Revisión bibliográfica

El efecto de la ozonoterapia en el tratamiento de las úlceras del pie diabético: revisión de la literatura.

The Effect of Ozone Therapy on the Treatment of Diabetic Foot Ulcers: a review.

Paula Cristina Alves Simões Martins
Nurse, Maxillofacial Surgery and Plastic Surgery, Coimbra University Hospital Center, Coimbra, Portugal

Palabras clave
ozono; agua ozonizada; aceite ozonizado; pie diabético; bolsa de ozono

Resumen
La diabetes mellitus es una de las enfermedades metabólicas más frecuentes y constituye una de las principales causas de muerte en la sociedad moderna. El aumento prolongado de glucosa en la sangre y la orina produce complicaciones graves en varios órganos del cuerpo. Una de las principales complicaciones es la úlcera del pie diabético, responsable de numerosas hospitalizaciones, amputaciones, asociadas con una morbilidad y mortalidad significativas, además del inmenso impacto social, psicológico y financiero. Teniendo en cuenta los beneficios del ozono y sus múltiples aplicaciones, su aplicación en el tratamiento de las úlceras del pie diabético se considera relevante. El uso del tratamiento con ozono está indicado por sus propiedades estimulantes de la circulación, que favorecen la oxigenación de los tejidos, además de su efecto analgésico, antiinflamatorio y germicida. El objetivo de este trabajo fue conocer una de las principales complicaciones de la diabetes y su tratamiento con ozono: aplicación tópica. La metodología utilizada fue la revisión bibliográfica realizada en la Revista Española de Ozonoterapia. Los descriptores utilizados fueron: ozono, agua ozonizada, aceite ozonizado, pie diabético y bolsa de ozono. Se asume que la aplicación de ozono en las úlceras del pie diabético es una terapia eficaz y segura, con resultados positivos en el tratamiento y en la mejora de la calidad de vida de las personas con esta patología, evitando la aparición de complicaciones como es el caso de amputaciones. Podemos afirmar que la evidencia clínica apoya el uso de ozono en el tratamiento de las úlceras del pie diabético.

..
El efecto de la ozonoterapia en el tratamiento de las úlceras del pie diabético: revisión de la literatura

Keywords
- ozono
- aguas ozonizadas
- aceite ozonizado
- pie diabético
- bolsa de ozono

Abstract

Diabetes Mellitus is one of the most common metabolic diseases and one of the main causes of death in modern society. The prolonged increase of glucose in the blood and urine causes serious complications in various organs in the body. One of its main complications is the diabetic foot ulcer and it is responsible for numerous hospitalisations, amputations, being associated with significant morbidity and mortality, in addition to its immense social, psychological and financial impact. Taking into account the benefits of ozone and its multiple applications; its application in the treatment of diabetic foot ulcers is considered to be adequate. The use of ozone treatment is encouraged for its circulation stimulating properties which favour tissue oxygenation in addition to its analgesic, anti-inflammatory and germicidal effects. The aim of this work is to get acquainted with one of the main complications of diabetes and its response to ozone treatment- topical application. The methodology used was the literature review carried out in the Spanish Journal of Ozone Therapy. The descriptors used were: ozone, ozonized water, ozonized oil, diabetic foot and ozone bag. The application of ozone in diabetic foot ulcers is assumed to be an effective and safe therapy with positive results in improving the quality of life of those living with the pathology, by avoiding the occurrence of complications such as amputations. Therefore, we can affirm that clinical evidence supports the use of ozone in the treatment of diabetic foot ulcers.

Sugerencia sobre cómo citar este artículo:

Autor para correspondencia: Paula Cristina Alves Simões Martins. Nurse, Maxillofacial Surgery and Plastic Surgery, Coimbra University Hospital Center, Coimbra, Portugal. Rua do forno, Relves, 3150-263 Condeixa, Portugal. Tel. +351963297074. E.mail: psimoes52@gmail.com
Abbreviations
MAK – Maximum ozone concentration allowed by the German authority
PI – Peroxide index

Financing
The author was not sponsored to carry out this article.

Introducción

Diabetes mellitus is a very common metabolic disease and constitutes one of the main causes of morbidity and mortality in contemporary society. It is classified as pre diabetes (in adults with health risk factors), type 1 diabetes mellitus (in childhood and youth, where there is an insulin deficit and individuals are dependent insulin), type 2 diabetes mellitus and gestational diabetes (in adults who have hyperglycemia however the pathogenic mechanisms are different).

Complications of diabetes are hypoglycaemia, diabetic ketosis, hyperosmolar coma, retinopathy, ischemic heart disease, cerebrovascular disease, vascular disease and peripheral neuropathic disease. Of the latter, the diabetic foot is one of the most important due to the negative impact on the quality of life of the patient and family, the high economic and social costs of treatment and the high risk of lower limb amputation.

The diabetic foot, as defined by the International Consensus on Diabetic Foot, is infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and varying degrees of peripheral vascular disease in the lower limbs. These ulcers tend to heal slowly and can be challenging, in most cases surgical intervention is required.

Studies in the areas of biochemistry, immunology and microbiology suggest ozone therapy as an important therapeutic resource in a number of clinical conditions, namely in peripheral vascular diseases and in the treatment of wounds that are difficult to heal, such as diabetic foot ulcers. Among the effects of ozone, stands out bactericidal action, virucidal, fungicidal, the stimulating properties of the circulation, the favouring of oxygenation of tissue cells, analgesic and anti-inflammatory effects and the improvement of glucose and lipid metabolism. Ozone therapy can be used as an adjunct to conventional therapy, as its main function is not to replace drugs, but to improve the results of clinical and pharmacological treatment.
In the local treatment of diabetic foot ulcers, ozone therapy is applied through ozonised oils, ozonised water and cutaneous bags. In addition to its antimicrobial power, it stimulates the formation of new vessels in the affected region, increases local irrigation, accelerates the formation of granulation tissue and decreases the healing time and may also be a way of inducing adaptation to oxidative stress. However, the treatment of ulcers should not negate the use of forms of systemic application of ozone.

According to the Madrid Declaration (2015), ozone presents therapeutic concentrations, ineffective concentrations and toxic concentrations. Therapeutic concentrations according to their type of action are divided into three types: low doses, which have an immunomodulatory effect and are used when the immune system is suspected to be compromised; medium doses with an immunomodulatory effect stimulate the antioxidant enzyme of the defence system and are useful in chronic degenerative diseases; the high doses, with an inhibitory effect of the mechanisms that occur in autoimmune diseases, have application in ulcers or infected lesions and are used in the preparation of oils and ozonised water. Therefore, the ozone concentrations must be adjusted according to each case and according to the characteristics of the ulcer, in granulation or with signs of infection.

The aim of this work was to do an up-date of one of the main complications of diabetes, the diabetic foot ulcer, and review the effects of ozone therapy in its treatment.

**Methodology**

As methodology, an integrative review was used in the Spanish Ozone Therapy Magazine/Ozone Therapy Global Journal, about the treatment of diabetic foot ulcers with ozone therapy. The keywords used were: ozone, ozonised water, ozonised oil, diabetic foot and ozone bag. From this research, 18 articles were found. As an inclusion standard, articles that refer to “diabetic foot” in the title were selected, leaving only 6 articles. After excluding repeated articles, 3 articles were selected for analysis in this study.
**Results**

The research carried out identified 18 articles, leaving the review with 3 articles for analysis and discussion. To facilitate the understanding and discussion of the articles, they were coded as A⁹, B¹⁰ and C¹¹.

Table 1 shows the respective articles related to the title, magazine and year of publication, authors and their nationality.

**Table 1. Identification of the analysed articles in Ozone Therapy Global Journal (former Spanish Journal of Ozone Therapy).**

<table>
<thead>
<tr>
<th>Article</th>
<th>Title</th>
<th>Date</th>
<th>Authors</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Article B</td>
<td>Treatment of diabetic foot ulcer with cold probe ozone: a case study</td>
<td>2016</td>
<td>Héctor José Martínez Arizpe</td>
<td>Mexico</td>
</tr>
<tr>
<td>Article C</td>
<td>Diabetic foot. Multidisciplinary medical treatment and ozone therapy</td>
<td>2018</td>
<td>Ana María Rivera Soto et al.</td>
<td>Mexico</td>
</tr>
</tbody>
</table>

In Table 2, the main characteristics of each case study of the analysed articles are summarised, namely the patient's gender and age, the pharmacological treatment performed prior to ozone therapy, the characteristics and classification of the ulcer, the presence of pain and signs of inflammatory disease, ways of applying systemic and local ozone therapy, the presence of complementary measures, pharmacological and surgical treatment simultaneously with ozone therapy, the results and conclusions.
Table 2. Summary of the main results of the articles.

<table>
<thead>
<tr>
<th></th>
<th>Article A</th>
<th>Article B</th>
<th>Article C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1 Female</td>
<td>1 Female</td>
<td>4:2 Females e 2 Males</td>
</tr>
<tr>
<td>Age</td>
<td>48 years old</td>
<td>64 years old</td>
<td>Between 55-63 years old</td>
</tr>
<tr>
<td>Pharmacological treatment prior to ozone therapy</td>
<td>- Oral hypoglycemics</td>
<td>X</td>
<td>- Oral hypoglycemics</td>
</tr>
<tr>
<td></td>
<td>- Antibiotic therapy in 2 patients</td>
<td></td>
<td>- Antibiotic therapy in 2 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Antiplatelet therapy in 1 patient</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Ulcerative lesion on the right foot with necrosis of the 4th toe with fistula and drainage of purulent content with proposal for supracondylar amputation</td>
<td>Ulcerative lesion of the 1st toe of the right foot</td>
<td>Chronic infected lesions</td>
</tr>
<tr>
<td>Ulcer Classification</td>
<td>Wagner's Grade IV</td>
<td>Wagner's Grade I and II</td>
<td>Wagner's Grade IV</td>
</tr>
<tr>
<td>Pain</td>
<td>Intense on palpation</td>
<td>Yes - unable to walk</td>
<td>X</td>
</tr>
<tr>
<td>Inflammatory signs</td>
<td>Yes (edema, flushing and heat)</td>
<td>Yes (inflammation and pain)</td>
<td>Yes (godet sign)</td>
</tr>
</tbody>
</table>
| Systemic ozone therapy |  | - Ozonised saline solution at 5 µg/mL for the first 3 days; after sepsis is stable, daily application at 3µg/mL.  
- Post surgery: daily rectal ozone therapy until improvement; subsequently 3x/week with low dose. | - Ozonised saline solution at 2 µg/mL, weekly sessions for 8 weeks |
|------------------------|--|---------------------------------------------------------------|--|--------------------------|
| Local ozone therapy    | - Ozonised double-distilled water at 80 µg/mL, continuous flow, for 10 min;  
2. Cutaneous bag at 80 µg/mL for 30 min for the first 3 sessions;  
3. Topical application of ozonised oil at 800 PI (San-O₃®), followed by an elastic bandage;  
4. Daily application of ozonised oil with compression bandage. | 1. Washing with saline solution at 80 µg/mL, 2x/day;  
2. Bag application at 80 µg/mL with the introduction of a catheter in the fistula for 10 min;  
3. Ozonised oil at 800 PI. | 1. Washing with ozonised double-distilled water at 80 µg/mL, continuous flow, for 10 min;  
2. Cutaneous bag at 80 µg/mL for 30 min for the first 3 sessions;  
3. Topical application of ozonised oil at 800 PI (San-O₃®), followed by an elastic bandage;  
4. Daily application of ozonised oil with compression bandage. |
Ozone concentration allowed by the German authority
- 5 sessions 1x/week were performed with:
  1. Washing the ulcer with ozonised water;
  2. Application of the cold probe;
  3. Application of ozonised oil.
- Performed daily:
  1. Washing the ulcer with ozonised water;
  2. Application of sterile dressing with ozonised oil on the ulcer.

<table>
<thead>
<tr>
<th>Pharmacological treatment simultaneously with ozone therapy</th>
<th>- Antibiotic therapy for one week</th>
<th>X</th>
<th>- Oral hypoglycemics - Venotropics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery during</td>
<td>Yes - 4th finger</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ozone therapy</td>
<td>amputation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Complementary measures | X | X | - Buerguer-Allen vascular exercises performed twice a day  
- Circulatory bypass massage (perilesional) weekly lasting 20 minutes  
- Diet |
| Results | Elimination of the negative culture infectious agent; clean ulcer closure; no metabolic complications | Elimination of microorganisms present in the lesion; healing of the ulcerated lesion; elimination of pain from the first application | In the middle of treatment, in the 4th week, a reduction in glycaemia, edema, exudate and ulcer diameter was observed; at the end of treatment, on the 8th week, a metabolic improvement and total remission of ulcers in the four cases was observed |
| Conclusion | Ozone therapy as a first-line treatment; Avoided supracondylar amputation | Safe and effective ozone therapy, with low risk and easy application | Ozone therapy is highly effective in the treatment of chronic infected ulcers - diabetic foot ulcers. Favourable results and recovery of the affected limb, improvement of the patient's quality of life. |

Legend: X, no data declared in the manuscript.
Discussion

In the three articles analysed, it was found that the six patients that underwent study are mostly female adults, four women and only two men, in an age range between 48 and 64 years of age. As for pharmacological treatment before ozone therapy, five patients underwent oral hypoglycemics, or antibiotics, or antiplatelet therapy. All six patients had diabetic foot ulcers with inflammatory signs and five of these ulcers were infected. According to Wagner's classification, five ulcers were classified as grade IV and one as grade I and II. The feet of diabetic patients are vulnerable to complications from daily exposure to recurrent trauma. Wounds tend to heal slowly and are often associated with infection that is difficult to resolve, since most infections are polymicrobial, with *Staphylococcus aureus* being the most isolated pathogen, and bacterial multi-drug resistance a common denominator. Treating these wounds becomes complex, especially those that are infected and are deep, which contributes to a greater possibility of amputation.

Regarding pain, articles A and B refer to patients that had severe or disabling pain, article C does not mention the assessment of this vital sign. In article B, it is important to highlight that the pain decreased immediately after the first ozone therapy application. Scientific research recognises that ozone has an analgesic and anti-inflammatory mechanism.

In articles A and C, the treatment of Wagner's grade IV infected ulcers was performed with local ozone therapy and systemic ozone therapy, using ozonised saline solution with medium and high ozone concentrations. Local ozone therapy was applied to all patients, by washing the ulcer with saline solution/ozonised water followed by the application of ozonised oil. In infected ulcers, articles A and C, treatment with a bag at high concentrations was also performed. In the uninfected ulcer, article B, treatment with a cold plasma probe was performed. Diabetic patients are those who benefit most from ozone treatment, as this therapy is considered useful from the etiopathogenesis to its complications. In both prevention and treatment, an ozone administration route that has systemic activity should be used and combined, if necessary, with other pathways (bags, oils, platelet-rich plasma). Beneficial effects that stand out include the improvement of glucose and lipid metabolism, the anti-inflammatory and modulating action of the immune response, with increased tissue growth factors, and the germicidal action. Improvements in blood perfusion and modulation of oxidative stress are also suggested.
Ozonised saline is a method that consists of pre-saturation of the physiological saline solution with ozone. It’s systemic administration to the patient uses very low doses of ozone. The concentrations used for ozonising of saline solution depend on the treatment objectives, in each specific case and are calculated according to the patient's weight. Thus, 3 types of dosage are used: low dose (1 µg/kg), medium dose (2 µg/kg) and high dose (5 µg/kg). Medium doses are used for chronic inflammatory diseases of different aetiologies and high doses are used to treat infectious diseases. Since saline is a plasma expander, it ozonises a large amount of blood compared to larger autohemotherapy. It is a safe and effective procedure.1, 8

In local treatment, the bactericidal action of ozone is related to the inactivation of microorganisms, through the oxidative rupture of their membranes, through the peroxidation of phospholipids and lipoproteins.14 Ozonised water/saline solution and ozonised oil are applied to infected wounds and ulcers in different concentrations: high, medium and low, depending on the type of tissue and what you want to achieve, disinfect or regenerate.

Ozonised water/saline solution at 80 µg/mL is indispensable for the elimination of pus, necrotic zones and the elimination of germs.14 When these signs are remitted, the use of ozonised water/saline solution in a lower concentration is recommended.1, 8 Results of studies suggest that ozonised water induces new formation of blood vessels and migration of osteoclasts, without affecting the new formation of bone. Its anti-inflammatory properties is an important factor in wound healing.14 Studies have shown that saline improves wound treatment by stimulating cell proliferation.14

Ozonised oils have a wide antimicrobial spectrum and are therefore suitable for the treatment of polymicrobial infections such as neuro infectious diabetic foot ulcer. In addition to antimicrobial activity, ozonised oils promote the release of growth factors, the activation of local anti-oxidant mechanisms and the activation of other tissue repair mechanisms. The recommendation for the use of ozonised oils is fundamentally based on the concentration of existing peroxides.15 Ozonised oil of 800 PI is indicated in severe cases of infected wounds and ulcers. When granulation tissue is observed, the concentration is reduced to 600-400 PI.1, 8, 15 It is important to highlight that with the use of ozonised oil, the phenomenon of microbial resistance does not occur, since it acts by oxidising the microbial walls. The effective results of its application, reduce the excessive costs that patients have in the acquisition of medical materials.1
Cutaneous bags are very useful in diabetic foot ulcers and should complement systemic treatment.\textsuperscript{2} Prior to the bag, the wound should be washed with ozonised water.\textsuperscript{1} In the application of cutaneous bags, concentrations between 70 to 80 µg/mL are used when there are signs of infection for a period of 20 to 30 min. When infection control is observed and granulation tissue is observed, the frequency of application and the concentration should be reduced to 40-30 and 20 µg/mL in order to accelerate the healing process.\textsuperscript{1,8}

Regarding pharmacological treatment, it was carried out concurrently with ozone therapy, antibiotics in the case of article A and oral and venotropic hypoglycemics in the four cases of article C. Inefficient protection and accidental injuries can cause ulcers that in most cases require surgical interventions and in more severe cases, lead to amputation of part or all of the limb.\textsuperscript{6} It should be noted that the major amputation surgery initially foreseen in case A, was reverted to a minor amputation after the ozone therapy treatment.

Several studies validate that ozone therapy seems to accelerate the healing of ulcers and reduce the need for amputation.\textsuperscript{6} Ozone has clinically significant benefits that support its use, with analgesic effect, antimicrobial, germicidal and fungicidal action, indicated as a great alternative for treatment in injuries resulting from diabetes mellitus.\textsuperscript{7} The use of ozone therapy reduces the cleaning time for purulent and necrotic wounds, favouring regeneration processes. This therapy, compared to conventional treatments, allows for a reduction in hospital stay times, a reduction in the number of amputations, disability and the number of deaths.\textsuperscript{1}

Regarding complementary measures, they were only applied to four patients in Article C. The therapeutic action for a diabetic foot ulcer must be multifactorial, magnify metabolic control, local and infection treatment (in the presence of infection), restoration of tissue perfusion, ascertain the cause and prevent recurrences, as well as providing education for the health of the patient/caregivers.\textsuperscript{2}

Regarding the results, it appears that there was healing of all diabetic foot ulcers. In the cases of articles A and C, there were no metabolic complications that coincide with the cases that underwent systemic ozone therapy. In the case of Article B, it should be noted that pain has been eliminated since the first application of ozone therapy.

The release of ozone in wounds is considered to favour the healing process not only by local disinfection but by favouring the release of cytokines locally with reparative effects.\textsuperscript{15}
The limitations of this review are bound by the bibliographic research of only one scientific journal of ozone therapy and the small number of articles analysed does not allow generalising of results to the population. It was also not possible to carry out a comparative analysis of studies with conventional treatment versus ozone therapy in the treatment of diabetic foot ulcers.

**Conclusions**

In the three articles analysed, it was evident that ozone therapy, in its different forms of application, is an effective and safe treatment in this area of the diabetic foot. It has positive results in improving the quality of life of diabetic patients, reducing the negative consequences of the condition. Ozone therapy should be considered as a complementary treatment, and not an alternative one, as it appears that associated with conventional therapy favours the healing of diabetic foot ulcers.

A broader search in scientific databases is suggested, thus allowing to infer results on the effect of ozone therapy in the treatment of diabetic foot.

**Conflict of interests**

The author declares that there is no conflict of interests in this article.
REFERENCIAS BIBLIOGRÁFICAS


