Use of Transcutaneous Application of CO\textsubscript{2} in Diabetic Foot Pathology

Igor Frangez\textsuperscript{1*}, Jure Colnaric\textsuperscript{1}, Danijela Truden\textsuperscript{2}

\textsuperscript{1}Department of Traumatology, University Medical Centre Ljubljana, Zalo\v{s}ka Cesta, Ljubljana, Slovenia
\textsuperscript{2}Center for Peripheral Vascular Rehabilitation, Kopraska Ulica, Slovenia

Corresponding Author: Igor Frangez, Department of Traumatology, University Medical Centre Ljubljana, Zalo\v{s}ka Cesta, Ljubljana, Slovenia, Tel: +386 1 522 3255; E-mail: ifrangez@gmail.com

Abstract

In neuropathic foot ulcers, the most prominent finding is the loss of peripheral sensation and is typically seen in diabetic patients. In addition, vasculopathy may lead to foot ulcerations in diabetic patients. CO\textsubscript{2} therapy was found to improve chronic wound healing in patients with vascular impairment. It refers to the transcutaneous and subcutaneous application of CO\textsubscript{2} as well as CO\textsubscript{2} water baths for therapeutic purpose. In the method used, gaseous CO\textsubscript{2} is applied transcutaneously using the PVR system\textsuperscript{®}. CO\textsubscript{2} is applied by means of a single-use, low-density polyethylene bag which is wrapped around the leg being treated and secured with an elastic strap. The advantages of this method, compared to injecting CO\textsubscript{2} into subcutaneous tissue, are non-invasiveness, the absence of pain and protection against infection. Compared to CO\textsubscript{2} balneotherapy this approach enables the use of higher CO\textsubscript{2} concentrations, application to chronic wound patients and, with appropriate precautionary measures, prevents the increase of CO\textsubscript{2} in the surrounding air. Finzgar et al. observed that the transcutaneous application of gaseous CO\textsubscript{2} caused a significant increase in the Laser Doppler (LD) flux in cutaneous microcirculation in vivo in humans. The favourable clinical and microcirculatory effects of gaseous CO\textsubscript{2} have further been observed in studies of patients with intermittent claudication as well as patients with primary and secondary Raynaud’s phenomenon. The reviewed studies suggest that the increased delivery of CO\textsubscript{2} to the ulcerated area will cause vasodilation and an increase in blood flow. The improved angiogenesis and oxygenation will result in healing of the chronic wound. This principle may be applied in the treatment of diabetic foot ulceration. Moreover, the effect on blood flow may also be important in preventive and curative treatment of patients with impaired mobility due to organic or functional causes. Further work is needed for the development of therapeutic strategies to optimize CO\textsubscript{2} use in diabetic foot patients.

Keywords Carbon dioxide therapy; Microcirculation; Contralateral limb; Vasculopathy; Polyneuropathy

Introduction

Carbon dioxide therapy refers to the transcutaneous and subcutaneous application of CO\textsubscript{2} as well as CO\textsubscript{2} water baths for therapeutic purposes. CO\textsubscript{2} rich water bathing has been used since 1930 and was found to improve chronic wound healing in patients with vascular impairment. With neuropathic foot ulcers, the most prominent finding is the loss of peripheral sensation and is typically seen in diabetic patients. Repeated stress and lack of sensation lead to trauma, breakdown of overlying tissue and eventual ulceration. At pressure points, vascular impairment may additionally lead to ulceration.

One major goal of treatment is to improve microcirculation and thereby oxygen supply and the transport of metabolic pathway end-products. The effects of CO\textsubscript{2} therapies on skin microcirculation have been studied in animal models. Duling BR [1] observed increased microvascular diameter and increased perivascular pO\textsubscript{2} at sites of exposure to a CO\textsubscript{2} aqueous solution. The increased diameter was due to the vasodilatory effect of topical CO\textsubscript{2}, the phenomenon also known as active hyperaemia. The increased perivascular pO\textsubscript{2} was due to the effect of CO\textsubscript{2} on the oxyhemoglobin dissociation curve. Irie et al. [2] demonstrated that CO\textsubscript{2} immersion induced the production of plasma vascular endothelial growth factor (VEGF), resulting in no-dependent angiogenesis associated with the mobilization of endothelial progenitor cells. Hayashi et al. [3] showed that CO\textsubscript{2} immersion increased blood flow in feet to a much higher extent than plain water and it improved the limb salvage rate in critical limb ischemia patients without the option of revascularization. These results showed the potential role of topical CO\textsubscript{2} in effective adjunctive treatment to prevent diabetic ulcer exacerbation.

Materials and methods

Gaseous CO\textsubscript{2} with 99.995% purity (medical grade) was applied transcutaneously using the PVR system\textsuperscript{®} (produced by DermaArt Ltd., Brezice, Slovenia). The PVR system consists of a compressor, a CO\textsubscript{2} level monitoring sensor and a conduit tube for CO\textsubscript{2}. CO\textsubscript{2} was applied by means of a single-use, low-density, polyethylene bag which was wrapped around the leg being treated and tightened with an elastic strap. The 35-minute therapies are performed twice a week over a period of 5 weeks. The PVR system enables the safe and controlled application of a high concentration of CO\textsubscript{2} to the body. The method of application is completely safe and prevents any inhalation of CO\textsubscript{2}. The device also has an electronic sensor system which constantly monitors the air quality in the room.

Discussion

Brandi et al. [4] studied the effect of the subcutaneous application of gaseous CO\textsubscript{2} in the treatment of chronic lower limb ischemia. Laser Doppler flux and transcutaneous pO\textsubscript{2} were measured in two groups. In one group, CO\textsubscript{2} therapy was used in addition to the standard methods of treatment for such lesions. The patients in the control group were
treated using only standard methods. In the group that underwent subcutaneous treatment with CO₂, a significant increase in tissue oxygenation values were observed. They showed progress in healing and a decrease in size of the injured area.

Finzgar et al. [5] conducted a study of the effect of the transcutaneous application of gaseous CO₂ on cutaneous blood flow in vivo in humans. The Laser Doppler (LD) flux in cutaneous microcirculation was measured simultaneously in a group of 33 healthy men during rest and a 35-minute CO₂ therapy. One lower limb of each subject was exposed to gaseous CO₂. The contralateral limb was the control, being exposed to air. The CO₂ therapy caused a statistically significant increase in the LD flux of the studied extremity, whereas in the LD flux of the control extremity was not statistically significant. Aside from a minor decrease in heart rate, no systemic effects were found. The LD flux change is most likely an indirect sign of the successful diffusion of CO₂ molecules through the skin into microcirculation and a direct indicator of the vasodilatory effect of CO₂.

Favorable clinical and microcirculatory effects of gaseous CO₂ were further observed in studies of patients with intermittent claudication [6] and patients with primary and secondary Raynaud’s phenomenon [7]. The same principle is applied in the treatment of diabetic foot ulceration. The reviewed studies suggest that CO₂ therapy can be a safe outpatient treatment option for patients with chronic wounds [8]. There are a number of other possible application for CO₂ therapy as well. Indications include intermittent claudication, peripheral artery disease and arteriolar blood flow occlusion/disorders, diabetic feet, diabetic vasculopathy and polyneuropathy, and bedsores. Contraindications include acute pyretic diseases, consumptive diseases and ulcers, severe hypertension, new cardiac infarctions, aortic and mitral valve stenosis, severe congenital heart failure, cor pulmonale, broncho pulmonary diseases accompanied by hypercapnia and acute inflammatory vascular diseases [9].

Conclusion

The reviewed studies suggest that the increased delivery of CO₂ to the ulcerated area results in vasodilation and an increase in blood flow. The improved angiogenesis and oxygenation enhances the healing of chronic wounds. This principle may be applied in the treatment of diabetic foot ulcerations. The effect on blood flow may be important in the preventive and curative treatment of patients with impaired mobility due to organic or functional causes. Further work is needed for the development of therapeutic strategies to optimize CO₂ use in diabetic foot patients.

References

1. Duling BR (1973) Changes in microvascular diameter and oxygen tension induced by carbon dioxide. Circulation Research 32: 370-376.
2. Irie H, Matsumi T, Takamiya M, Zen K, Takahashi T, et al. (2005) Carbon dioxide-rich water bathing enhances collateral blood flow in ischemic hindlimb via mobilization of endothelial progenitor cells and activation of NO-cGMP system. Circulation 111: 1534-1539.
3. Hayashi H, Yamada S, Kumada Y, Matsuo H, Toriyama T, et al. (2008) Immersing feet in carbon dioxide-enriched water prevents expansion and formation of ischemic ulcers after surgical revascularization in diabetic patients with critical limb ischemia. Ann Vasc Dis 1: 111-117.
4. Brandi C, Grimaldi L, isi G, Brafå A, Campa A, et al. (2010) The role of carbon dioxide therapy in the treatment of chronic wounds. In Vivo 24: 223-226.
5. Finzgar M, Melik Z, Cankar K (2015) Effect of transcutaneous application of gaseous carbon dioxide on cutaneous microcirculation. Clin Hemor Microcir 60: 423-435.
6. Fabry R, Monnet P, Schmidt J, Lusson JR, Carpentier PH, et al. (2009) Clinical and microcirculatory effects of transcutaneous CO₂ therapy in intermittent claudication. Randomized double-blind clinical trial with a parallel design. Vasa 38: 213-224.
7. Schmidt J, Monnet P, Normand B, Fabry R (2005) Microcirculatory and clinical effects of serial percutaneous application of carbon dioxide in primary and secondary Raynaud’s phenomenon. Vasa 34: 93-100.
8. Cankar K, Finzgar M, Melik Z (2014) The effect of transcutaneous carbon dioxide application on cutaneous microcirculation. Cardiovasc Res 103: 453-460.
9. http://www.mesotherapyworldwide.com/images/pdf/Carbon_Dioxide_Bath.pdf.