The Treatment of Wounds Occurring in Radiated Tissue with Nitric Oxide / Plasma Therapy

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Background

Radiation therapy has been used in the treatment of certain cancers for over 100 years with variable results. (1) Even though it is effective in treating selected malignancies, the potential damage to normal tissues can be significant. The most frequently injured tissue is the skin overlying or surrounding the area of treatment. These injuries may be acute occurring within 10-14 days of starting radiation therapy or chronic occurring 3 months or more after therapy. (1) These effects of radiation therapy, both acute and chronic, may be the result of death of and damage to cells especially fibroblasts, loss of circulation to the tissues due to microcirculation damage, and development of an abnormal inflammatory reaction in the tissues that may be prolonged. (1,2,3,4)

Nitric oxide is a molecule generated normally in the body by nitric oxide synthase and functions as an intracellular signaling molecule. There is significant evidence that nitric oxide plays a major role in wound healing by stimulating collagen synthesis and wound strength, stimulating angiogenesis, reducing inflammation, killing bacteria, stimulating microvascular vasodilatation, inhibiting platelet and erythrocyte aggregation, reducing leukocyte adhesion, and stimulating endothelial and fibroblast proliferation and differentiation. (5,6) It functions as an anti-microbial killing bacteria by its direct effect on bacteria and by combining with the superoxide anion to form an antimicrobial agent (NO + O2 = ONOO-). The nitric oxide/plasma energy combination has been found to penetrate up to 3cm into intact tissue making it effective in treating certain conditions under intact skin. It plays a large role in vasodilatation of the microcirculation by restoring the function of endothelial nitric oxide synthase (eNOS). (7,8,9)

Treatment of wounds with nitric oxide has proved to be difficult because the molecule has a very short half-life, in the range of seconds. In an attempt to restore normal nitric oxide activity to tissues and improve healing in chronic wounds, attention was turned to a device first developed in Russia by Drs. Pekshev and Shekhter. The NO-therapy device uses plasma energy to deliver nitric oxide to the tissues. (10,11) The combination of atmospheric oxygen and nitrogen at high temperatures generated by an electric arc results in nitric oxide and plasma energy (N2 + O2 = 2NO + 181 KJ energy). (10,11) This combination of plasma energy and nitric oxide results in the molecule having an extended half-life long enough to be clinically useful in the treatment of wounds and infections. After generation, the nitric oxide/plasma flow is cooled to ~35C, and nitric oxide is delivered to the tissues in a “dose” between 800 and 1000 ppm. (11) The nitric oxide is generated out of the surrounding air without the need for additional gases. During the treatment of the patient no part of the device touches the patient, so there is no need for disposable parts or sterilization of the device.

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Nitric oxide promotes wound healing by stimulating angiogenesis, reducing inflammation, killing bacteria, stimulating microvascular vasodilatation, inhibiting platelet and erythrocyte aggregation, reducing leukocyte adhesion, and stimulating endothelial and fibroblast proliferation and differentiation. (12,13) All of these effects would benefit the radiated wound and help with healing. (14,15)

This study was done to evaluate the efficacy of plasma / nitric oxide for the treatment of acute and chronic wounds occurring in radiated tissue.

References

1. Dormand E, Banwell P, Goodacre E. Radiotherapy and Wound Healing. *Int Wound J* 2005;2:112-127
2. Jacobson LK, Johnson M, Raj D, et al. Impaired Wound Healing after Radiation : A Systematic Review of Pathogenesis and Treatment. *JPRAS Open* 2017;13:92-105
3. Manna B, Cooper JS. Radiation Therapy Induced Skin Ulcer. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 10, 2022
4. Schaffer M, Weimer W, Wider S, et al. Differential Expression of Inflammatory Mediators in Radiation Impaired Wound Healing. *J Sur Res* 2002;107(1):93-100
5. Lou J, Chen AF. Nitric Oxide: A Newly Discovered Function on Wound Healing. *Acta Pharmacologica Sinica* 2005;26(3):259-264
6. White MB, Barbul A. Role of Nitric Oxide in Wound Repair. *Amer J Surg.* 2002;183:406-412
7. Schaffer MR, Tantry U, et al. Diabetes-impaired Healing and Reduced Wound Nitric Oxide Synthesis: A Possible Pathophysiologic Correlation. Surgery 1997;121:513-519
8. Nisikawa T, Edelstein D, et al. Normalizing Mitochondrial Superoxide Production Blocks Three Pathways of Hyperglycaemia Damage. *Nature* 2000;404:787-790
9. Hink U, Li H, et al. Mechanisms Underlying Endothelial Dysfunction in Diabetes Mellitus. *Cir Res* 2001;88:E14-22
10. Shekhter AB, Kabisov RK, Pekshev AV, et al. Experimental and Clinical Validation of Plasmadynamic Therapy of Wounds with Nitric Oxide *Bulletin of Experimental Biology and Medicine,* 1998;126(8): 829
11. Shekhter AB, Vladimir A, Serezhenkov B, Tatiana G. Beneficial Effect of Gaseous Nitric Oxide on the Healing of Skin Wounds *Nitric Oxide* 2005;12: 210–219
12. White MB, Barbul A. Role of Nitric Oxide in Wound Repair. *Amer J Surg.* 2002;183:406-412
13. Schaffer MR, Tantry U, et al. Diabetes-impaired Healing and Reduced Wound Nitric Oxide Synthesis: A Possible Pathophysiologic Correlation. Surgery 1997;121:513-519
14. Shekhter AB, Vladimir A, Serezhenkov B, Tatiana G. Beneficial Effect of Gaseous Nitric Oxide on the Healing of Skin Wounds *Nitric Oxide* 2005;12: 210–219
15. Treadwell TA, Walker D, Alston J, Murray S, Nicholson BJ, Taylor M, Pickens A, Chaviano K. The Use of Nitric Oxide/Plasma Therapy in the Treatment of Recalcitrant Wounds. Peer reviewed Clinical Research Poster Presented at the Symposium on Advanced Wound Care, Orlando, FL, April 24-27, 2014

Methods and Treatment

After IRB approval of the protocol, a series of 5 patients with acute or chronic wounds occurring in tissue following radiation therapy were enrolled in the study. The wounds have been present from 3 to 20 years with an average of 6.8 years. Each wound was debrided and treated with the nitric oxide/plasma energy therapy once per week for an average of 6 minutes per treatment.

Cases

96 y/o lady with unhealed wound of ankle following radiation of a squamous cell carcinoma 13 years previously. Wound never healed despite multiple treatments.


Wound at 1st treatment


Wound after 5 treatments


Wound healed

Patient with radiation wound of leg for 3 years following radiation for basal cell carcinoma. Despite HBO and skin grafts the wound did not heal.


Wound at 1st Treatment


Wound 80% closed and treatments continue

89 y/o lady with wound of leg following radiation for squamous cell carcinoma of leg. Wound recurred 4 years later and had been unhealed for 3 years despite. HBO and skin grafts.


Wound at 1st treatment


After 4 treatments


Healed After 6 treatments

73 y/o man with history of oral cancer and radiation. Incision of neck had not healed since procedure 12 years prior.


Wound at initial visit


Wound after 6 treatments and treatments continue

57 y/o man with sarcoma of leg treated with radiation. After 15 years, the wound of leg recurred and has been unhealed for 3 years and has been unresponsive to therapy


Wound at 1st visit


Wound following debridement


Wound currently with treatment continuing

Results

Each patient showed an immediate reduction in the size of the wound in the radiated tissue. With treatments once per week for 6 minutes each time, 2 patients have healed, and 3 have had a significant reduction in size of the wound and continue with therapy. Continued work with the nitric oxide / plasma energy therapy is warranted to determine its ideal treatment duration and interval.