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Chlorine dioxide treatment for diabetic foot ulcers: Three case studies

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Foot ulcers are a major source of morbidity and mortality for individuals suffering from diabetes mellitus. Currently, available treatments for these wounds are often ineffective, which can lead to the progression of these lesions to a point that requires amputation of the affected limb. Despite amputation, these individuals subsequently suffer from an increased risk of mortality. A novel therapy has been suggested to ameliorate diabetic foot ulcers. This treatment is chlorine dioxide, which is a broad-spectrum antimicrobial agent that is safe when administered in low doses. Three case reports are presented of individuals with diabetic foot ulcers who responded to treatment with chlorine dioxide.

Key words: Diabetes mellitus, diabetic foot ulcers, antimicrobial, wound healing.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine disorders in the world, affecting nearly 6% of the world's population. Both genetic and environmental factors contribute to the development of DM (Adeghate et al., 2006).

Diabetic foot ulcers (DFUs) are a common and serious complication of DM. DFUs may affect the skin, soft tissue, and bone in the lower limbs. Globally, the prevalence of DFUs is increasing, in part because the number of people who are developing DM is growing (Yingsakmongkol et al., 2011). The prevalence of foot ulcers is 4 to 10% higher among individuals with DM than

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in the general population, and the lifetime risk of infection is 25% (Singh et al., 2005; Richard and Schuldiner, 2008). DFUs are the most common cause of morbidity among individuals with DM, and DFUs are the most common reason for hospitalization in this population (Kruse and Edelman, 2006; Lim et al., 2017). Numerous factors contribute to DFUs including hyperglycemia, vasculopathy, peripheral neuropathy, infection, chronic inflammation, and impaired wound healing (Davis et al., 2018; Marston, 2006; Ramirez-Acuña et al., 2019; Singh et al., 2005).

Many individuals with DFUs undergo lower extremity amputation as a result of having treatment-refractory ulcers. Limb amputation is 10 to 30 times more frequent in patients with DM than in the general population and it is estimated that an individual with DM undergoes an amputation every 30 seconds somewhere in the world (Richard and Schuldiner, 2008; Singh et al., 2005). These procedures are associated with a grim prognosis. Approximately, 50% of individuals who undergo amputation will go on to develop ulcerations and infections in the contralateral limb within 18 months. Also, 58% of these amputees will have a contralateral amputation within 3-5 years after losing their first limb (Kruse and Edelman, 2006). Mortality rates following amputation are abysmal with approximately 20% of amputees dying within the first year after surgery, 40% by 3 years, and 60-70% within 5 years (Apelqvist et al., 1993; Jupiter et al., 2016). This 5-year mortality rate is equivalent to or worse than the mortality rates for breast, colon, and prostate cancer (Armstrong et al., 2007). Pre-clinical trials have demonstrated topical chlorine dioxide (ClO_2) to be a safe and effective treatment for DFUs (Al-Bayaty and Abdulla, 2012; Mawas et al., 2022). These results suggest that ClO_2 may be a safe and effective treatment for DFUs in humans as well. It was previously hypothesized that ClO_2 promotes the healing of DFUs through the following mechanisms improves glucose control and reduces hyperglycemia, improves vasculopathy by increasing angiogenesis and tissue oxygen tension, slows the progression of neuropathy by improving blood supply to neurons, reduces inflammation, reduces infection via antimicrobial effects, and improves wound healing via enhanced formation of granulation tissue along with regeneration of healthy tissue. There is also indirect evidence that ClO_2 may promote neovascularization by increasing the production of H_2O_2 (Callisperis et al., 2024). Numerous applications have been reported for ClO_2, yet this therapeutic agent remains relatively unknown in the medical community. Therefore, the following review of its development and medical applications is provided to familiarize the reader with this promising treatment.

MATERIALS AND METHODS

Chlorine dioxide

ClO_2 is a synthetic molecule that was first produced in 1802 (Sidgwick, 1950). In the second half of the 19th century, ClO_2 was utilized as a water treatment in Europe (Benarde et al., 1965), and by the 1970's its use had expanded to more than 500 water treatment plants throughout the world (Clarke and Berman, 1983).

Today, in addition to its use as a water-purifying agent, ClO_2 has numerous potential medical applications (Callisperis et al., 2024). These include an over-the-counter treatment for viral, bacterial, and fungal infections (Frontier Pharmaceutical, Inc., 2022), an agent for the prevention or treatment of COVID-19 (Karnik-Henry, 2020; Aparicio-Alonso et al., 2021; Kály-Kullai et al., 2020) and influenza (Miura and Shibata, 2010; Ogata and Shibata, 2008), a treatment for wounds (Aparicio-Alonso, 2022), and cancer therapy (Aparicio-Alonso and Torres-Solórzano, 2023). In addition, potential mechanisms of action for ClO2 as a treatment for DFUs have been described (Callisperis et al., 2024).

Due to its high chemical reactivity, ClO_2 is rapidly reduced in oral and gastric secretions to chlorite anion (ClO_2^-), which becomes the active molecule responsible for many of this agent's systemic actions. ClO_2 can act as either an oxidant or antioxidant, depending on its concentration.

Safety/Toxicity

The toxicological profile of ClO_2 and its first reducing product ClO_2^-, has been extensively studied in animal studies and reviewed in successive US government technical reports as a safe compound (US EPA, 2000; US ATSDR, 2004). In these studies, toxic reactions have been reported at higher exposure levels following oral and inhalation routes. After a thorough review, the US Agency for Toxic Substances and Disease Registry (US ATSDR) (2004) concluded that the no adverse effects level (NOAEL level) is 3 mg/kg/day for the oral administration of ClO_2^-. The lowest observed adverse effects level (LOAEL) was reported as 5.7 mg/kg/day, which is equivalent to 400 mg/day for an average 70kg adult human. These levels were obtained following an animal study mandated by the US Environmental Protection Agency (US EPA).

Only a few clinical accounts of human toxicity involving ClO_2 have been reported. In one of the first human studies mandated by the US EPA (Lubbers et al., 1982), acute tolerance to an increasing dose of orally administered chlorinated water disinfectants was evaluated. No systemic toxicity was detected below 24 and 2.4 mg/L ClO_2^-. These were ingested twice daily in doses taken 4 hours apart. In a sub-chronic toxicity experiment, daily oral ingestion of ClO_2 at a concentration of 5 mg/L for 12 consecutive weeks produced no obvious adverse effects. The absence of human toxicity of ClO_2^- below this US ATSDR NOAEL has been reported in recent controlled clinical trials. In a phase I placebo-controlled safety and tolerability study in patients with amyotrophic lateral sclerosis (ALS), Miller et al. (2014) tested single ascending doses of 0.2, 0.8, 1.6, and 3.2 mg/kg intravenous $NaClO_2$. After treatment, participants were monitored for a variety of safety and clinical status variables at 8 hours after infusion, and again at one, four,

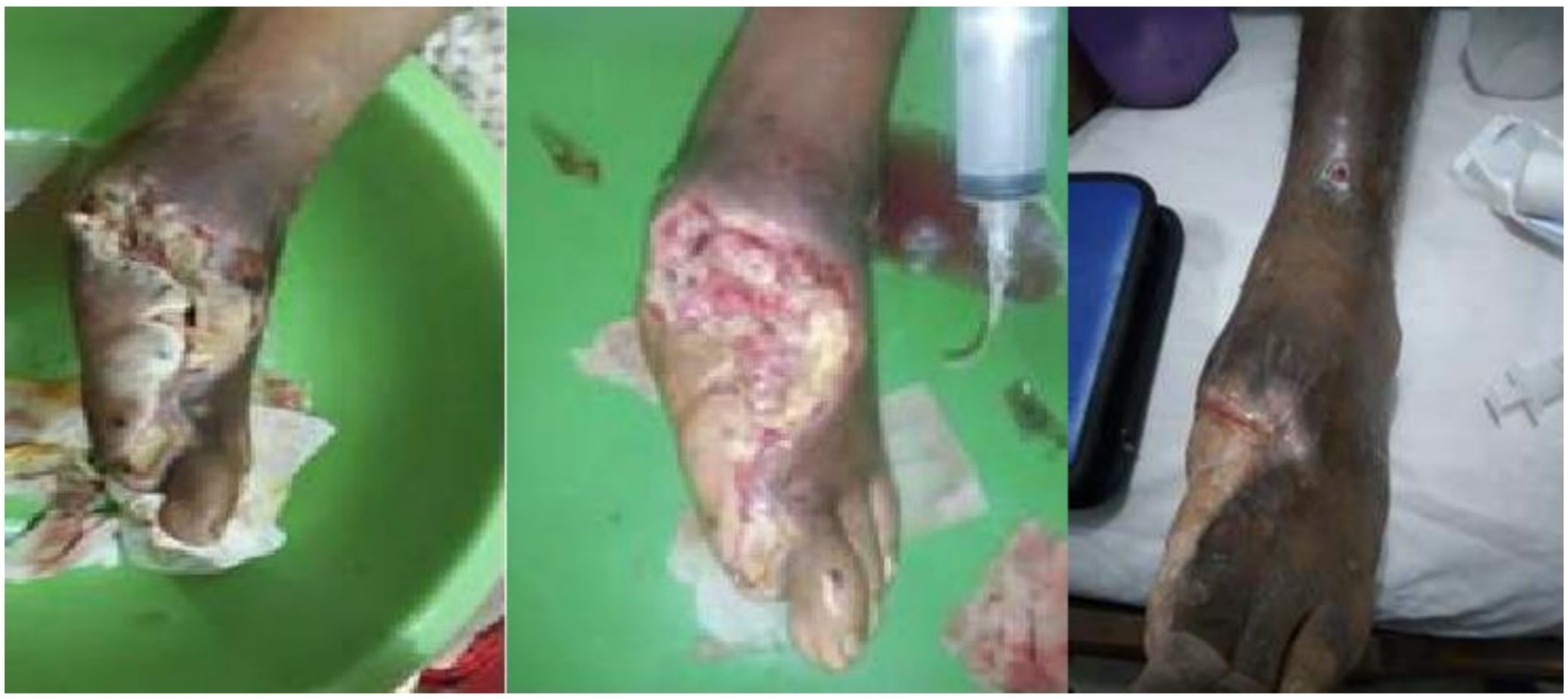

Figure 1. Patient number 1 pre-, during, and after 2 months of treatment.

and seven days after dosing. All doses were generally safe and well tolerated and there were no treatment-related serious adverse events. In an additional phase II study in ALS patients, no adverse effects were observed when 2 mg/kg/day was administered intravenously at a frequency of 1-3 times per day (Miller et al., 2015). Adverse effects have been described following the ingestion of very high doses of $NaClO_2$, which is a precursor molecule used to generate ClO_2. Three case reports describe adult males who attempted suicide by drinking high doses of $NaClO_2$. All three made a full recovery after receiving appropriate medical treatment (Lin and Lim, 1993; Romanovsky et al., 2013; Gebhardtova et al., 2014). Finally, the current experimental evidence demonstrates that administering ClO_2 in doses below 3 mg/kg/day poses no risk of systemic toxicity or significant abnormalities in relevant clinical parameters. This dose is equivalent to a dose of 210 mg ClO_2 per day for an average 70 kg adult.

RESULTS

Three case reports are presented to describe the successful use of ClO_2 as a treatment for DFUs. The first involves the concurrent use of both oral and topical ClO_2. The second individual responded to treatment with oral ClO_2 alone, and the third responded to topical ClO_2 only.

Patient 1

A 54-year-old male presented to the clinic with a history of poorly controlled Type II DM and an infected wound of 6 months duration. This wound was characterized as a stage C and D grade III ulcer. The patient was hospitalized for intravenous treatment with amoxicillin/ clavulanic acid, ceftriaxone, and gentamicin. After observing no improvement, the patient was scheduled for surgical cleaning and amputation of the 1st and 2nd left toe. Subsequently, due to persisting infection, amputation of the left foot was proposed.

The patient then came to a medical center where oral treatment with 10 ml of ClO_2 at a concentration of 3,000 ppm in 1000 ml of water was initiated. He drank 100 ml of this solution (30 ppm) every hour. Also, a surgical dressing was applied that was saturated with a solution of 30 ml ClO_2 in 1000 ml of physiological solution. Daily dressings were then applied with a solution of 20 ml ClO_2 in 1000 ml of physiological solution along with the application of dimethyl sulfoxide (DMSO) and ClO_2. His DFU healed in two months. Figure 1 shows photos of the patient's DFU.

Patient 2

An 81-year-old male presented with a greater than 30-year history of Type II DM. His present problem was a diabetic foot ulcer, which had begun about 15 days

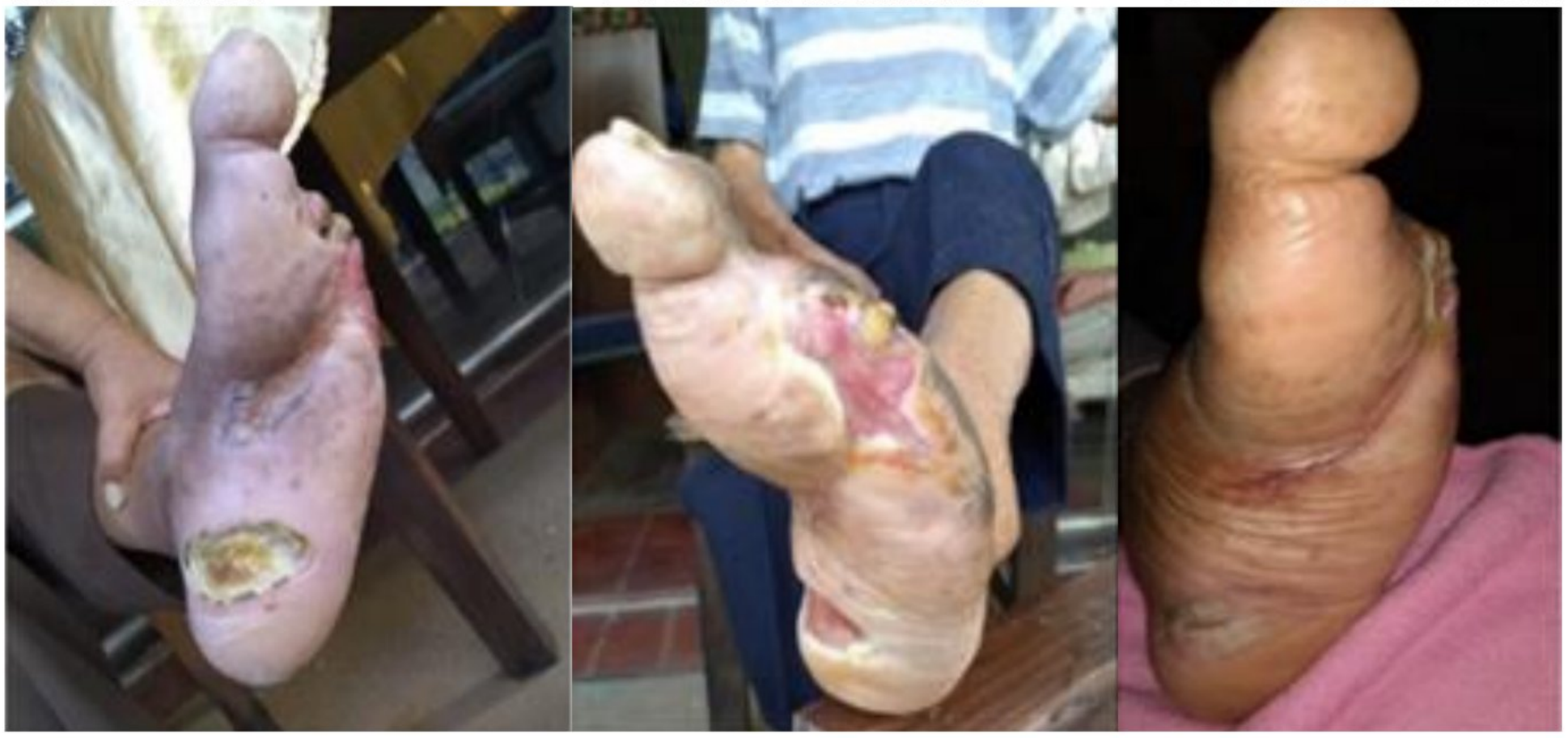

Figure 2. Patient number 2 pre -treatment, 7, and 15 weeks of treatment.

earlier. Previously he had been treated with metformin and insulin. However, his DM was not well controlled, and he required a progressively increasing dose of insulin. At the clinic, he was prescribed ClO_2 20 ml (60 ppm) by mouth daily along with Moringa tablets. His wound was also cleansed with vinegar daily.

After the first month of treatment, he was able to walk without assistance and he no longer required insulin. His blood sugar levels were in the normal range without any pharmaceutical medication. Following seven weeks of treatment, his DFUs were markedly improved, and by 15 weeks, his DFUs were nearly resolved as shown in Figure 2. At the six-month follow-up, his DFUs were fully healed and at a 3-year follow-up, he had experienced no recurrence of DFUs, and his blood sugars remained in the normal range without pharmaceutical treatment.

Patient 3

This 58-year-old male with DM was hospitalized for 3 months on a general surgery service for treatment of a DFU that was refractory to treatment with debridements, hyperbaric oxygen, and topical treatments including Betadine, Dakin's Solution, Silvadene, and saline. The patient's DFU included a chronic infection which progressed with every debridement. Each debridement was also followed by a loss of tissue. Despite multiple courses of intravenous antibiotics and the aforementioned topical treatments, the wound progressively worsened.

The patient was then started on a topical chlorine dioxide gel (Citronex Gel ® - Frontier Pharmaceutical). The wound became purulent for 1 week. Subsequently, the infection was eradicated and the progression of the tissue destruction stopped. Over the next three weeks, debridements were continued and there was no further progression of the ulcer, which began to granulate. The patient was released from the hospital and his ulcer continued to heal as shown in Figure 3.

DISCUSSION

Three cases are presented describing the safe and effective use of ClO_2 as a treatment for DFUs. To the best of our knowledge, these cases include the first descriptions of oral ClO_2 being utilized successfully as a treatment for DFUs. Oral ClO_2 was an effective treatment when used both with and without topical ClO_2. Topical ClO_2 was also an effective treatment when used both with and without oral ClO_2.

Each of these three cases demonstrates marked improvement within 2-4 months of initiating treatment with ClO_2. This is remarkable as each of these cases involved treatment-resistant DFUs that had failed to respond to multiple conventional treatments. Also, each of these cases involved patients who had previously undergone

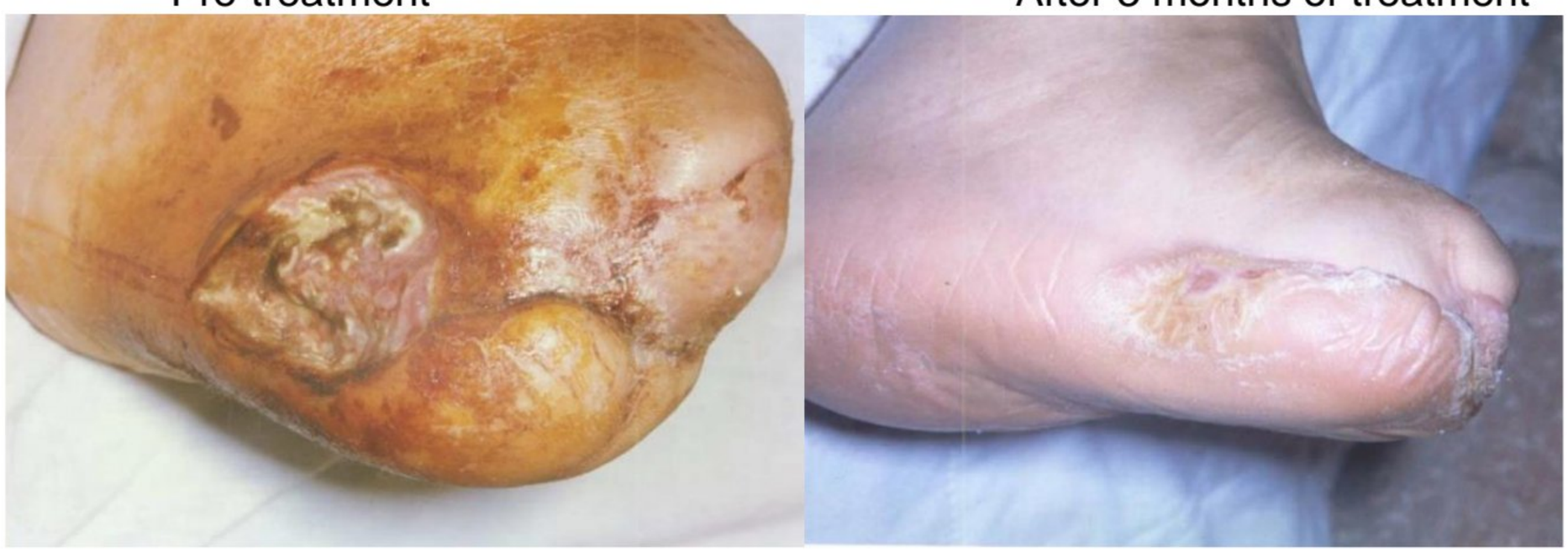

Figure 3. Patient number 3 pre –treatment and after 3 months of treatment.

amputation of a part of the affected foot, indicating the presence of advanced disease in the affected limb. Despite the poor prognosis associated with these three cases, all experienced complete resolution of their DFUs following treatment with ClO_2.

It was previously hypothesized that ClO_2 promotes the healing of DFUs through several mechanisms including improved glucose control and reduced hyperglycemia. This reduction in blood sugar produces an improvement in vasculopathy due to increased angiogenesis and improved tissue oxygen tension. Reduction in blood sugar also slows the progression of neuropathy by improving blood supply to neurons. ClO_2's antimicrobial effects are hypothesized to contribute to the healing of infected DFUs as well. Finally, ClO_2 improves wound healing via enhanced formation of granulation tissue along with regeneration of healthy tissue and also reduces chronic inflammation.

DFUs are a major healthcare problem due to their high rates of morbidity and mortality. Furthermore, due to their multifactorial etiology, finding a single treatment that addresses all of these confounding factors has been a major challenge. The resistance of many DFUs to conventional treatments compounds the difficulty involved in effectively treating these wounds. Novel treatment approaches are needed to address these challenges and to find a solution to this global health issue. ClO_2 is found to be a safe and inexpensive treatment with demonstrated efficacy in the treatment of DFUs.

Based upon the positive clinical results presented in this paper, along with the findings of our previous review describing ClO_2's potential mechanisms of action, we suggest further research into the potential benefits of ClO_2 as a treatment for DFUs is indicated. The majority of pharmacokinetic studies carried out thus far have primarily involved animals. Randomized, double-blind, placebo-controlled human studies are needed to determine the optimal dosage range for this medicine. Also, investigations into the efficacy of different routes of administration are needed. Different treatment arms comparing single routes of administration (e.g. oral versus topical versus intravenous) and multiple routes (e.g. oral and topical versus intravenous and topical, etc.) will be important to determine the most effective routes of administration.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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