Efficacy of phenytoin phonophoresis on pressure ulcer healing

Sara Nabil Mohamed[1], Amal Mohamed Abd El Baky[1], Ashraf El-Sebaie Mohamed[2], Shaimaa Mohamed Ahmed Elsayeh[1]

1. Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Giza, Egypt.
2. Department of Plastic Surgery, General Surgery Department. Cairo University, Cairo, Egypt.

Corresponding author: Sara Nabil Mohamed

Email: Saraselim946@gmail.com

Abstract

Background: Pressure ulcers refer to damage done to the skin and its surrounding tissues by sustained pressure in one or more areas. As a result, the skin's tissues and cells can become damaged, and in extreme cases, die, from a lack of blood supply.

Aim of study: The objective of the study was to assess the therapeutic effects of phenytoin phonophoresis on the healing process of pressure ulcers

Design: A single blind randomized controlled trial.

Setting: Inpatient setting.

Participants: Thirty-two female and male patients suffering from pressure ulcer, they were between the ages of 40 and 60 and were enrolled from the hospitals of El Kasr El Ainy in Giza, Egypt. Participants were screened for inclusion in the study and then randomly split into two groups (A and B), each including the same number of participants. Group (A) received phenytoin phonophoresis “pulsed mode”, while

group B received sham phenytoin phonophoresis. Patients in both groups received the same routine conventional therapy (repositioning and support surface), medical treatment (wound care and using antibiotics), and topical phenytoin applied into selected area once a day.

Intervention: Treatment lasted for a total of six weeks, with three sessions a week.

Outcome measures: Before and after six weeks of treatment, the wound volume of the pressure ulcer was measured.

Results: The volume of pressure ulcers changed by 64.1% in the phenytoin phonophoresis group after 6 weeks of treatment, compared to 36.2% in the sham phenytoin phonophoresis group.Comparing the volume of pressure ulcers in the phenytoin phonophoresis group to the volume in the control group showed a statistically substantial difference ($p = 0.01$).

Conclusion: It is possible to conclude that phenytoin phonophoresis is more efficient for pressure ulcer healing than topical phenytoin alone.

Key words

Pressure ulcer, phenytoin, phonophoresis.

Introduction

Pressure ulcers are defined as wounds that develop when one or more areas of skin are subjected to constant pressure. As a result, the skin's tissues and cells suffer damage and, in extreme cases, death from the reduced blood supply. [1]

Inpatients are at a higher risk for developing a pressure ulcer on the skin and soft tissues around their extremities and bony extensions like the sacrum and heel. In intensive care units, where patients have limited mobility, pressure ulcers are quite prevalent and have a high incidence rate. Pressure ulcer risk factors include immobility, general skin condition, poor perfusion, poor sensory perception / responsiveness, Diabetes Mellitus (DM), poor nutrition, dampness, as well as low albumin.[2]

In the elderly, the development of a pressure ulcer will result in lengthy hospital stays, considerable physical-social & self-care malfunction, depression, osteomyelitis, sepsis, as well as a mortality rate of up to 60%.[3]

As prevention is preferable to treatment, the techniques for preventing pressure ulcers, such as turning and moving patients to maintain circulation or rather relieve any pressures on the skin, skin care through the use of creams and dressings, control of incontinence also nutritional support, should be foremost in the minds of caregivers.[2,4]

If the pressure ulcer occurred, there are many treatment methods like debridement, dressings, nutrition, and surgical repair such as (skin graft and free flaps). In addition, adjuvant therapies including such hyperbaric oxygen, low-energy laser irradiation, as well as therapeutic ultrasound are employed to hasten wound healing. Electrical stimulation, vacuum-assisted closures, also warm-up therapy have been shown to enhance healing of pressure ulcers in stages III and IV.[5]

Regarding the topical treatment of pressure ulcer, phenytoin (diphenylhydantoin) has today the best challenge in wound healing. It is applied directly to the skin as a cream, lotion, or dressing infused with medication. In 1939, it was noted that patients receiving oral phenytoin to control epileptic seizures experienced gingival hyperplasia, which may aid in the healing of pressure ulcers by stimulating fibroblast proliferation, collagen deposition, vessels ingrowth, antibacterial activity, and increasing the number of macrophages in the wound, since it has been suggested that topical phenytoin may increase the number of macrophages in the wound.[6,7]

To improve the skin's percutaneous absorption of active substances, phonophoresis (also known as sonophoresis) uses ultrasonic radiation at frequencies ranging from 20 kHz to 16 MHz.Some high molecular weight medications, such as insulin, erythropoietin, interferon, as well as low molecular weight heparin, have been proven to be more effectively trans dermally delivered by low frequency phonophoresis.[8,9]

Materials and methods

This study was a single-blinded (participants), randomized control trial. Participants were enrolled in the study at the inpatient departments of El Kasr El Ainy hospitals in Giza, Egypt, between June 2022 and October 2022.Ethical approval for the study (P.T.REC/012/003632) was approved by the physical therapy faculty.Clinical Trial Registry was contacted prospectively, and registration for the trial was completed (NCT05542589).

Patients with pressure ulcers were all evaluated to see if they eligible for the study. All patients with a pressure ulcer at any stage were enrolled, and the inclusion criteria also required participants to be of both sexes and to be between the ages of 40 and 60.If a participant had any of the following conditions, they were excluded: Patients having a documented hypersensitivity to phenytoin, Pregnancy, patients who were

critically ill, Patients with advanced diabetic foot, radiotherapy in the ulcer area, as well as the use of antineoplastic therapies or systemic glucocorticosteroids, osteomyelitis in the ulcer area, venous ulcers, burned wound, leprosy trophic ulcer, as well as other traumatic wounds.Patients who refused to take part or sign the consent form were also eliminated.

The calculation of sample size was done by G*POWER statistical (G*power version 3.1) with power of 90%, α-level of 0.05 and effect size 1.2.

Thirty-two patients took part in the trial; all of them were requested to sign a written consent form after being fully briefed on the study's nature, goals, and potential benefits.The participants were divided at random into two groups of equal number,Group A received phenytoin phonophoresis, whereas Group B received a sham treatment; both groups' identities were concealed by using sealed envelopes containing cards with their respective names.The chosen card determined which group each participant would join. Treatment initiation dates were determined following the first week of randomization.

Study design

Interventions

Patients in both groups received the same standards of medical wound treatment, involving saline wound cleaning, application of antimicrobial creams (including bacitracin, silver sulfadiazine, neomycin, also phenytoin), and application of topical phenytoin once/day, and the same conventional physical therapy (repositioning and using of support surface).[10]

Patients in the study group (A) were managed by phenytoin phonophoresis, they were asked to assume a comfortable position (supine, prone or side lying according to

wound placement), After removing the dressings, the wound was debrided of any remaining dressing material or foreign debris and then cleansed with a saline injection. A thin film of topical phenytoin 2% cream mixed by ultrasound gel was applied to cover wound cavity by using a plastic spatula then sterilized glove filled by ultrasound gel fixed by surgical plaster on wound followed by ultrasound therapy application, the parameters were 0.5 W/cm^2 "low intensity", 1MHZ frequency, and pulsed mode "20 % on-off cycle" for five to ten minutes according to the ulcer size. The ultrasound head was moved in slow, circular motions, contacting the wound area as it moved along the wound's periphery and on sterilized glove that cover the wound cavity at approximately four cm/second, with an overlap one-half the width of the sound head. The applicator head always moving. The ultrasound head were cleaned before and after each session by alcohol solution. Total period treatment consisted of three sessions each week, for a total of six weeks.[11,12]

While patients in the control group (B) managed by sham phenytoin phonophoresis in which the treatment procedure was the same as group A, but the ultrasonic device intensity was zero.[13]

The outcome measure was the wound volume using the saline injection method. The wound was filled with saline solution to its maximum capacity while the patient was in a relaxed and comfortable position. Using a sterile twenty cubic centimeters syringe filled with saline and the saline was injected into the pressure ulcer until its filling. The amount of the saline solution injected was measured in cubic centimetres. wound volume was measured before and after 6 weeks of intervention. [14]

Statistical analysis

Descriptive statistics and unpaired t-test were conducted for comparison of age between groups. Chi squared (Fisher exact) test were conducted for comparison of sex

and ulcer location distribution between groups. Mann–Whitney U test was conducted for comparison of ulcer stage between groups. Unpaired t test was conducted for comparison of ulcer volume between groups. Paired t test was conducted for comparison between pre and post treatment mean values of ulcer volume in each group. The level of significance for all statistical tests was set at $p < 0.05$. All statistical measures were performed through the statistical package for social studies (SPSS) version 25 for windows (IBM SPSS, Chocago, IL, USA).

Results

The flow chart of the patients is illustrated in Figure 1. The general and medical characteristics of the subjects of both groups listed in Table 1 &2. Table 1 revealed that there was no substantial difference between groups in the mean age and sex and in the median (IQR) value of ulcer stage ($p > 0.05$) and Table 2 illustrated thefrequency distribution and Fisher Exact test for comparison of ulcer location distribution in bothgroupswhich also revealed no significance difference ($p > 0.05$).

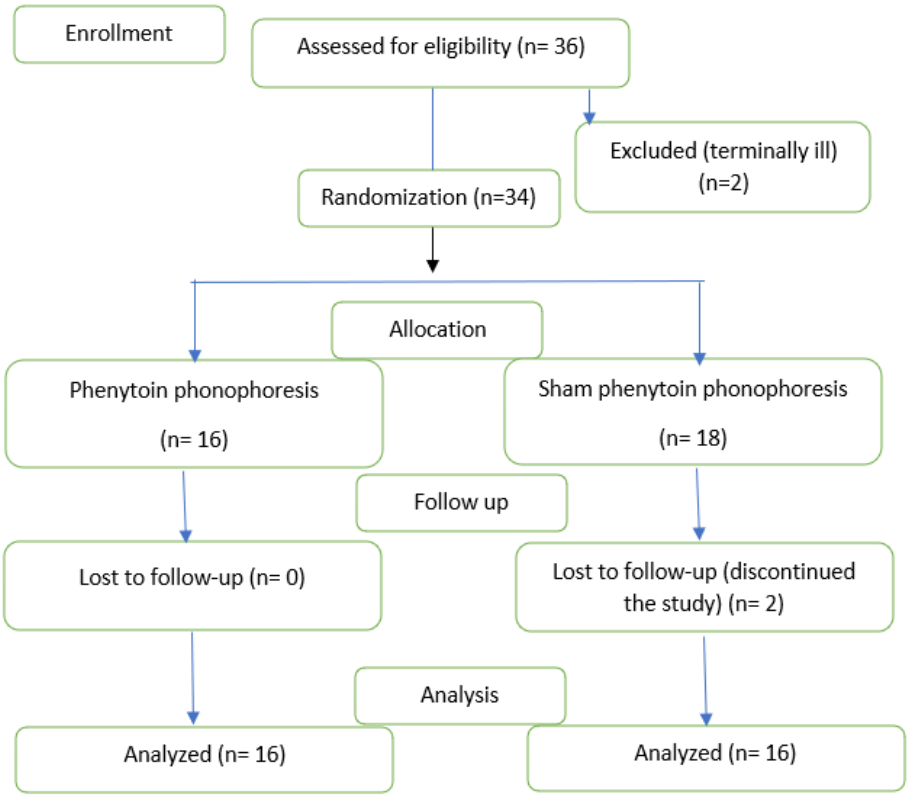

Figure (1): Flow diagram showing the progress of subjects at each stage of the clinical trial.

Table 1. Participants' demographic and clinical characteristics of both groups.

Variables	Phenytoin phonophoresis group	Sham phenytoin phonophoresis group	P values
	$\bar{X}$ ± SD	$\bar{X}$ ± SD	
Age (years)	52.25 ± 5.61	52.56± 6.21	0.88
Sex (Female –Male)	Female 9 (56%)	Female 8 (50%)	0.72
	Male 7 (44%)	Male 8 (50%)	
	Median (IQR)	Median (IQR)	
Initial ulcer stage	2 (3-1)	2 (3-1)	1

X : Mean SD: Standard deviation p value: Probability value.

Ulcer location	Phenytoin phonophoresis group	Sham phenytoin phonophoresis group	χ^2	**p-value**
Achilles tendon	0 (0%)	1 (6.3%)	2.9	1

Buttock	4 (25%)	3 (18.8%)	1	
Femoral epicondyle	1 (6.3%)	2 (12.5%)		
Gluteal tuberosity	3 (18.8%)	2 (12.5%)		
Heel	2 (12.5%)	1 (6.3%)		
Iliac tuberosity	1 (6.3%)	1 (6.3%)		
Low back	1 (6.3%)	1 (6.3%)		
Sacrum	4 (25%)	3 (18.8%)		

Table 2. The frequency distribution and Fisher Exact test for comparison of ulcer location distribution in both groups both groups.

χ^2 : Chi squared value **p value: Probability value**

Within group comparison: There was a substantialdecline in the post intervention values of ulcer volume in both groups when compared with the obtained values at the baseline (p = 0.001 in both groups), Table 3.

Between group comparison: There was no substantial difference in ulcer volume at the baseline between both groups (p = 87), while post-intervention comparison revealed that there was a substantialdecline in the ulcer volume in favor of the phenytoin phonophoresis group (p = 0.01).

Table 3. Mean values of ulcer volume for both groups.

Ulcer volume	**Phenytoin phonophoresis group**	**Sham phenytoin phonophoresis group**			
	Mean ± SD	**Mean ± SD**	**MD**	**t-value**	**p value**
Pretreatment	1.56 ± 0.95	1.61 ± 0.81	-0.05	-0.16	0.87
Post treatment	0.56 ± 0.38	1.03 ± 0.54	-0.47	-2.76	0.01
MD	1	0.58			

% Of change	64.10 %	36.02 %	
t- value	6.06	7.34	
	p = 0.001	**p = 0.001**	

Discussion

Findings from the present study showedstatistical improvements in ulcer volume in both groups and the phenytoin phonophoresis groups had more substantialdecline in the ulcer volume when compared with the sham phenytoin group ($p< 0.001$). the treatment group compared to the other group ($p< 0.001$).

Most ICU patients are at increased risk for developing pressure ulcers because of their prolonged hospital stays. Pressure ulcers substantially affect physical-social, self-care, psychological, and financial aspects of life. Severe and constant pain cause emotional problems such as low mood, anxiety, and depression lead to restrictions in activities of daily living and social isolation because of long hospital stay. Non-treated pressure ulcer can complicate with osteomyelitis, sepsis, and death.[15,16]

To the researchers' knowledge, nevertheless, no study has looked specifically at adding phenytoin to ultrasound to reduce the size of wounds in pressure ulcer patients. Instead, most previous studies have looked at how ultrasound works as a physiotherapy modality for wound healing. The results of our trial were similar to those of other studies, which found that phenytoin phonophoresis has a positive effect on healing pressure ulcers.[17-20]Pressure ulcer healing was also aided by placepo phenytoin phonophoresis in the control group. According to previous studies, the topical phenytoin used in this study also accelerated the healing process.[21-24]

The improvement in both groups is explained by the topical phenytoin's impact in decreasing the wound volume by accelerating the neovascularization, and collagenization, increasing accumulation of sulfated glycosaminoglycans in fibroblast, decreasing

polymorphonuclear and eosinophil cell infiltration and the extracellular breakdown of collagen and sulfated proteoglycans, affecting the membrane transport of cations that cause alteration of cytokines and growth factors activities that effect on inflammatory and fibroblast cells indirectly, and elimination of Staphylococcus aureus, E. coli, Klebsiella spp.as well as Pseudomonas spp.[25-28]

While the superior effect of the phenytoin phonophoresis can be justified by the cavitation and the altered structure of stratum corneum's lipids induced by phonophoresis, Ultrasound is preferable to topical phenytoin administration because it causes the skin's lipid bilayers to become disoriented and forms aqueous channels, increasing the skin's permeability and allowing for more effective transdermal medication transport.[29]

Also, the parameters of ultrasound used in our study contributed to this improvement. Hence there is a reverse relation between the frequency and the cavitation effect of ultrasound and penetration, Our trial ultrasound frequency of 1 MHz was chosen because it is predominantly absorbed by tissues at depths of 3-5 cm, making it the best option for treating deeper injuries and patients with more subcutaneous fat. Ultrasound frequencies of 3 MHz are typically used for superficial lesions at depths of l-2 cm. We used low-intensity ultrasound (0.5 W/cm^2) as its more suitable to treat open wounds or acute injuries. Finally, pulsed mode (20%) is more effective due to its lower thermal and stable cavitation effects than the continuous mode which has thermal and unstable cavitation effect.[30,31]

The research does include a few drawbacks. The first issue is the limited size of the study group. So, a bigger sample size is required to to provide better statistical data analysis. Second, there was insufficient follow-up on both groups to determine the lasting impact of phenytoin phonophoresis on pressure ulcer. Third, the use of different modes of ultrasound

to investigate which one is more effective to enhance the transdermal drug delivery in pressure ulcer. Consequently, additional studies are needed to cover our limitations.

Our randomized trial results suggest that physical therapists as well as other health professionals should think about the effects of incorporating phenytoin phonophoresis into conventional treatments for pressure ulcer patients.

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Declaration of conflict of interest

Potential conflicts of interest in conducting the research were not addressed.

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