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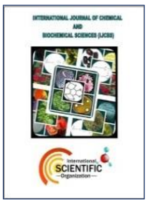

Efficacy of Gentamicin Iontophoresis on Infection and Healing of Chronic Wound

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Abstract

This study was designed to evaluate the impact of gentamicin iontophoresis as a development approach of physical therapy on infection and healing of chronic wound. Sixty participants with chronic wound infection, with an average age between 20 and 45 years old, were randomly classified into equivalent groups: the gentamicin iontophoresis group (A), and the topical gentamicin group (B). 3 sessions a week for six weeks to both groups / 20 minutes every session. Wound volume and wound culture were measured before, and at the end of treatment sessions. There was a non-significant difference in age ($p = 0.35$), and sex distribution ($p = 0.41$) between both groups. There was a non-significant difference pre-treatment in wound volume ($p = 0.82$), and wound culture ($p > 0.05$), while there was a significant reduction post-treatment in wound volume and wound culture in both groups ($p = 0.001$). There was a significant reduction post-treatment in wound volume and wound culture in group (A) compared with group B ($p = 0.001$). In comparison of wound culture post-treatment, there was a significant reduction in infected wounds in the iontophoresis group (A) compared with the topical gentamicin group (B) ($p<0.001$). Six weeks of gentamicin iontophoresis have a remarkable reduction of bacterial growth in the infected wound, wound volume, and an accelerating healing process. It is considered a better treatment for chronic wound infection

Keywords: Chronic Wound Infection, Iontophoresis, and Gentamicin

Full length article **Corresponding Author*, e-mail: ptrservices2022@gmail.com

1. Introduction

Wound healing process is affected by specific local or systemic factors. On the one hand, local factors include infection, pain, hypothermia, and oxygenation. On the other hand, systemic factors related to general health conditions can affect the response of wounds to healing. Furthermore, age, sex, and nutritional state (vitamin, protein, and mineral incompetence), in addition to other factors, help delay or expand healing time. [1]. Bacteria are an essential part of healthy skin and wounds. Although existing bacteria and biofilm formation are the critical thresholds that could affect or delay the healing process, regardless of the recent progress in bacterial or fungal infection management, it is one of the most combined and painful conditions, which leads to various complications. [2]. The secondary complication of wound infection is skin barrier damage, which affects physiological functions, leads to prolonged hospital stays and morbidity complications, and may lead to death. [3,4].Wound care is an essential part of the treatment routine. Chronic wound management is commonly associated with using proper antibiotics at an adequate time to reduce morbidity and improve quality of life. Strategies of wound management used to promote wound healing include cell therapy, growth factor techniques, and drug delivery systems (DDS). [5,6]. Systemic treatments are the first line of therapy for infection, but they have clear disadvantages such as poor tissue penetration and various side effects such as kidney function impairment. When antibiotics are administered intravenously, the bacterial strains elevate minimum inhibitory concentrations of certain drugs, which causes restrictions on treatment and the demand for high doses of antibiotics. This leads to secondary complications and effects on the intestinal flora. The method to solve such problems and reduce their side effects is by delivering antibiotics topically with high drug concentrations directly to the target site without any systemic complications. [7,8,9]. Topical antibiotics have many potential advantages over their systematic use. It is a recommended prophylaxis treatment for multiple cases, such as ophthalmic, orthopedic, urological, general surgeries, and infected wounds. [10]. According to a study approved by the Food and Drug Administration (FDA) about safety and efficacy of gentamicin, wound infection responded to topical gentamycin, there was a positive effect on perineal wound infection, and an improved healing process post-abdominal perineal resection (APR). [7]. Gentamicin sulfate is one of the drugs used for wound management. It is a water-soluble aminoglycoside antibiotic that has a broad-spectrum bactericidal effect and can inhibit both gram-type microorganisms. It can inhibit bacterial protein synthesis via binding with the 30S ribosomal subunit. [11]. Aminoglycoside antibiotics, including gentamicin, when administrated topically or injected intradermally, can create continuous new type VII collagen, improve wound closure, and decrease new blister formation. The systemic administration of gentamicin leads to severe side effects such as renal and ototoxicity. [12]. Transdermal drug delivery is one of the most valuable, noninvasive strategies that can be used for the topical treatment of pain, inflammation, infections, and cancer. [13]. According to a study, iontophoresis is a physical therapy modality capable of delivering drug molecules rapidly by applying a low electrical current through the skin surface, enhancing the transport of drug molecules. It is a simple mechanism that acts as charge-repelling and opposite-charge-attracting and can transport pharmacological molecules over a short period of time. [14,15,16]. Physical therapy procedures were used in previous studies to treat wounds, such as iontophoresis, are known by their mechanism (iontophoretic transport). The electro migration process, in which the ionized molecule transfer is directed to the electrode with opposite polarity, and the electro osmosis process, in which the solvent volume migrates by the effect of current, results in the rapid transmission of other non-charged molecules. [17]. Gentamicin is a selected medicine that can be administered by the iontophoresis technique. Through its bactericidal activity and its ability to decrease new blister formation, it can improve wound closure. [11,12,13,18]. The primary goal of the current study was to investigate the efficacy of gentamicin iontophoresis on the infection and healing of chronic wounds. According to the author's information, the efficacy of gentamicin iontophoresis on chronic wound infection has not been studied recently. Hence, the application of direct current iontophoresis is important for its effect on bacterial growth and the healing of chronic wounds. [19].

2. Materials and Methods

This study was prospective randomized clinical trial, single-blinded, pre- and post-test. The ethical committee of the Faculty of Physical Therapy, Cairo University, confirmed the research conduct before initiating (approval No. 012-003576). The participants were allocated from Dar El Salam Hospital and El Kasr El-Aini in Cairo, Egypt, from November 2022 to May 2023. All participants provided their informed consent by agreeing that all their personal information would remain confidential for the study only.

2.1. Participants

Sixty participants, who had chronic wound infection, were asked to participate in this study. They were classified randomly into two groups: the iontophoresis group (A) consisted of 18 males and 12 females, and the topical gentamicin group (B) consisted of 21 males and 9 females. The mean± standard deviation of age for both groups A and B were 38.03 ± 6.16 and 39.37 ± 4.77 respectively. All patients were under the supervision of a surgery specialist, and the referral was made according to their medical history and evaluation. The following were the inclusion criteria: All patients with chronic localized wound infections (venous ulcer, bed sore). Patients who participated in this study were male and female. All participants' relatives enrolled in the study gave their informed consent, their ages ranged between 20 and 45 years old. Patients were excluded if they had any other dermatological disease, lesions over the glandular area, suspected or diagnosed heart disease, cardiovascular instability, polyneuropathy, epilepsy, severe hypotension, pacemaker, nails, or metal, and all patients with sensory disorders were excluded from the study.

2.2. Randomization

Randomization was completed for 60 participants. The researcher prepared 60 closed envelopes; everyone had a card labeled as either Group A or Group B. Each participant was requested to choose one closed envelope through 1:1 simple randomization, which detected whether they were classified into the iontophoresios group (A) (n = 30) or the topical group (B) (n = 30).

2.3. Intervention

The participants were classified into equivalent groups randomly; each group included 30 patients. Explanations about the objective of the study and the efficacy of treatment were discussed with all participants. Everyone has written their informed consent before starting the study procedure. Everyone was informed to avoid taking any other medical substance for wounds before starting with adequate time, and surgical specialists at the end of the study did re-evaluation.

Group (A) (Iontophoresis Group) included thirty patients with chronic localized wound infection who received the same regular line of physical therapy routine in the form of gentamicin sulfate, which was introduced to the wound site by iontophoresis application for 20 minutes in the form of low-intensity direct current (1 to 5 mA), which was increased gradually until a numbness or tingling sensation was reported (3 times /week) for six weeks in addition to medical care. Patients were encouraged to be active, and to keep wound area in the appropriate position. Healthy nutrition and regular wound care (debridement and dressing routine) were maintained, recommended, and asked for during the study.

Group (B) (Topical Gentamicin Group) included thirty patients with chronic localized wound infection who received topical gentamicin sulfate applied directly to the affected site after describing the instructions, method, and time of application (3 times /week) for six weeks in addition to medical care. Patients were encouraged to be active, and to keep wound area in the appropriate position. Healthy nutrition and regular wound care (debridement and dressing routine) were maintained, recommended, and asked for during the study.

2.4. Outcome measures

The assessor's author evaluated and measured the wound volume, and wound culture for bacterial growth pre-treatment, and at the end of treatment.

2.5. Measurement equipment

2.5.1. Wound volume assessment tools

A simple techniques was used for healing process follow-up, and investigate the efficacy of treatment. A graduated syringe was filled with a known quantity of normal saline and then injected into the wound. Calculate the volume of saline drained into the wound by subtracting it from the original amount; the results indicate the volume of the wound. [21].

2.5.2. Wound culture

Wound culture is a microbiological investigation of wound environmental samples; swaps were taken and kept in a sterilized jar, sent to the clinical laboratory within one hour, and kept for 24 hours at 37°C. The growth of the bacterium was assessed by biochemical tests and microbiological investigations. [22].

2.6. Therapeutic equipment and tool

1. Gentamicin Sulfate .
2. Iontophoresis device Iomed PM850 phoresor II iontophoresis system (non –invasive drug delivery) used to introduce the drug to group A (Study Group), with its ability to produce conditions of direct current, it has digital screen. Made in USA by IOMED, Model number: PM850. For adjusting dose (mA/min), time (min/sec) and current intensity (mA).Direct current unite, low intensity iontophoresis.

2.7. Statistical analysis

2.7.1. Sample size

G-Power statistical software (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany) was used to perform calculations based on the results of wound volume from a pilot study that involved five participants in group A and five participants in group B. This showed that the sample size needed for this study was 60 participants. The calculation was done with $\alpha = 0.05$, effect size = 0.74, and power = 80%.

2.7.2. Shapiro-Wilk test

Shapiro-Wilk test was implanted for data of normal distribution.

2.7.3. Levene's test

Levene's test was implanted to ensure homogeneity between groups (A) and (B). The significance level set at $P < 0.05$. Statistical analysis was preceded by a statistical package for the social sciences (SPSS), version 22 for Windows (IBM SPSS, Chicago, IL, USA).

3. Results and discussion

3.1. Subject characteristics

Sixty participants diagnosed with chronic wound infection were involved in this study. As shown in table (1), there was a non-significant difference in age and sex distribution between groups ($p > 0.05$). Chi-squared test was implemented to compare sex between both groups. Unpaired t-test was implemented to compare age between both groups.

3.2. Impact of treatment on wound volume, and wound culture

3.2.1. Within-group comparison

1. Paired t-test: was implemented to compare wound volume between pre-treatment and post-treatment in the iontophoresis group (A) and topical gentamicin group (B).

2. Mc Nemar-Bowker test: was implemented to compare wound culture between pre-treatment and post-treatment in the iontophoresis group (A) and topical gentamicin group (B). As shown in Table 2, in comparison of wound volume, the result showed that there was a significant reduction post-treatment compared to pre-treatment in both group ($p < 0.001$). The percentage of change in the iontophoresis group (A) was 58.86%, and in the topical gentamicin group (B) was 39.69%. As shown in Table 3, in comparison of infected wound cultures, the result showed that there was a significant reduction post-treatment compared to pre-treatment in both groups ($p < 0.001$). The number of patients who had infected culture post-treatment in group (A) there were five (16.7%), and in group (B) there were thirteen (43.3%).

3.2.2. Between-group comparison

1. Unpaired t-test: was implemented for comparison of wound volume between the iontophoresis group (A), and the topical gentamicin group (B).

2. Chi-squared-test: was implemented for comparison of wound culture between the iontophoresis group (A), and the topical gentamicin group (B). As shown in Table 2. The results revealed a non-significant difference in wound volume pre-treatment between the iontophoresis group (A) and the topical gentamicin group (B) ($p>0.05$), while there was a significant difference post-treatment in the iontophoresis group (A) than that in the topical gentamicin group (B) ($p < 0.001$). As shown in Table 3. The result revealed a significant reduction in infected wound culture in the iontophoresis group (A) post-treatment compared to the topical group (B) ($p < 0.05$). Wound infection is associated with multiple complications that cause deterioration of general health conditions and affect many aspects of patient life. It leads to function loss, and morbidity finally leads to death. Microorganisms' presence in wounds contributes to delays in the healing process due to pro-inflammatory mediators and bacterial toxins released. Contaminated wounds can be controlled by using antibiotics for a long time. However, continued usage of antimicrobials leads to bacterial resistance that delays the healing process. [17]. Systemic antibiotics are the first choice for infection treatment, but they have several side effects. The topical application can increase drug deposition at the target site with minimal systemic complications. Some studies stated that topical antibiotic application was not agreeable in several countries due to its remarkable complications, including adverse drug reactions (ADR), bacterial resistance, hypersensitivity, and drug restriction to skin and subcutaneous tissue. They received limited approval of the surgical prophylaxis guidelines due to contact reactions, and many other problems were observed. In addition to the difficulty of variation in agent, dose, and formulation, which interfere with the healing process, some other studies recommended transdermal administration as a favorable method to avoid these side effects. [9,23,24]. Despite this, topical use of antibiotics is distinguished from systemic use due to the inadequate penetration of intravenous drugs. So, the alternative method to avoid this problem is to deliver drugs topically directly to the target site with high concentrations to subside the systemic toxicity. [7,9,25]. Several studies reported that the application of gentamicin sulfate had a more positive and significant effect on infected wounds than the other applications; Garrine et al., (2023) reported that gentamicin exactly has a positive effect on gram-negative bacteria, and a high impact on psudonomous-aeruginosa and staphylococci associated with infections. [26]. Gentamicin released into an infected wound resulted in significant bacterial growth inhibition ($p<0.05$), as reported by Son et al., (2014). [27]. The topical application of gentamycin significantly increases the clinical efficacy rate and is associated with a faster and shorter time for recovery in cases of localized wound infection (Wang et al., 2019). [24]. Topical gentamycin applied to the contaminated wound significantly reduced surgical site infection (Chang et al., 2013). [28]. The current study is designed to evaluate the effectiveness of gentamicin iontophoresis on wound volume and bacterial growth in patients with chronic wound infection among two different groups (A and B). According to the results of this study, all outcome variables within every group showed significant differences before and after six weeks of treatment. The comparison of wound volume and wound culture between the iontophoresis group (A) and the topical gentamicin group (B) post-treatment versus pre-treatment after six weeks revealed a significant decrease in wound volume post-treatment compared to pre-treatment in both groups ($P<0.001$), with (58.86 %) in the iontophoresis group (A), and (39.69 %) in the topical gentamicin group (B). The comparison of infected wound cultures between the iontophoresis group (A) and the topical gentamicin group (B) post-treatment versus pre-treatment after six weeks revealed a significant reduction of infected wound cultures ($p<0.001$) post-treatment than pre-treatment in both groups. The patients' number who had an infected wound culture post-treatment in the iontophoresis group (A) was 5 patients (16.7%) and 13 patients (43.3%) in the topical gentamicin group (B). This improvement is attributable to existence of electric current stimulation as an alternative non-pharmacological method for reducing wound infection and accelerating the healing process, which is in agreement with the findings of Wang et al., (2019); Caplin and Garcia, (2019), who stated that there were various developed methods to administer antimicrobials locally with high concentrations to enhance the impact of the drug and restrict its complications. [24,29]. Atieh et al., (2022) confirmed that electrical stimulation applied with low intensity activated the skin fibroblasts, considered the better stimulation for cell proliferation that enhanced wound potential and the healing process. [30]. In a research by Luo et al., (2021) the electrical current stimulation applied in direct, lower, and constant current (0.5 mA/cm2) had antibacterial effects on wounds, accelerating the healing process by reducing the number of wound pathogens with fewer side effects on cells. [31]. Rahim et al., (2022) stated that there were numerous clinical trials studied the iontophoresis technology and approved its therapeutic benefits in increasing the quantity and depth of administered medical substances. [32]. Wang et al., (2021) reported that iontophoresis technology is widens scope of transdermal drug delivery, which when applied with a small current, drug permeation would be increases through the intact skin. [33]. Prentice, (2011) examined the efficacy of iontophoresis, the results revealed a decrease in absorption lag time and an increase in the rate of drug delivery when compared with passive application. [34]. Another study reported by Shayesteh et al., (2016) showed that specific topical agents could be used as maintenance therapy by iontophoresis application, as it is considered a non-invasive approach and allows a high concentration of the topical charged drug molecules.[35]. Nosseir et al., (2018) concluded that a combination of estrogen and stem cells delivered through the iontophoresis technique in diabetic foot ulcer patients had a positive effect and was better than a single delivery for one of them. The result revealed a reduction in wound volume and an improved healing process. [36]. Most drugs couldn't penetrate through the skin barrier, and to achieve a maximum therapeutic effect, the development modality suggested by many studies, iontophoresis was the most likely approach to enhance transdermal drug delivery (Banga and Panus, 2017). [37]. Several studies investigated the effect of electrical current stimulation, and the results showed that there was a bactericidal effect on both Gram types when electrical current was adjusted from 0.1 to 5 mA for 30 min. They summarized that electric current is a promising approach to inhibiting bacterial growth, as reported by Viola et al., (2023). [17]. Schwass and Meledandiri, (2014), [38]. explained the antibacterial effect on both gram types seen after the application of direct current (DC).

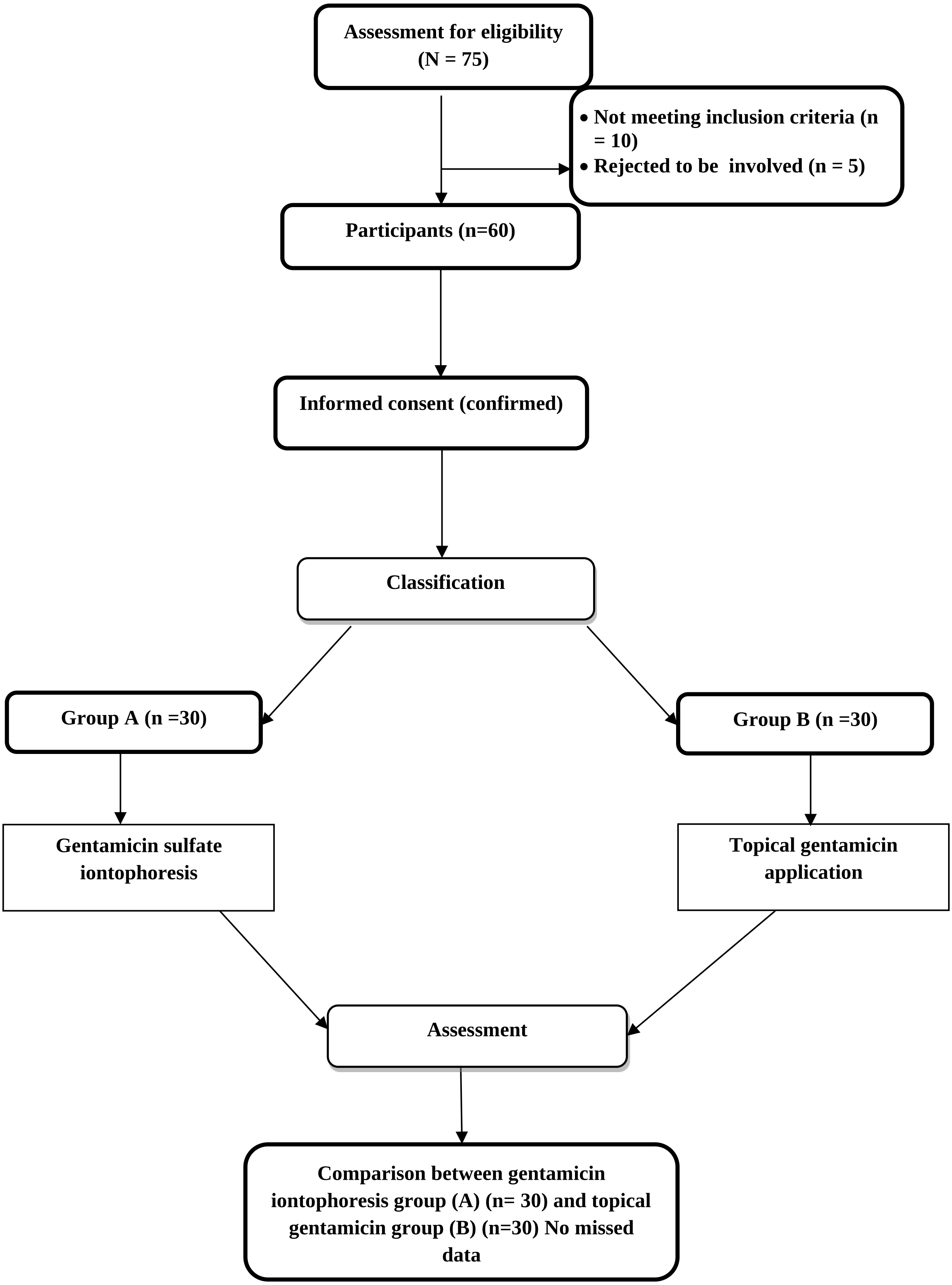

Figure 1. Flow chart revealed experimental design of the study

Table 1. Comparison of age and sex between the iontophoresis group (A) and the topical gentamicin group (B)

	Group A	Group B	MD	t-value	p-value
	Mean ± SD	Mean ± SD			
Age (years)	38,03± 6,16	39.37 ± 4.77	-1.34	-0.39	0.35
Sex, N (%)					
Females	12 (40%)	9 (30%)	-	($\chi2$ =0.65)	0.41
Males	18 (60%)	21(70%)	-		

SD: Standard deviations; **MD:** mean difference; **χ^2:** Chi squared value; **p value:** Probability value.

Table 2. Mean wound volume at pretreatment, and post-treatment of iontophoresis (A) and topical groups (B).

Wound volume (cm^3)	Group A	Group B			
	mean ± SD	mean ± SD	MD	t- value	p-value
Pre-treatment **Post-treatment**	3.16 ± 0.66 1.30 ± 0.53	3.20 ± 0.79 1.93 ± 0.57	-0.04 -0.63	-0.22 -3,35	0.82 0.001
MD	1.86	1.27			
% of change	58.86	39.69			
t- value	19,42	13,26			
	p = 0.001	***p = 0.001***			

SD: standard deviation; **MD:** mean difference; **p-value:** probability value.

Table 3. Wound culture frequency pre-treatment and post-treatment of iontophoresis (A) and topical group (B)

Wound culture	**Group A**	**Group B**	**χ^2- value**	**p-value**
	Frequency	**Frequency**		
Pre-treatment				
Infected	30 (100%)	30 (100%)	-	-
Not Infected	0 (0%)	0 (0%)		
Post-treatment				
Infected **Not Infected**	5 (16.7%) 25 (83.3%)	13 (43.3%) 17 (56.7%)	5.07	0.02
χ^2- value	23.08 **p = 0.001**	15.05 **p = 0.001**		

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

This finding was in agreement with Ita K, (2017), [39]. who stated that direct currents have an antibacterial influence on planktonic cells, and with Freebairn et al., (2013), [40]. who reported that direct current was able to reduce staphylococcus and biofilm formation. Direct current (DC) application revealed a reduction of bacteria, yeast, and biofilm formations when measured within 12 hours of DC application, and the positive effects were observed after 36 hours, as reported by Ruiz-Ruigomez et al., (2016). [41]. All previous studies reported that the gentamicin antibiotic has a clinical effect on wounds and enhances the healing process; multiple types of research have scientifically proven that iontophoresis is effective on bacteria. It has a wide range of uses as a delivery system for topical drugs through the skin instead of oral or systemic use; most scientific research stated that topical usage of gentamicin was much better than intravenous or intramuscular uses to prevent systemic toxicity and other side effects; a lot of researchers approved delivering gentamicin by iontophoresis technology. In (2011), a study proved a combination of iontophoresis with gentamicin as a noninvasive technique through interrupted direct current for 15 minutes 3 times a week for 5 weeks. Results revealed that there was a reduction of wound area by about 65.7% and bacterial growth from high to low or inactive growth. The study reported that iontophoresis gentamicin had a positive effect on the healing of wounds for the participants in the study. [42].Certain studies concentrated on the effect of iontophoresis, but no recent one applied to wound infection. The objective of iontophoresis for wound infection has been experimented with as topical drug delivery; however, the studies are infrequent about the antibacterial effects of iontophoresis, which could be a spectacular strategy for managing chronic wound infection combined with enhancing drug effects. According to current study results, physical therapists must consider the impact of iontophoresis combined with gentamicin in treating wound infections. However, the researchers of this study confirmed that multiple studies were required before this could be beneficial and effective. As a result, both gentamicin iontophoresis and topical gentamicin sulfate were effective therapies for improving the healing process and reducing chronic infections. Gentamicin iontophoresis appears to be more suited for improvement than topical application due to the many beneficial properties of iontophoresis itself combined with the positive effects of gentamicin. The mystery of therapeutic success lies behind technological development and its successful uses, which demand scientific knowledge about therapeutic indications. Researchers in the field can develop the electrical delivery of gentamicin sulfate as a physical therapy method to benefit from the distinctive influence of iontophoresis as transdermal delivery and the positive effect of gentamicin as a topical medication.

3.3. Limitations

The inability to blind the participant might restrict this study; this returned to the fact of therapeutic application. The lack of re-evaluation and follow-up for all patients in both groups was considered another critical issue that might also limit this study. So, incoming research must proceed to evaluate the extended monitoring of gentamicin iontophoresis on chronic wound infection patients; other wound types should be studied in similar approaches with a longer length of time, and incoming studies should be done on a larger set of participants.

4. Conclusions

According to the measured outcome results of the current study, the most remarkable conclusions were that gentamicin iontophoresis was a positive antibacterial approach and much better than the topical application of gentamicin cream on infection and healing of chronic wounds. This developmental technique of drug delivery has been of interest in both the physical therapy and medical fields due to its advantages over systemic use, such as the high deposition of drug molecules into the wound cavity, passing the primary hepatic drug clearance, and avoiding gastrointestinal side effects.

Recommendation

The results of this study considered the following considerations: Further research should include the effects of other physiotherapeutic modalities, different assessment methods, and different variables; the study must be undertaken with a larger number of involved participants to get a better statistical analysis of the data; and it can be done on different types of wounds. A similar study may be conducted to compare the study treatment modalities with other physiotherapy treatments.

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Conflicting interests

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