Impact of using zinc oxide versus Moist Exposed Wound Ointment (MEBO) in treatment of second stage pressure ulcer: A randomized control clinical trial.

Project Title:

Impact of using Zinc Oxide versus Moist Exposed Wound Ointment (MEBO) in treatment of second stage pressure ulcer: A randomized control clinical trial.

Acronym

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Sponsor: King Abdullah Medical City in Holy Capital

Introduction

A pressure ulcer (PU) is a local skin injury caused by pressure or a combination of pressure and tensile forces on the bony prominences. The sacrum, hips, and heels are the most common sites for pressure ulcer. Within 2 to 6 hours of applying pressure to the tissue, pressure ulcers start to form. As a result, it should be avoided by keeping the pressure on the tissue capillaries below 30 mmHg [1,2].

Age, poor nutrition, reduced mobility, decreased body mass, anemia, hypoalbuminemia, friction, impaired sensory awareness, a history of pressure ulcers, smoking, and a lack of vitamins A, C, and E are contributing factors in the development of pressure ulcers [3].

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Pressure ulcers can be avoided by changing the patient's position every two hours, cleaning the area around the wound, and avoiding coming into contact with their urine or feces. Additionally, a daily evaluation of the wound's location, size, depth, and smell should be made. It's also important to note any scarring, infections, necrosis, and necrosis smells. To prevent bacterial growth, debridement should be done if necessary [4].

Pressure ulcers require significant costs on both the health care system and patients [5]. In addition to the gangrene and cellulite-related pain and suffering, these wounds have the potential to result in amputation, diminished quality of life, and even death [6]. Pressure ulcers can be treated in a number of ways, including wound cleaning, debridement, improved dressings, patient optimization, antibiotics, and reconstructive surgery. Additionally, more recent alternatives for treatment are offered, including cell therapy, hyperbaric oxygen therapy, and negative pressure wound therapy [7].

Pressure ulcers have been treated in China using traditional Chinese remedies such as herbal medicinal ointments, particularly Moist Exposed Burn Ointment (MEBO), acupuncture, and moxibustion [8–10]. MEBO was successfully used to treat burns in clinical settings in earlier investigations. It consists of sesame oil, b-sitosterol, berberine, and other Chinese herbal plant ingredients [11].

Additional clinical and experimental research has revealed that MEBO not only has analgesic and antibacterial benefits but can also hasten the healing process for burn wound patients [12–15]. Additionally, it can either promote debridement and epithelial repair or lower treatment expenses for patients and their families [11,16]. MEBO has also reportedly been shown to aid in the healing of neurogenic and chronic ischemic ulcers [12,15].

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Topical zinc oxide aids in the re-epithelialization process, which is important for wound healing. Clinical research has shown that people with low zinc levels had slower healing of ulcers [17], and zinc can be administered topically or orally to help these patients recover more quickly [18].

The incidence of PU is still very high despite established risk factors and the attentiveness of healthcare professionals. In the range of 22.5% to 66.6% of patients, PU develops at some point during prolonged hospitalization. Each patient's ulcer costs around 1.71-470.49 Euros per day to treat, depending on the context. Although there are many different dressings and topical medications available, none has been proven to be better than the others [19-21].

To our knowledge, no study exists in the literature comparing the effects of local application of mebo and oxide zinc ointment in treatment of stage II pressure ulcer. Therefore, the present study was designed to compare the effects of zinc oxide versus MEBO in treatment of second stage pressure ulcer.

Significance of the study

Pressure Ulcers are associated with decreased quality of life and increased morbidity, mortality, and cost. A systematic review found that the cost of PU treatment varied from 1.7 to 470.5 € per patient per day across different settings. Additionally, PUs may cause emotional distress to patients and their families and frequently lead to their dissatisfaction with the health-care system and mistrust of the health-care providers [22].

Pressure ulcer risk assessment, prevention and management are important to reduce PU burden in ICU patients. Comprehensive evidence-based guidelines on PU prevention and care were recently updated. However, clinical studies about this topic are uncommon and mostly of low-to-moderate

quality. They emphasize the need for a multifaceted care approach and multidisciplinary involvement [23.24].

Globally, the incidence of pressure ulcers varied from 2 - 20 ulcer/1000 patient-days, depending on the institution and the population of patients studied. Also, the prevalence varied from 5-13% [25-27]. Nationally a study done by Al-Hashemi (2019) at King Abdulaziz Medical City (KAMC) – Jeddah-Saudi Arabia revealed that the calculated incidence 1.6 ulcer/1000 patient-days and prevalence 5.7% in this study is very close to the figures published in the literature previously [28].

A network meta-analysis (2017) about dressings and topical agents for treating pressure ulcers (Review) of data from 39 studies (evaluating 21 dressings and topical agents for pressure ulcers) concluded that consequently we are unable to determine which dressings or topical agents are the most likely to heal pressure ulcers and more research is needed to determine whether particular dressings or topical agents improve the probability of healing of pressure ulcers [29]. Moreover Boyko et al. (2018), in a review of the current management of pressure ulcers, stated that despite many treatments available, none of them is superior to the other, and pressure ulcers remain a debilitating and costly issue. They recommended additional research to develop products more effective in preventing and treating pressure ulcers [20].

The incidence of pressure ulcers will possibly grow rapidly in the future due to increased life expectancy and aging. However, although various methods are used to treat pressure ulcers, no standard therapy has previously been established. After searching the literature there no studies done before to compare the effects of zinc oxide versus MEBO in treatment of second stage pressure ulcer and because there is no standardization for this practice this clinical trial will be conducted to compare the effects of zinc oxide versus MEBO in treatment of second stage pressure ulcer and determine which one is superior to other.

OBJECTIVES:

The **primary objective** of this study is to:

- To evaluate the efficacy of using zinc oxide versus moist exposed wound ointment in treatment of second stage pressure ulcer.

Secondary Objectives

- To determine the recovery time for both ointments.

Objective measures

For the primary objective

Wound healing will be assessed by using Bates–Jensen Wound Assessment Tool (BWAT) daily for both treatments.

For the secondary objective

The duration of treatment will be record at the assessment sheet so Recovery time will be determined from this sheet.

Research Design:

- Open label randomized control clinical trial study with a pilot study-using questionnaire.

Inclusion Criteria:

- Subjects ≥ 18
- Willing to participate.
- KAMC cases in medical ward, neuroscience ward, and intensive care unit.
- Newly cases diagnosed with second stage pressure ulcer according to the European pressure ulcer advisory panel/national pressure ulcer advisory panel (NPUAP) guidelines.

Exclusion Criteria:

- Subjects under 18
- Not consenting to participate
- Patients with suspected hypersensitivity reactions to any of the topical formulation's ingredients.
- Either a category III or IV pressure ulcer.
- Evidence of deep tissue injury (exudative drainage, purple or maroon localized area of discolored intact skin or blood-filled blister due to pressure damage).
- Signs of wound infection (pus draining from the ulcer, a foul-smelling odour, tenderness, heat and increased redness in the surrounding skin and fever).
- Patients who undertaking other therapies that could affect healing, such as corticosteroids, radiation therapy, or chemotherapy for cancer.
- Heavy smoking (more than 20 cigarettes a day).
- Concomitant chronic disease (e.g., diabetes mellitus or frank vascular disease such as Buerger's disease).
- Patients who unable to continue the study because of death, discharge, or change in the care setting.

Randomization

Simple randomization method will be used through electronic randomization. The randomization list was generated electronically through R using the Random Allocation Rule by research center member who did not directly participate in trial recruitment and enrolment. Research center member will define

the participant for this concealment. Allocation sequence will be generated, and the oblique envelops will be created with the sequence in it and each envelop only open after patient consented and enrolled in the study to determine which treatment the participant will receive.

Blinding

Open label study as True blinding for patients and the research nurse who will apply the topical agent will be difficult as there is a significant difference among the two treatment methods in presentation, colour, density, and odour. the author who will enroll the patients to the study will be blind to treatment assignment. To maintain the blinded status on assessment of outcomes, outcome assessors will be also blinded to treatment allocation.

Study Procedure:

After getting official permission from KAMC IRB, the subject will be randomized using electronic randomization 1:1 ratio. The randomization list was generated electronically through R using the Random Allocation Rule. The data will be collected using Assessment sheet of patient with second stage pressure ulcer tool. Patients will equally be allocated into 2 groups randomly. The zinc oxide group will receive topical zinc oxide twice every 12 hours daily and patients in the MEBO group will receive topical MEBO ointment twice every 12 daily.

The research nurse will be instructed on how to apply the ointment on different surface areas (into and around the edge of ulcers) according to the fingertip unit (FTU). One FTU contains approximately 0.5 g of the ointment. Amounts that were applied to different parts were 7 FTUs for back, 3 FTUs for 1 arm, 1 FTU for both sides of 1 hand, 6 FTUs for 1 leg, and 2 FTUs for 1 foot. The number

of FTUs applied will be altered by the size of the ulcer. For example, if the patient has a large ulcer on the heel, more ointment was applied in comparison to a small ulcer on a patient's back. For infection prevention, povidone iodine will be used to clean pressure ulcers before MEBO or zinc oxide intervention. Then, the pressure ulcers will be cleansed with normal saline gauze. MEBO will be smeared successively onto the wounds at a thickness of 1mm twice daily with a sterile gloved finger. The same application will be used as for zinc oxide ointment.

Furthermore, removal of the possible causal factors (pressure, shear, and friction) and control of the related general condition (such as nutrition, cleaning of the wound, and management of comorbid disease and other medical factors such as blood sugar level that might interfere with the healing process) will be considered for all patients as standard of care.

To eliminate the possible complicating factor of treatment interactions, all patients in both groups will receive position change every 2 hours, and mattress that helps to protect the vulnerable skin. If a patient has more than one ulcer, all the ulcers will be treated by the same method of cleansing, applying and changing positions and the same treatment.

Patient will be examined daily till complete healing for the pressure ulcer and maximum one month as it was reported by Li et al. (2017) reported that the use of MEBO for one week did not significantly affect the improvement of pressure ulcer grades [29]. Moreover, a study done by Palese 2015 reported that to achieve complete re-epithelialization in Stage II PUs, it takes approximately 23 days. This is quite a long time if we consider that pressures of only 60 to 70 mm Hg for between 30 and 240 minutes are needed to cause tissue damage. On average, a small ulcer heals 12 days faster compared with those with a surface of 3.1 cm2 or greater [30] so patient will follow for maximum one month. If

the pressure ulcer not healed within the month of the treatment duration this patient will return to routine care of the hospital. If the any patient will be unable to continue the study because of death, discharge, or change in the care setting the researcher will be excluded from the study.

Pilot study:

It will conduct before data collection on 10% of patients to explore feasibility for future RCT, the efficiency, internal validity and fundamentally, the delivery of proposed trial and identify barriers and facilitators. Zinc oxide will be applied to 4 patients twice daily and MEBO will be applied to 4 patients twice daily till complete healing for the pressure ulcer and maximum one month. The study' tool will be tested, and these patients will be excluded from the study, after completion the patient will have routine care for pressure ulcer treatment.

Sample Size calculation:

The sample size for the study calculated using the following formula based on the study of Li et al (2017).

$$\text{Sample size}(n) = \frac{p_1(1-p_1) + p_2(1-p_2)}{(p_1 - p_2)^2} * C$$

n = Sample size for one group that we need to find out

p1 and p2 = Proportion of two groups

C = Standard value for the corresponding level of α and β selected for the study $(0.84+1.96)^2$.

n= 0.5 (1-0.5) + 0.167 (1-0.167) $(0.84+1.96)^2$ / $(0.5-0.167)^2$ = 27.5 ≈ 28 patients, in addition to attrition rate 20 % therefore sample size will be 34 patients for each group.

A total number 76 patients will be included in the study. A number of eight participants will be included in the pilot study which will equal 10% of the total study number and will be excluded from the study.

Duration of the Study: 12 months in total. The enrolment will be for six months. Follow up will be for maximum 1 months for each subject. A period of 6 months will be for analysis and closing.

Setting:

This study will be carried out at medical ward, neuroscience ward, and intensive care unit at King Abdullah Medical City, Holy Makkah.

Data Collection and Management:

After the official approval from KAMC IRB and the local authority approval. The principal investigator will have a meeting with the team for study implementation overview to ensure the quality and compliance. Researcher will explain the study to the participants and take written consent if they want to participate. For unconscious patient written approval will be taken from there Legally Acceptable Representative. The participation will be voluntary and anonymously. In case of passing away the collected data will not be used and safety reports will be submitted as per the local gaudiness. In case of discharge the collected data will not be used and the patient will be excluded. All data collection sheets will be kept in a locked file cabinet with the researchers.

Study outcome measurement:

Data will be collected through one tool that will be collected by the assessor daily. It will include two sections as follows:

Section I: Patients' demographic data

This section was developed by the PI based on relevant literature. It will include demographic and medical history data will be collected from the patients' medical records without identifier such as age, sex, body mass index, history of smoking, diagnosis at the time of admission, and laboratory parameters including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) will be recorded. Nutritional status of patients will be evaluated considering route of nutritional support (enteral or parenteral). Subject will be identify via serial codes.

Section II: Pressure ulcer assessment.

This section will be adopted from Bates-Jensen 2010 [31]. The Bates–Jensen Wound Assessment Tool (BWAT) will be used to evaluate wound healing. It is a validated wound assessment tool which is used in many healthcare settings for wound assessment. BWAT is straight forward to use and allows nurses to have an objective, comprehensive assessment of wounds. It consists of 13 items to evaluate wound size, type and depth, amount of necrotic tissue, amount and characteristics of exudate, the presence of granulation tissue, epithelialization, and peri- 6 wound skin. PU length and width was measured with a disposable ruler and expressed as cm2. Patient will be examined daily till complete healing for the pressure ulcer and maximum one month. If the pressure ulcer not healed within the month of the treatment duration this patient will return to routine care of the hospital. If the any patient will be unable to continue the study because of death, discharge, or change in the care setting the researcher will be excluded from the study.

Each item is graded on a scale of 1 to 5, where a score of 1 indicates progress toward healing while a score of 5 indicates the absence of healing or wound deterioration. Cumulative BWAT scores vary

from 13 to 65. The English version of BWAT has been reported to have good reliability (Cronbach alpha=0.91 and an interrater reliability coefficient of 0.99).

The ulcer status will be completed by the assessor when the pressure ulcer healed or the end of the month, the ulcers will be examined blindly and assessed as "Completely Healed," "Partially Healed," "Without Improvement," or "Worsening.". "**Completely healed**" was defined as an intact dermis and epidermis, and no abrasion or ulceration. "**Partially healed**" was defined as any decrease in ulcer size compared with the baseline ulcer tracing but excluding complete healing. "**Without improvement"** was defined as no change in ulcer size compared with the baseline ulcer tracing. "**Worsening**" was defined as any increase in ulcer size compared with the baseline ulcer tracing. Duration of treatment will be record at the assessment sheet.

Statistical Analysis Plan

Data obtained from the study will be coded and transformed into coding sheets. The results will be checked. Then, the data will be entered into SPSS system files (SPSS package version 22). Following data entry, checking and verification process will be carried out to avoid any errors during data entry. Finally, analysis and interpretation of data will be conducted. Categorical variables will be expressed as number and percentage while continuous variables will be expressed as mean and standard deviation.

Publication:

The results of this research will be published to either national or international publications. The main credit in publication will go to King Abdullah Medical City in Holy Capital and to the principal investigator and co-investigators. Others who have contributed less substantially will have an acknowledgement in the manuscript.

Ethical Part & Confidentiality:

Ethical approval will be sought from KAMC IRB, local authority as applicable and will do study accordingly. Researcher will explain the study to the participants and take written consent if they want to participate. The participation will be voluntary and anonymously.

REFERENCES

1. Kumar A, Sinha V. Comparative study of EUSOL and Silverstream in healing of pressure sore in traumatic spinal cord injury patients. International Journal of Orthopaedics. 2018;4(1):228-34.
2. Asghar M, Naseem S. Risk factors of pressure ulcer in elderly non-operative femur fracture patients. International Journal of Recent Scientific Research. 2018;9(7):28088-90.
3. de Almeida Medeiros AB, Fernandes MIdCD, de Sá Tinôco JD, Cossi MS, de Oliveira Lopes MV, de Carvalho Lira ALB. Predictors of pressure ulcer risk in adult intensive care patients: A retrospective case-control study. Intensive and Critical Care Nursing. 2018; 45:6-10.
4. Saghalein S, Dehghan K, Shadvar K, Mahmoodpoor A, Sanaie S, Ostadi Z. Bedsore: Epidemiology; Risk Factors; Classification; Assessment Scales and Management. Archives of Anesthesiology and Critical Care. 2016;2(3):226-30.
5. Coleman S, Smith IL, McGinnis E, Keen J, Muir D, Wilson L, Stubbs N, Dealey C, Brown S, Nelson EA, Nixon J. Clinical evaluation of a new pressure ulcer risk assessment instrument, the Pressure Ulcer Risk Primary or Secondary Evaluation Tool (PURPOSE T). Journal of Advanced Nursing. 2018 Feb;74(2):407-24.
6. Yap TL, Kennerly SM, Horn SD, Bergstrom N, Datta S, Colon-Emeric C. TEAM-UP for quality: a cluster randomized controlled trial protocol focused on preventing pressure ulcers through repositioning frequency and precipitating factors. BMC Geriatrics. 2018;18(1):54.
7. Bhattacharya S, Mishra R. Pressure ulcers: current understanding and newer modalities of treatment. Indian journal of plastic surgery: official publication of the Association of Plastic Surgeons of India. 2015;48(1):4.

8. Zhang QH, Yue JH, Sun ZR. Electroacupuncture for pressure ulcer: a study protocol for a randomized controlled pilot trial. Trials 2014; 15:7.
9. Zhang QH, Yue JH, Li CR, et al. Moxibustion for the treatment of pressure ulcers: study protocol for a pilot, multicentre, randomized controlled trial. Br Med J Open 2014;4: e006423.
10. Yue J, Zhang Q, Sun Z, et al. A case of electroacupuncture therapy for pressure ulcer. Acupunct Med 2013; 31:450–1.
11. Hirsch T, Ashkar W, Schumacher O, et al. Moist exposed burn ointment (MEBO) in partial thickness burns: a randomized, comparative open mono-center study on the efficacy of dermaheal (MEBO) ointment on thermal 2nd degree burns compared to conventional therapy. Eur J Med Res 2008; 13:505–10.
12. Li JH, Zhang L, Tang QL, et al. Clinical observation on effect of MEBO on neurogenic ulcer. Liaoning J Tradit Chin Med 2012; 39:1095–6. (In Chinese).
13. Jewo PI, Fadeyibi IO, Babalola OS, et al. A comparative study of the wound healing properties of moist exposed burn ointment (MEBO) and silver sulphadiazine. Ann Burns Fire Disasters 2009; 22:79–82.
14. National Pressure Ulcer Advisory Panel (NPUAP). PUSH Tool. Washington, DC: National Pressure Ulcer Advisory Panel; 2010.
15. Wang QS, Tang QL, Zhang L, et al. MEBO for treating 47 cases of chronic ischemic ulcer in lower limber. Chin J Burns Wound Surface Ulcer 2005; 17:296–7. (In Chinese).
16. Jurjus A, Atiyeh BS, Abdallah IM, et al. Pharmacological modulation of wound healing in experimental burns. Burns 2007; 33:892–907.
17. Haley JV. Zinc sulfate and wound healing. J Surg Res. 1979; 27:168–74.
18. Golden MH, Golden BE, Jackson AA. Skin breakdown in kwashiorkor responds to zinc. Lancet. 1980; 1:1256.
19. Andrade CC, Almeida CF, Pereira WE, et al. Costs of topical treatment of pressure ulcer patients. Rev Esc Enferm USP. 2016; 50:295–301.
20. Boyko TV, Longaker MT, Yang GP. Review of the current management of pressure ulcers. Adv Wound Care (New Rochelle). 2018; 7:57–67.

21. Demarré L, Van Lancker A, Van Hecke A, Verhaeghe S, Grypdonck M, Lemey J, et al. The cost of prevention and treatment of pressure ulcers: A systematic review. Int J Nurs Stud 2015; 52:1754 74.
22. Haesler E, editor. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. Osborne Park, Australia: Cambridge Media; 2014.
23. Qaseem A, Mir TP, Starkey M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Risk assessment and prevention of pressure ulcers: A clinical practice guideline from the American College of Physicians. Ann Intern Med 2015; 162:359 69.
24. Gibbons W, Shanks HT, Kleinhelter P, Jones P (2006) Eliminating facilityacquired pressure ulcers at Ascension Health. The joint commission journal on quality and patient safety 32(9): 488-496. 8.
25. Zaratkiewicz S, Whitney JD, Lowe JR, Taylor S, O'donnell F, et al. (2010) Development and Implementation of a Hospital-Acquired Pressure Ulcer Incidence Tracking System and Algorithm. Journal for Healthcare Quality 32(6): 44-51.
26. Catherine VanGilder MB, Amlung S, Harrison P, Meyer S (2009) Results of the 2008–2009 International Pressure Ulcer Prevalence™ Survey and a 3-year, acute care, unit-specific analysis. Ostomy Wound Management 55(11): 39-45.
27. Al-Hashemi, H., Alqurashi, K., Jan, R., Farran, A., Al-Sabban, B., & Thomson, J. (2019). Incidence, prevalence, and complications of pressure ulcers in general medical and surgical units using a multidisciplinary model (Prospective cohort). Biomedical Journal of Scientific & Technical Research, 18(1), 13340-13343.
28. Westby, M. J., Dumville, J. C., Soares, M. O., Stubbs, N., & Norman, G. (2017). Dressings and topical agents for treating pressure ulcers. Cochrane Database of Systematic Reviews, (6).
29. Li W, Ma Y, Yang Q, Pan Y, Meng Q. Moist exposed burn ointment for treating pressure ulcers: A multicenter randomized controlled trial. Medicine. 2017;96(29).
30. Palese, Alvisa, et al. "What is the healing time of stage II pressure ulcers? findings from a secondary analysis." Advances in skin & wound care 28.2 (2015): 69-75.

31. Harris, C., Bates-Jensen, B., Parslow, N., Raizman, R., Singh, M., & Ketchen, R. (2010). Bates-Jensen wound assessment tool: pictorial guide validation project. Journal of wound, ostomy, and continence nursing: official publication of The Wound, Ostomy and Continence Nurses Society, 37(3), 253–259. https://doi.org/10.1097/WON.0b013e3181d73aab

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