White Paper

CHEMICAL AND BIOLOGICAL EFFECTS OF PLASMA/OZONE SYSTEMS FED WITH AMBIENT AIR AND PURE OXYGEN IN TOPICAL GAS INFUSION NEGATIVE PRESSURE WOUND THERAPY (NPWT)

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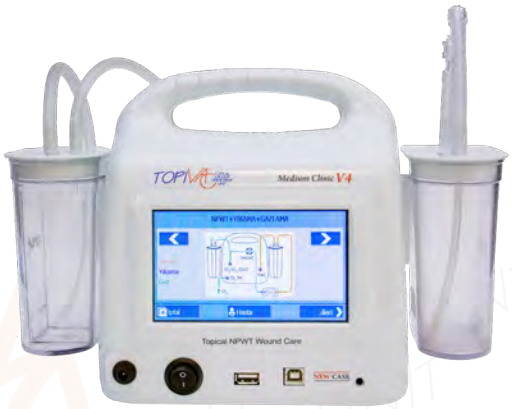

ABSTRACT

Topical Gas Infusion Negative Pressure Wound Therapy (NPWT) provides a synergistic mechanism for the management of chronic and infected wounds.

The synthesis quality of ozone (O_3) and reactive oxygen species (ROS), which are used as therapeutic agents in these systems, is directly dependent on the composition of the generator feed gas.

This white paper examines the chemical kinetics of the outputs generated when the ozone generator is supplied with pure medical oxygen (99.5% grade O_2) compared to ambient air (21% O_2, 78% N_2), as well as their histopathological effects on the wound bed and their implications for device mechanics.

The cytotoxic, necrotic, and protein-denaturing effects of nitrogen oxides (NO_x) and nitric acid (HNO_3) derivatives generated when ambient air is used as the feed gas are demonstrated at the molecular level through comparative parameters.

KEYS
NPWT, TENS, Irrigation, Ozone, Oxygen, Biofilm, Microcirculation, Granulation, Amputation

1. INTRODUCTION AND SYSTEM BACKGROUND

Chronic wounds (diabetic foot ulcers, pressure ulcers, and venous stasis ulcers) are characterized by local tissue hypoxia, persistent bacterial biofilms, and a prolonged inflammatory phase. While conventional NPWT systems promote wound healing by removing wound exudate, reducing edema, and stimulating granulation through microdeformation, next-generation devices have integrated topical oxygen/ozone gas infusion into this process.

Ozone (O_3), with its high oxidation potential ($E° = +2.07$ V), is a powerful antimicrobial and biofilm-disrupting agent. However, during ozone synthesis within a medical device using controlled electrical discharge (corona discharge or cold plasma), the purity of the gas entering the reactor chamber is the most critical parameter determining whether the gas mixture delivered to the wound bed will be therapeutic or cytotoxic.

2. REACTOR KINETICS AND GAS SYNTHESIS CHEMISTRY

In corona discharge reactors, gas molecules passing between two electrodes are exposed to a high-voltage electric field and converted into the plasma phase. Under these conditions, molecular bonds are broken, generating free radicals.

A. Pure Oxygen (O_2) Feed Kinetics

When only pure medical oxygen is supplied to the reactor chamber, the reaction pathway involves only oxygen allotropes:

$$O_2 + e^- \rightarrow 2O^{\bullet} \text{ -}$$

$$O^{\bullet} + O_2 + M \rightarrow O_3 + I$$

(Here, M represents a third body/molecule that absorbs excess energy during the reaction.)
As a result of this clean reaction pathway, the output gas consists exclusively of medical oxygen (O_2) and pure ozone (O_3). The formation of any by-products or foreign radicals is impossible.

B. Ambient Air Feed Kinetics (78% N_2, 21% O_2, 1% Ar, H_2O)

When ambient air is passed between the electrodes, the triple bonds (945 kJ/mol) of dinitrogen (N_2), the major component of air, are broken by the high-energy electrical discharge. This initiates the formation of a series of toxic gases known as nitrogen oxides (NO_x) in plasma chemistry:

$$N_2 + e^- \rightarrow 2N^{\bullet} + e^-$$

$$N^{\bullet} + O_2 \rightarrow NO + O^{\bullet}$$

$$NO + O_3 \rightarrow NO_2 + O_2$$

When the natural moisture present in ambient air (water vapor, H_2O) participates in this radical reaction pathway, the process becomes significantly more destructive. Free hydroxyl radicals (OH·) combine with nitrogen dioxide (NO_2) to form nitric acid (HNO_3) and nitrous acid (HNO_2) in the gas phase:

$$OH^{\bullet} + NO_2 \rightarrow HNO_3$$

$$LC_2O + 2NO_2 \rightarrow HNO_3 + HNO_2$$

As a result of these reactions, the generator output ceases to be a therapeutic gas. Instead, it becomes a corrosive gas mixture containing low concentrations of ozone together with high concentrations of nitrogen oxides and acidic vapors.

3. HISTOPATHOLOGICAL AND MOLECULAR EFFECTS ON THE WOUND BED

The interaction of the gas delivered to the wound through the NPWT infusion line with biological tissue directly initiates microscopic changes at the cellular level.

A. Chemical Burns, Coagulation Necrosis, and pH Disruption

The pH of a healthy wound bed ranges from 6.5 to 7.5 (slightly acidic to neutral), which is optimal for cellular migration. Nitric acid (HNO_3) vapor present in the gas mixture generated from ambient air rapidly dissolves in wound exudate. This causes the local wound bed pH to drop abruptly to below 4.0. Effect: This highly acidic environment causes chemical burns and coagulation necrosis in angiogenic (new blood vessel-forming) tissues within the wound bed. Granulation tissue becomes dull, pale, and loses its viability.

B. Cellular Cytotoxicity (Fibroblast and Keratinocyte Inhibition)

The primary cellular mediators of wound closure are dermal fibroblasts (responsible for collagen synthesis) and keratinocytes (responsible for epithelialization). Effect: The high concentrations of NO_2 and associated peroxynitrite ($ONOO_x$) radicals generated by air-fed systems induce lipid peroxidation in cell membrane lipids. As membrane integrity is compromised, fibroblasts lose their proliferative capacity and undergo apoptosis (programmed cell death). Consequently, wound healing enters a state of chronic stagnation.

C. Extracellular Matrix (ECM) and Protein Denaturation

Growth factors within the wound bed (VEGF, FGF, and PDGF) are protein structures linked by peptide bonds.
Effect: Nitric acid, being a strong inorganic acid, denatures the secondary and tertiary structures of these proteins by disrupting hydrogen bonds, thereby rendering them biologically inactive. As a result, collagen synthesis is inhibited, and the balance of matrix metalloproteinases (MMPs) shifts toward tissue degradation.

D. Difference from Physiological Nitric Oxide (NO)

One of the greatest misconceptions is confusing endogenous nitric oxide (NO), produced by macrophages, with the NO_x gases generated during corona discharge. Under physiological inflammatory conditions, macrophages produce NO at picomolar or low nanomolar concentrations, promoting vasodilation and immune signaling. In contrast, an air-fed ozone generator delivers uncontrolled concentrations of NO at the millimolar (ppm) level to the wound, accompanied by NO_2. This dosage is thousands of times higher than physiological levels and directly causes tissue destruction.

4. COMPARISON OF SYSTEM PARAMETERS

The table below clearly compares the technological, chemical, and biological performance metrics of the two different feed gas architectures.

TECHNICAL AND BIOLOGICAL PARAMETERS	PURE MEDICAL OXYGEN FEED (>99.5% O_2)	AMBIENT AIR FEED (~21% O_2)
Ozone Production Concentration	High (60–150 g/m³ / 6–15% by weight)	Low (10–30 g/m³ / 1–3% by weight)
Output Gas Composition	Pure O_3 + Pure O_2	O_3, O_2, N_2, NO, NO_2, N_2O, HNO_3
Effect on Wound Bed pH	Stable (Neutral / Slightly Acidic)	Severe Acidification (pH < 4.0 due to acid accumulation)
Tissue Response	Angiogenesis stimulation, Neovascularization	Chemical burns, Microvascular thrombosis, Necrosis
Cellular Proliferation	Fibroblast and Keratinocyte activation	Cellular toxicity, Reactive Nitrogen Species (RNS) damage
Biofilm and Bactericidal Effect	Selective high oxidation (Cell wall lysis)	Uncontrolled chemical corrosion (Including healthy tissue)
Device and Consumable Lifetime	Long service life (Corrosion-free pathways)	Very short (Nitric acid corrosion and salt deposition)

5. DEVICE MECHANICS, RELIABILITY, AND CORROSION ANALYSIS

The use of ambient air as the feed gas not only poses a risk to the patient but also directly compromises the structural integrity of the NPWT device.

Nitric Acid Sludge Formation and Short Circuits: Nitric acid (HNO_3) present in the gas phase condenses on the electrode surfaces within the reactor, forming microscopic moisture films. Over time, this moisture reacts with trace amounts of ammonia or metal ions in the environment, resulting in the formation of nitrate salts and an acidic sludge layer.

This accumulation causes dielectric breakdown within the corona discharge chamber, localizes electrical arcing, and ultimately leads to short circuits and permanent generator failure.

Degradation of Consumables and Valve Components: The precision solenoid valves, manifolds, and wound dressing components (drapes, connectors) used in NPWT systems to regulate negative pressure and gas flow contain polyurethane and silicone materials. When exposed to nitric acid vapor, these polymers rapidly undergo degradation through polymer chain scission.

As a consequence, internal gas leakage develops within the device, leading to failure of the pressure control algorithms (mmHg) and compromising the overall performance of the NPWT system.

6. CONCLUSION AND CLINICAL RECOMMENDATIONS

In Topical Gas Infusion Negative Pressure Wound Therapy (NPWT) systems, clinical efficacy and patient safety are two fundamental requirements that cannot be compromised. Chemical reactor analysis and histopathological tissue evaluations clearly demonstrate that the use of ambient air in ozone generators results in the direct delivery of toxic nitrogen oxides and nitric acid vapor to the wound bed. This practice is unacceptable because it completely impairs chronic wound healing, destroys healthy cells, and causes corrosion-related damage to the device hardware.

Clinical and Industrial Standard:

In advanced wound care systems, the industrial standard is to supply the reactor with medical-grade oxygen of at least 93%–99.5% purity, provided either by an integrated oxygen concentrator or an external oxygen cylinder.

By delivering only pure O_2 and controlled O_3 to the wound bed, the bactericidal properties of ozone can be utilized effectively. Subsequently, as ozone rapidly decomposes into pure oxygen within the tissue, cellular proliferation can be maximized.

The complete elimination of nitrogen from the reaction process is an absolute prerequisite for the therapeutic success of this technology.