Non-invasive Physical Plasma (NIPP) for Center Prevention: From Preclinical Insights to Clinical Application

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Abstract: Non-invasive physical plasma (NIPP) shows promise in treating cervical intraepithelial neoplasia (CIN) with minimal side effects. Preclinical studies identified ferroptosis as a key mechanism of plasma-induced cell death. Clinical trials demonstrated high remission rates, in CIN I-III patients, compared to 5% in controls. NIPP also resulted in significant HPV clearance highlighting its potential as an effective, non-invasive alternative for CIN and other precancerous conditions like vulvar intraepithelial neoplasia (VIN).

1. Introduction

Cervical intraepithelial neoplasia (CIN) represents a spectrum of precancerous changes driven by persistent human papillomavirus (HPV) infection. Without intervention, CIN can progress to invasive cervical cancer, which causes approximately 270,000 deaths annually worldwide (1). Current treatment approaches are invasive, often leading to complications such as bleeding, infertility, and obstetric issues. Non-invasive physical plasma (NIPP), capable of generating reactive oxygen and nitrogen species (RONS), offers a novel therapeutic approach. Preclinical and clinical investigations have demonstrated its potential to address CIN effectively and safely.

2. Methodology

Preclinical studies characterized plasma properties using an argon-based electrosurgical instrument under various gas compositions and humidities. Key plasma parameters, including electron density, gas temperature, and RONS production, were measured. The ferroptosis pathway was explored in cervical cancer cells treated with plasma-activated medium (PAM), focusing on the role of oxidative stress, iron dependency, and the degradation of ferroptosis suppressor protein (FSP1). Clinical trials assessed NIPP in patients with CIN I-III. The procedure involved superficial cervical treatment with argon plasma under colposcopic guidance, targeting abnormal tissue without excision. Remission rates, HPV clearance, and cytological normalization were evaluated at three and six months post-treatment. Control groups were included for comparison, reflecting spontaneous remission rates.

3. Results

Preclinical findings demonstrated that plasma treatment consistently produces electron densities of approximately 10^{16} cm^{-3} and gas temperatures around 1500 K, both of which are critical parameters for determining the effectiveness of plasma in therapeutic applications. The generation of reactive oxygen and nitrogen species (RONS) in plasma-treated solutions (PTS) was found to be influenced by the surrounding gas composition. Specifically, higher concentrations of argon in the plasma reduced the production of nitrite and nitrate, indicating that the presence of different gases can significantly impact the types of reactive species formed during treatment. Further investigation into the biological mechanisms revealed that ferroptosis, a form of iron-dependent programmed cell death, plays a significant role in plasma-induced cytotoxicity. This process is modulated by intracellular oxidative stress, as plasma treatment increases the generation of reactive species that induce lipid peroxidation. Moreover, ferroptosis is influenced by intracellular iron levels, with plasma exposure exacerbating oxidative damage when iron is abundant, thereby triggering cell death. These findings emphasize the role of oxidative stress and ferroptosis in driving the therapeutic efficacy of plasma treatment.

The clinical study showed that NIPP achieved high remission rates across CIN grades. For CIN I-II, remission was 86.2% in treated patients compared to 40.4% in controls. Among CIN III patients, remission reached 44.0%, markedly higher than the 5.0% spontaneous remission in controls. High-risk HPV clearance and cytological normalization were significant in treated groups.

4. Conclusions

NIPP represents a groundbreaking non-invasive approach for CIN treatment, demonstrating effectiveness across CIN I-III and a substantial reduction in high-risk HPV prevalence. Preclinical studies highlighted ferroptosis as a key mechanism, guiding clinical applications. Clinical outcomes show high remission rates, particularly in advanced CIN III, with minimal side effects, suggesting NIPP's potential to replace invasive procedures. Its application warrants further exploration in other precancerous conditions such as vulvar intraepithelial neoplasia (VIN).

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