Effect of Hyaluronic Acid Iontophoresis on Healing of Chronic Venous Ulcer

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ABSTRACT

Purpose: The purpose of the study is to evaluate the effect of hyaluronic acid iontophoresis on healing of chronic venous ulcer. Methods: Forty patients of both genders suffering from chronic venous ulcer in area below the knee and above the ankle with area (5-20 cm²) with less than 50% necrotic tissue participated in this study. Their ages ranged from (45 to 60) years. They were selected from Vascular Surgery Department, Al Ahrar Teaching Hospital between June 2022 and January 2023. Patients were divided randomly into 2 equal groups; each one had 20 patients. Group (A) received Hyaluronic acid iontophoresis 1 session per day, 3 sessions per week, for 4 weeks, and follow up 4 weeks after the end of the treatment. Group (B) received conventional medical treatment and traditional care. Group (B) received conventional medical treatment and traditional care (ulcer cleansing, debridement, dressing, compression, medication, exercise). Measurements were done by photographic digital camera for wound Surface area (WSA) and wound volume using saline injection into a wound cavity before treatment and after 4 weeks of treatment. Results: The findings of this study indicated significant decrease in WSA and wound volume after treatment in all groups A, B (p<0.001) at day 60 post treatment. There was significant decrease in ulcer surface area and ulcer volume at day 60 post treatment of study group (group A) compared with that of control group (group B) (p = 0.001). Conclusion: Hyaluronic acid iontophoresis for 6 weeks is an effective and safe adjuvant therapy in treatment of unhealed venous ulcers through accelerating wound healing, reducing Wound Surface area (WSA) and wound volume.

Keywords: Hyaluronic Acid, iontophoresis, Chronic Venous leg ulcers, Wound Healing.

INTRODUCTION

Venous ulcer is open skin lesion that occurs in an area affected by venous hypertension1. The prevalence of venous ulcers in the United States ranges from 1% to 3%. In the United States, 10% to 35% of adults have chronic venous insufficiency, and 4% of adults 65 years or older have venous ulcers. Poor prognostic signs for healing include ulcer duration longer than three months, ulcer length of 10 cm (3.9 in) or more, presence of lower limb arterial disease, advanced age, and elevated body mass index2. Adequate wound and skin management is central to promoting the healing process, and regular wound cleansing and debridement to remove necrotic tissue and fibrin are key elements of therapy. If conservative measures fail to provide a satisfactory outcome, further treatment should be considered; options include topical and systemic medications, sclerotherapy, and surgery3.

MATERIALS AND METHODS

A statistical power analysis suggested that sample size was (40) participants (20) per group were required to achieve more than 80% power. Forty patients of both genders suffering from chronic venous ulcer in area below the knee and above the ankle with area (5-20 cm²) with less than 50% necrotic tissue participated in this study. Their ages ranged from (45 to 60) years complaining from stage 3 of chronic venous ulcer located between knee and ankle joint 2 months and 1 year duration. They were randomly divided into 2 equal groups; each one has 20 patients (Group A and Group B). They were selected from Vascular Surgery Department, Al Ahrar Teaching Hospital, Zagazig, shariah government, Egypt. Patients were excluded from this study if they had Skin diseases in the area to be treated, Pregnancy or epilepsy. Patients with associated diseases (Diabetes, infectious diseases and autoimmune disease) that will interfere with the healing process. Group A received Hyaluronic acid iontophoresis transmitted through (--ve) electrode by intensity adjusted between 1 and 5 mA increased very slowly until the patient reports feeling a tingling or prickly sensation for 20 min., 1 session per day, 3 sessions per week, for 4 weeks, and follow up 4 weeks after the end of the treatment. In addition to their conventional, medical treatment and traditional care. Group B received their conventional medical treatment and traditional care (ulcer cleansing, debridement, dressing, compression, exercise and medication).

Study design and randomization: The study was designed as a prospective randomized clinical trial in which patients were assigned randomly into two groups. Randomization was used to eliminate the researches' bias and was carried out by a blinded and an independent research assistant who opened sealed envelopes that contained a computer generated randomization card. Measurements were done before the starting of treatment and at the end of treatment 4 weeks and follow up 4 weeks for patient of two groups.

Computerized photographic WSA assessment was performed by using (digital camera Nikon D3500 and J Image 1.5.5 software) for measurement of wound surface area (Length x Width). The subject’s wound was placed under a lighted, and a digital camera was mounted 50 cm perpendicular to the subject’s wound it took a clear photo of the ulcer area. Image J free open source software was used to analyze the photograph by marking the edges of the wound and calculating the number of pixels under the marked wound area to measure distances and angles. It can create density histograms and line profile plots. Photographs were visualized with Image J software and wound surface measurement was achieved by using a straight line tool a line was pulled along the ruler. The examiner pulled 1 cm over the ruler. The distance in pixels of the line was calculated by the software then set scale then known distance the unit of length (mm). The software automatically recalculated the number of pixel/mm. By using “freehand selection tool the wound boundaries were be drawn and traced according to the wound shape with the track pad of the laptop. Analyze menu then measure. The area in mm² was calculated. Wound volume assessment was performed by using sterilized syringe and saline was injected to wound area for measuring wound depth filling the sterilized syringe of 5cm³ with Saline. Then filling the wound by the known volume of the saline. It is an easy accurate method for wound volume estimation.

A verbal explanation about the treatment of the research and main points of experimental procedure design was explained to every patient. Patient history was taken in relation of the study. Patient was informed of the treatment and its purpose. For group A; gel containing HA (0.2%) was applied to the negative electrodes as a carrier of the electric current. Placed the electrode a rectangular adhesive 4 X 6 cm² in size with 24 square grids of 1 cm² each, fixed as near as possible for the wound proximal and distal to the ulcer site 20 min was applied. In addition they received...
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RESULTS

Table 1 showed the subject characteristics of the study and control groups. There was no significant difference between groups in age, sex, affected side and type of surgery distribution (p>0.05).

Table 2: Comparison of ulcer surface area and ulcer volume between groups.

Table 3: Comparison of ulcer surface area and ulcer volume between day 1, 14, 28 and day 60.

Table 4: Comparison of ulcer surface area and volume between study and control groups at day 1 (p > 0.05).

DISCUSSION

The pre-treatment results of the present study revealed no significant difference between the mean values of WSA and wound volume.

Post-treatment results of group A showed reduction in the WSA and wound volume with mean difference between day 1 and day 60 was 6.88 cm² and the percent of change was 73.74%. Respectively for WSA and with mean difference between day 1 and day 60 was 1.71 ml and the percent of change was 84.65% respectively for wound volume. So there was a significant decrease in ulcer surface area and ulcer volume in this group.

Hankrishna and Athirah, (2022) investigated the recovery of chronic wounds treated with hyaluronic acid-collagenase, which facilitates enzymatic debridement, helping prepare the wound bed for healing and closure on top of first-line therapy. The study observed a minimal to 100% reduction in wound size, notably diminished exudate excretion, healthy wound edge, and lower pain score. Nosseir et al., (2018) compared between the effectiveness of estrogen iontophoresis as physical therapy and cell therapy in the treatment of diabetic foot ulcers. Results showed that estrogen iontophoresis for 4 weeks in combination with stem cell therapy is effective, and better than each one separately, in treatment of diabetic foot ulcers through accelerating wound healing and reducing WSA, wound volume. Mendes et al., (2020) demonstrated significant improvements in outcome measures when used iontophoresis and hyaluronic acid (HA) combined with a gold nanoparticle (GNP) solution in an excisional wound model. The animals were induced to a circular excision, and treatment started 24 h after injury with microwells (300 MA) containing gel with HA (0.9%) and/or GNPs (30 mg/L) in the electrodes (1 mL) for 7 days. In addition, Dohner et al., (2012) had demonstrated that the GNPs associated to the HA + photobiomodulation contributed for a higher wound repair process. Victor et al., (2012) showed that HA, a molecule widely used in clinical practice, with GNPs, which have shown beneficial effects on tissue repair. Mendes et al., (2020) developing therapeutic interventions that promote the formation of new epithelial tissue. In this study used an electrophysical agent (MIC) capable of stimulating the infiltration of these molecules and promoting faster healing. Silveira et al., (2014) and Kim et al., (2013) stated that the associated use of MIC with GNPs-HA favors the tissue repair process by modulating important pathways related to inflammation and tissue formation. Lee et al., (2010) MIC allows for the transport of bioactive molecules when associated with some drugs, in a process called iontophoresis. Prentice, (2011) reported that
Iontophoresis decreases the absorption lag time, while it increases the delivery rate when compared with passive skin application.17

Walters et al. (2011) compared two transdermal delivery methods in regard to the transdermal permeation of drugs and has stated that iontophoresis guarantees the delivery of drugs in an optimized and controlled manner through the mechanisms of electro-migration and electro-osmosis, considered the main means of increased drug transport through the skin to the systemic circulation.18

Tomoda et al. (2012) observed that iontophoresis was applied to enhance the permeability of nanoparticles.19 Hühn et al. (2013) and this was RTC (n=89); venous leg ulcers Percentage of wound size reduction at day 45: 73 ± 4.6% in HA vs. 46 ± 9.6% in control (p=0.011); Number of healed ulcers: 31.1% in HA vs. 9.3% in control at day 45 and 37.8% vs. 16.3% at day 60; Pain intensity based on visual analogue scale lower in HA vs. control.20 Essa et al. (2002) stated that iontophoresis (0.8mA/cm², for 8h) improved drug penetration over passive delivery for all systems, with ultra-deformable vesicles performing best.21

Group B showed that the post-treatment results of this study showed reduced in the WSA and wound volume after the treatment, the mean difference between day 1 and day 60 was 3.8 cm² and the percent of change was 43.43% for WSA and, the mean difference between day 1 and day 60 was 1.71 ml and the percent of change was 84.65% for wound volume, so there was a significant decrease in group (B) regarding the ulcer surface area (p = 0.001) and wound volume. Hettick, (2009) that Compression therapy, delivered using compression hosiery or multi-layer bandaging, is the mainstream of treatments for venous leg ulcers that demonstrate that one of the goals of compression therapy is to enhance healing of a venous leg ulcer.22

Almond A. (2007); the exercise group participants performed an aerobic exercise and a resistance exercise with 8–12 repetition maximum (RM), recommended as an optimal intensity to enhance muscle strength. No significantly better effect of the conventional treatment plus tailored exercise training program on calf muscle strength when compared to the conventional treatment alone.23 Lanting et al. (2017) 12-week supervised exercise programme improved measures of cutaneous micro vascular reactivity in people being treated with compression therapy for venous ulceration.24

Kulprachakarn et al., (2022) Adding the tailored exercise training incorporated with the conventional treatment may provide a greater tendency on wound healing and have the potential to improve ankle mobility than the conventional treatment alone.25 Cardinal et al., (2009) two controlled, prospective, randomized pivotal trials of topical wound treatments on 366 VLU’s and 310 DFUs over 12 weeks. VLU’s had a significantly higher median wound surface area reduction following clinical visits with surgical debridement as compared with clinical visits with no surgical debridement (34%, p=0.019).26

CONCLUSIONS

From the obtained data of the present study, the most notable conclusions were: HA iontophoresis for 6 weeks is an effective adjuvant therapy in treatment of unhealed venous ulcers through accelerating wound healing, reducing Wound Surface Area (WSA) and wound volume. The results of current study showed that combination between HA iontophoresis and conservative treatment for ulcer care is the most effective in comparison to use of either method alone in treatment of unhealed venous ulcers.

REFERENCES