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Air plasma-generated nitric oxide in treatment of skin scars and articular musculoskeletal disorders: Preliminary review of observations

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ABSTRACT

The generation of gaseous mixtures containing nitric oxide (gNO) from different plasma sources has been widely used for various clinical applications. Concentrations of biologically active species generated in those discharges in addition to gNO were calculated for different gas temperatures. Synergistic actions of gNO with other plasma species are discussed. New therapeutic effects of gNO-containing plasmas achieved for the treatment of skin scars, rheumatoid arthritis, osteoarthritis and sport injuries are reported.

1. Introduction

Nitric oxide (NO) is a short-lived signaling molecule that plays an important role in a variety of physiologic functions, including inflammation and wound healing processes [1]. NO has important roles in the function of many tissues and organs, from the cardiovascular system to the brain [1]. Wound healing processes are known to involve a sharp increase of nitric oxide generation in wound tissue. This increase is caused by the activation of constitutive isoforms of NO-synthase (eNOS and nNOS) and by a markedly enhanced synthesis of inducible NOS (iNOS) [2]. These observations suggest a possible therapeutic use of various NO donors for the acceleration of wound healing.

Therapeutic effects of different plasma sources including plasma generated gaseous nitric oxide (gNO) have been utilized for various clinical applications [3–7]. Our previous studies [6,7] indicated that exogenous gaseous nitric oxide (gNO) flow produced by an air-plasma generator “Plason” acts beneficially on the wound healing. At present the therapeutic action of gNO is attributed to both direct and indirect gNO regulatory effects on inflammatory infiltration, anti-microbe macrophages activity, microcirculation and regeneration and nerve conduction. To understand the mechanism of this effect the NO levels in rat tissues were studied using exogenous NO spin traps, Fe^{2+} complexes with diethyldithiocarbamate (DETC)1 or N-methyl-D-glucaminedithiocarbamate (MGD). NO binding with these traps results in the formation of paramagnetic mononitrosyl iron complexes, MNIC–DETC or MNIC–MGD, which are soluble in lipophilic or hydrophilic media, respectively [7]. As a result of these experiments the sharp increase of MNIC–DETC and nitrosyl–heme–iron complexes in wound tissue has been revealed and considered as to be a response to successive short-lasting exposures of gaseous gNO flow. It was demonstrated that endogenous NO is responsible for the formation of these complexes, and NOS enzymes are involved in synthesis of this NO. The ESR experiments gave direct proof that gaseous NO treatment increased the stationary level of endogenous NO molecules in wound tissues. This beneficial effect is proposed to be caused by the mechanism involving peroxynitrite as an intermediate. Small doses of peroxynitrite may actually have a protective action in cell cultures and tissues. These results were attributed to mobilization of various antioxidant species by the presence of peroxynitrite as an intermediate [8]. This

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mobilization could diminish the amount of superoxide anions in wound tissue, thereby protecting endogenous NO molecules against superoxide attack. By implication, more endogenous NO molecules become available as signaling molecules to regulate the metabolic processes in wound tissue.

The antimicrobial effect of gNO as a part of its therapeutic action is proved now for more than 45 bacteria including gram-negative, gram-positive, spore-forming rods, alpha-hemolytic anaerobe, facultative anaerobe, cocci arranged in clusters, antibiotic-resistant bacteria as well as biofilms (S aureus) and other infections [9–14]. Nitric oxide is also a very effective agent against fungi [13–16] and parasites (Leshmaniasis) [17–18]. A main benefit of gNO bio-decontamination is its ability to treat a wide range of pathogens rather than a specific pathogen.

A number of biological synergistic actions of gNO with H_2O_2 and gNO with O_2 species, such as apoptosis induction and intensification of anti-cancer and bactericidal activity, have been shown in previous publications [19–24].

In previous publications [6,7] we briefly reported that the use of plasma-generated gNO provides significant therapeutic effects in treatment of several pathologies (Fig. 1). The results of clinical application of air plasma generated gNO mainly related to application of this treatment on open wounds, ulcers and mucosal surfaces.

In current paper we wanted to present for the first time some new observations on the clinical use of plasma gNO therapy in the treatment of soft tissues with undamaged skin surface. This is a short review of our own results and the observations of our collaborators regarding the application of air plasma generated gaseous streams in treatment of skin scars and articular musculoskeletal disorders. We also analyzed the composition of the gas stream generated from air plasma device "Plason". In particular, the most important findings include improvement of clinical appearance of excessive skin scars and dramatic reduce of keloid recurrence rate; long-lasting analgesic effects, physical and social performance in patients with musculoskeletal disorders, including osteoarthritis, rheumatoid arthritis and orthopedic sport injuries. We hypothesize that the observed biological responses may be attributed to synergistic action of gNO with other plasma gas species. We consider this paper as a preliminary report on the clinical effects of air plasma-generated NO-containing gas in a human cohort to attract attention of the professionals for more comprehensive study of the revealed phenomena.

2. Plasma generation of NO containing gas

Nitric oxide gas for therapeutic applications could be generated by several methods. A simple way to generate NO is by chemical synthesis in the reaction of ammonia oxidation:

$$4NH_3+5O_2=4NO+6H_2O.$$

However, the storage of chemically synthesized NO gas for further applications could be a problem because NO radicals are not stable and are converted into NO_2 gas in the reaction of recombination in the presence of oxygen.

Plasma chemical synthesis using plasma and atmospheric air could be an alternative method of NO generation for medical applications in situ. Plasma device "Plason" (see Fig. 2) based on arc discharge was developed for generating gas flow containing gNO with different configurations of the exit channels corresponding to the different medical applications: wound sterilization, blood coagulation, tissue destruction, therapeutic manipulator/stimulator [3–4,6–7]. As an example of operation conditions the "Plason" device in treatment of burns is shown in Fig. 3. Plasma temperature and nitric oxide content at the anode exit differ in different configurations of the manipulator, corresponding to different medical applications. The "Plason" system is based on the jet of hot air plasma providing relatively high NO concentration (200–2500 ppm) in the output gas flow with significant therapeutic effect [3,4].

The plasma device is used in two modes. In the first "hot mode" a plasma jet is used for rapid coagulation and sterilization of wound surfaces, destruction and desiccation of necrotic tissue and pathologic excrescences. In the second "cold mode" NO-containing plasma gas flow with a temperature of 20 to 40 °C and is used for wound sterilization, decrease of inflammation, stimulation of regenerative processes and wound healing. In the "hot mode" the temperature in the manipulator was 3000–4000 °C depending on the air flow rate. In the "cold mode" the manipulator was inserted in the special "cooler" mounted in the device. The temperature in the cooler output was 20–40 °C depending on

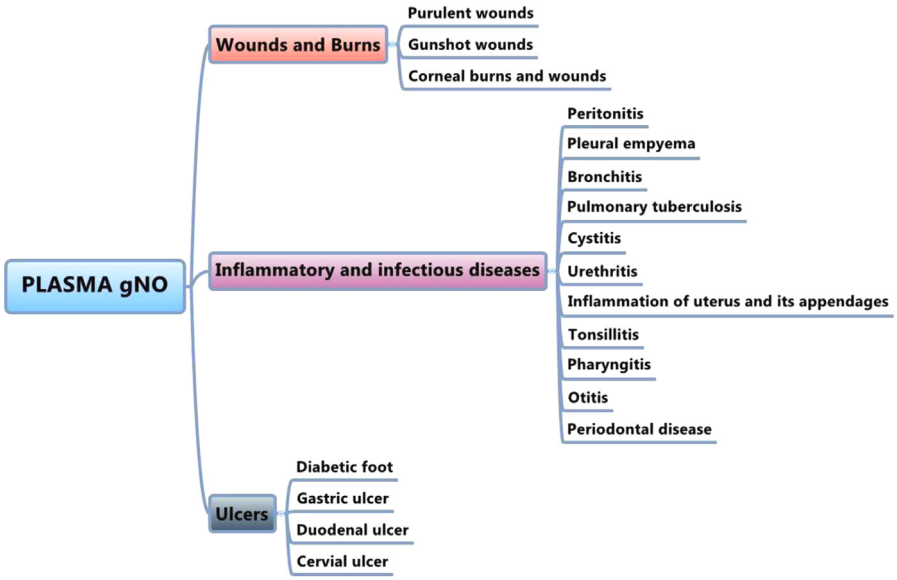

Fig. 1. Therapeutic applications of air plasma device "Plason".