce the number of bacteria and prevent infections in wounds. This result is evident from the decrease in BWAT values that begins in the second week of treatment. Chitosan's basic ingredients aim to kill bacteria in diabetic ulcers, thereby shortening the treatment time.[12] Zinc cream is effective in accelerating wound healing, preventing and treating bacterial infections in wounds, and promoting the formation of granulation tissue in the wound area.[31] Chitosan is an antimicrobial and antibacterial.[14]

## CONCLUSION

Zinc oxide chitosan is effective in stage III and IV wounds that still have a lot of slough and necrotic tissue. It is effective in accelerating the wound proliferation phase where there are noticeable changes in wound size, wound base color, accelerated application of necrotic tissue, and control of inflammatory markers, as well as the formation of granulating agents. The addition of other types of antimicrobial dressings needs to be considered in the development of future research, as the acceleration of bacterial growth in wounds can occur at all phases of wound healing. The effectiveness of chitosan zinc oxide also needs to be investigated for its effectiveness in chronic cancerous/fungating wounds, pressure ulcers, and infectious wounds.

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**Conflicts of Interest:** We all researchers hereby declare that there is no conflict of interest in writing this manuscript, either for individuals or companies.

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