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The Negative Impact of Vaping and Electric Cigarettes for Healing of Chronic Wounds: A Literature Review

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ABSTRACT

Non-smokers, particularly adolescents, face significant public health risks from e-cigarette use due to immediate health hazards, the potential for initiating tobacco use, and insufficient data on critical health outcomes, including wound healing. This study investigates vaping's impact on chronic wound healing, emphasizing e-cigarette chemical components. E-cigarettes contain common constituents: 1) Base liquids: Propylene glycol (PG) and vegetable glycerin (VG), 2) Nicotine, 3) Flavoring chemicals and additives, 4) Trace contaminants and toxins. Chronic wounds exhibit persistent inflammation, impaired proliferation, delayed remodeling, and environmental factors (e.g., ischemia, infection, trauma). E-cigarette components impair wound healing: VG induces osmotic effects and cellular toxicity, nicotine causes vasoconstriction, reduced oxygenation, and impaired angiogenesis. Flavoring chemicals contribute to cytotoxicity and modulate inflammatory responses, while contaminants like heavy metals induce oxidative stress and inflammation. Despite e-cigarettes' lower harm compared to traditional cigarettes, their effects on chronic wound healing remain poorly understood. Further research is essential to elucidate smoking's precise impact on chronic wound healing.

KEYWORDS: e-cigarettes, chronic wound, wound healing, cigarette smoking, nicotine

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INTRODUCTION[1-3]

Wound healing represents a fundamental physiological process essential for restoring tissue integrity following injury, involving a complex biochemical cascade. Chronic wounds, characterized by persistent tissue injury resistant to standard treatment modalities, pose substantial financial burdens on patients and healthcare systems. Estimates indicate a staggering cost of nearly US$50,000 per diabetic ulcer and an annual burden exceeding US$25 billion for chronic wounds globally. This problem is exacerbated by the rising prevalence of conditions such as diabetes and other chronic diseases, which impair wound healing processes.

Conventional smoking stands out as a prominent behavioral risk factor across various health domains due to its deleterious effects on human physiology. It is widely recognized as a significant risk factor for perioperative complications related to wound healing, contributing to prolonged healing times and increased susceptibility to wound infections. With growing awareness of the hazards associated with traditional cigarette smoking, alternative nicotine delivery systems, such as e-cigarettes, are gaining popularity. Marketed as ostensibly "safer" alternatives, e-cigarettes are perceived as less harmful than traditional cigarettes. However, emerging evidence suggests that e-cigarettes may induce similar physiological changes to conventional smoking and exert detrimental effects on wound healing mechanisms. Recent investigations reveal that e-cigarettes can impede tissue oxygenation akin to traditional cigarettes, as evidenced by reduced subcutaneous blood flow following e-cigarette use.

While the adverse effects of smoking on wound healing are well-established, the implications of e-cigarette use remain unclear. Studies examining the potential detrimental effects of e-cigarettes on wound healing outcomes have identified various hazardous substances present in these products. Of particular concern is the increasing use of e-cigarettes among non-smokers, including adolescents, raising public health alarms due to associated health risks and the potential gateway effect leading to tobacco smoking initiation. Mounting evidence suggests that vaping may share physiological similarities with traditional cigarette smoking,

thereby posing significant impediments to wound healing processes.

This study aims to elucidate the potential impact of vaping on wound healing, with a specific focus on chronic wounds within the realm of plastic surgery. By investigating the effects of e-cigarette use on wound healing dynamics, this research endeavors to fill critical gaps in understanding the implications of vaping for wound management strategies.

Overview of Vaping Devices and Chemical Composition[4-9]

In recent years, electronic cigarettes (e-cigarettes) have experienced a significant rise in popularity within the tobacco market. E-cigarettes function by simulating smoking through technical means, eliminating the combustion of tobacco. These devices typically consist of a power unit, an electric atomizer, and a replaceable cartridge containing a liquid that vaporizes upon inhalation through the mouthpiece.

The primary components of e-liquid formulations include propylene glycol, glycerine, various flavors (such as tobacco, fruit, chocolate, menthol, rum, coca cola, piña colada, ice cream, and candy floss), and typically nicotine, although nicotine-free options are also available. While these ingredients are generally recognized as safe for consumption in food, concerns arise regarding their safety when repeatedly inhaled over an extended period, as is the case with e-cigarette use.

Nicotine-containing liquids pose inherent risks due to the toxic and addictive nature of nicotine. However, even nicotine-free e-liquids may not be entirely benign. The main constituents, including propylene glycol, glycerine, and flavorings, have received regulatory approval for food use, yet this does not automatically ensure safety when inhaled over time, as in e-cigarette usage scenarios.

Currently, the long-term health effects of e-cigarette use remain uncertain, as there is a lack of comprehensive studies on the subject. The potential risks associated with each component of e-liquids warrant closer examination to assess their impact on human health over prolonged exposure periods. While some research has begun to outline potential health hazards associated with e-cigarette use, further investigation is necessary to fully understand the implications of long-term exposure to these substances, particularly in the context of vaping.

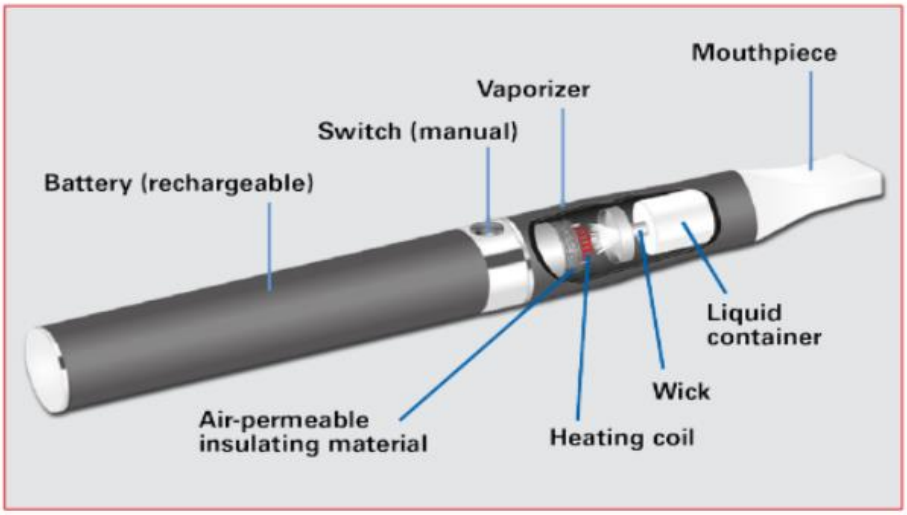

Figure 1. Components of electronic cigarettes[4]

Biological Process in Chronic Wound Healing[5-9]

Wound healing progresses through three distinct phases: the inflammatory phase, the proliferative phase, and the remodeling phase. Immediately after trauma, the inflammatory phase aims to eliminate dead tissue and prevent bacterial invasion. Acute inflammatory cells and neutrophils invade the wound site, triggering an inflammatory reaction characterized by tumor, calor, rubor, dolor, and functio laesa. The proliferative phase involves granulation tissue formation, angiogenesis, and extracellular matrix (ECM) deposition. Growth factors like vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) promote the growth of endothelial cells and fibroblasts, facilitating new blood vessel formation and collagen synthesis. The final phase, maturation and remodeling, encompasses scar tissue development and modification through ECM deposition and breakdown, a process that can take months or even years to complete.

Effective wound healing requires meticulous management; however, several factors can impede the process, leading to delayed healing. Excessive inflammation is a key contributor to wound pathology, perpetuating chronicity by causing ongoing tissue damage. Chronic wounds are characterized by high levels of neutrophils, pro-inflammatory macrophages, proteases, and Langerhans cells. Dysregulated immune cell function and elevated levels of specific immune cell subsets hinder proper repair. Neutrophils, when excessively primed, form extracellular traps that delay healing due to their cytotoxic nature. Elevated levels of wound proteases degrade ECM components and growth factors, further impairing

healing. Additionally, chronic wound fibroblasts exhibit reduced responsiveness to ECM-stimulating factors and increased senescence, exacerbating ECM deposition impairment.

Ischemia is a significant factor in wound healing impairment, primarily in chronic wounds. Reduced angiogenesis, tissue perfusion, and pressure-related ischemia contribute to wound hypoxia, prolonging inflammation and exacerbating tissue damage. Elevated levels of matrix metalloproteases in chronic wounds degrade tissue and hinder normal healing processes. Inflammatory cell accumulation and increased reactive oxygen species (ROS) production negatively impact ECM structure and cellular function, impeding tissue regeneration and closure.

Persistent wound infection, particularly by pathogens like Staphylococcus aureus and Pseudomonas aeruginosa, contributes to chronicity. Biofilm formation by these pathogens confers resistance to host defenses and antibiotics, prolonging inflammation and hindering healing. Abnormal activation of keratinocytes and production of senescence-associated secretory phenotypes (SASPs) further impair healing by increasing inflammation and oxidative stress. Elevated levels of advanced glycation end products (AGEs) in the wound environment also promote cellular senescence and inflammation, exacerbating tissue deterioration.

Repeated trauma and neuropathy exacerbate wound chronicity by attracting inflammatory cells to the wound bed and increasing protease production. Excessive protease activity in chronic wounds leads to ECM degradation, preventing progression to the proliferative phase and intensifying inflammation. Maintaining airway epithelial integrity is crucial for preventing infection and ensuring proper mucociliary clearance. E-cigarette aerosols interfere with essential processes for healthy mucociliary clearance, potentially exacerbating wound healing complications. Overall, understanding these factors is essential for developing effective strategies to promote timely and successful wound healing.

Biological Impact of Vaping on Chronic Wound Healing[10-14]

As previously described, electronic cigarette liquids (e-liquids) typically contain vegetable glycerin (VG) and propylene glycol (PG), common delivery vehicles, along with flavorings and nicotine. Both glycerol and propylene glycol irritate the airways. Many flavored e-liquids and their flavoring chemicals are cytotoxic, harming animal models' lungs. High nicotine concentrations in e-liquids can harm adults and children via ingestion, topical application, or inhalation. Short-term effects of nicotine exposure include tremors, elevated blood pressure, heart and respiratory rates, and heightened alertness. The vasoconstrictive properties of nicotine may cause tissue oxygen deficiency, peripheral vasoconstriction, and decreased tissue blood perfusion. It stimulates thromboxane production, constricting and narrowing arteries, hindering blood and nutrient delivery to wounds and medication administration for surgical site infections. Nicotine use compromises the immune system, promoting bacterial growth and biofilm formation, increasing infection risk, and delaying wound healing.

Various flavors are available for e-liquids, with menthol, ethyl vanillin, vanillin, cinnamaldehyde, and ethyl maltol being commonly used. Despite being considered safe for oral consumption, there is insufficient evidence regarding the safety of inhaling aerosolized flavoring ingredients, suggesting potential inhalation hazards. Aerosolized flavorants may produce tiny particles that deeply enter the lungs, increasing pro-inflammatory cytokines and reactive oxygen species (ROS) production, impacting wound healing. Copper nanoparticles found in e-cigarette vapes can alter mitochondrial reactive oxygen species (mtROS), damaging mitochondrial DNA and hindering wound healing through inflammatory milieu alterations.

Despite limited objective data, e-cigarettes should be treated like tobacco cigarettes, with vaping cessation recommended in the perioperative period to reduce wound healing complications. Similarities in chemical composition and detrimental effects between e-cigarettes and traditional smoking suggest comparable impacts on wound healing. Further research on the impact of e-cigarette on surgical outcomes and wound healing is needed.

Review of Clinical and Experimental Evidence[15-17]

The prevalence of electric cigarette (e-cigarette) usage has surged dramatically in recent times, coinciding with the emergence of evident toxic effects associated with their use. In 2018, both the US Surgeon General and the Food and Drug Administration (FDA) officially declared teenage e-cigarette usage an epidemic. According to a national survey conducted in 2021 on youth tobacco consumption, over 2 million American teenagers are current e-cigarette users, comprising 11.3% of high school students and 2.8% of middle school students. Of particular concern is the increasing preference for flavored e-cigarettes among users, soaring from 65.1% in 2014 to 84.7% in 2020. Various enticing flavors like fruit, mint, and menthol have especially captivated the youth demographic.

The onset of e-cigarette or vaping product use-associated lung injury (EVALI) cases in the United States from August 2019 onwards further underscores the risks associated with e-cigarette consumption. By February 18, 2020, EVALI had resulted in 2807 hospitalizations and 68 fatalities. Alarmingly, over half of the affected individuals were teenagers (15%) or young adults (37%), primarily engaging in excessive consumption of flavored and nicotine-containing e-cigarettes. Despite this, the underlying mechanisms behind EVALI remain poorly understood.

It is firmly established that smoking during the perioperative period detrimentally affects surgical outcomes. Specifically,

in plastic surgery procedures, nicotine significantly heightens the risk of complications such as skin flap necrosis and surgical site infections. For instance, smokers undergoing facelifts face a 13-fold increase in the risk of skin flap necrosis compared to nonsmokers. Similarly, smokers undergoing TRAM breast reconstruction exhibit elevated rates of mastectomy and abdominal skin flap necrosis, particularly among those with a smoking history of 10 pack-years or more. Notably, patients undergoing head and neck reconstruction experience significantly elevated wound complications when preoperative cotinine levels exceed 10 mg/dL, indicating a tangible threshold for the potential benefits of smoking cessation interventions.

Controversy persists regarding the impact of cigarette smoking on free flap outcomes, with conflicting findings. Some studies suggest smoking diminishes rates of microvascular anastomosis patency, leading to increased flap loss, while others find no such effect. Rinker comprehensively summarized the negative effects of smoking on a wide array of plastic surgery procedures in 2012.

With growing recognition of the detrimental effects of traditional cigarette smoking, alternative nicotine delivery methods are gaining traction. E-cigarettes, marketed as "healthier" and "cleaner" alternatives, are often perceived as less harmful than traditional cigarettes. However, nicotine delivery via e-cigarettes may be comparable to traditional cigarettes, albeit with discrepancies in labeled versus actual nicotine content and in plasma nicotine levels. Notably, e-cigarette vapor has been shown to exert cytotoxic effects on endothelial cells, irrespective of nicotine presence. Furthermore, while some studies report decreased nitrosamine levels in certain e-cigarette brands, significant variability persists among different brands, with some containing even higher nicotine levels than traditional cigarettes. Moreover, evidence suggests that e-cigarettes may impair tissue oxygenation similar to traditional cigarettes, as demonstrated by decreased subcutaneous blood flow in study subjects following e-cigarette use.

DISCUSSION[18-22]

Nicotine, hydrogen cyanide, and carbon monoxide are primary toxins associated with impaired wound healing. Their specific mechanisms causing delayed healing remain elusive, but they all impede tissue oxygenation. Nicotine, a colorless alkaloid swiftly absorbed during smoking, is extensively studied for its vasoconstrictive properties, notably diminishing blood flow. It induces the release of catecholamines from the sympathetic nervous system, reducing tissue perfusion and causing peripheral vasoconstriction. Moreover, catecholamines promote platelet aggregation, elevating blood viscosity and further impairing tissue perfusion. However, conflicting data exist regarding nicotine's effects on tissue perfusion and wound healing, challenging its sole attribution to vasoactive effects.

Recent research questions nicotine's exclusive role in reducing blood flow, tissue hypoxia, and subsequent wound complications. Intravenous infusion of 1.0 mg of nicotine, comparable to nicotine replacement therapy, transiently increased epidermal blood flow but drastically decreased subcutaneous blood flow, with no impact on tissue aerobic metabolism. Such findings, supported by other studies, suggest nicotine replacement therapy doesn't hinder acute wound healing unless administered in toxic doses, implying additional factors contribute to smoking's vasoactive effects and its connection to poor wound healing.

Smoking profoundly affects cellular activities during wound healing. Cigarette smoke reduces erythrocyte, white blood cell, and fibroblast proliferation. Diminished erythrocytes limit oxygen availability, inducing tissue hypoxia. White blood cells, particularly macrophages, crucial for phagocytosis and cytokine production, exhibit reduced activity due to smoking, impairing healing processes. Smoking also hampers fibroblast proliferation, crucial for collagen and fibronectin production, essential for granulation tissue formation and epithelialization. Smokers produce less collagen, diminishing wound tensile strength.

Collectively, these findings strongly implicate smoking in hindering wound healing, especially acute wounds. However, the impact on chronic wounds remains less explored, although evidence links smoking to increased pressure ulcer risk in individuals with spinal cord injuries. Proposed models illustrate smoking's adverse effects on chronic wound healing in conditions like diabetes, venous dysfunction, or prolonged pressure exposure, necessitating further research for clarity. Clinicians managing chronic wounds could benefit from evidence-based treatment recommendations outlined in clinical practice guidelines.

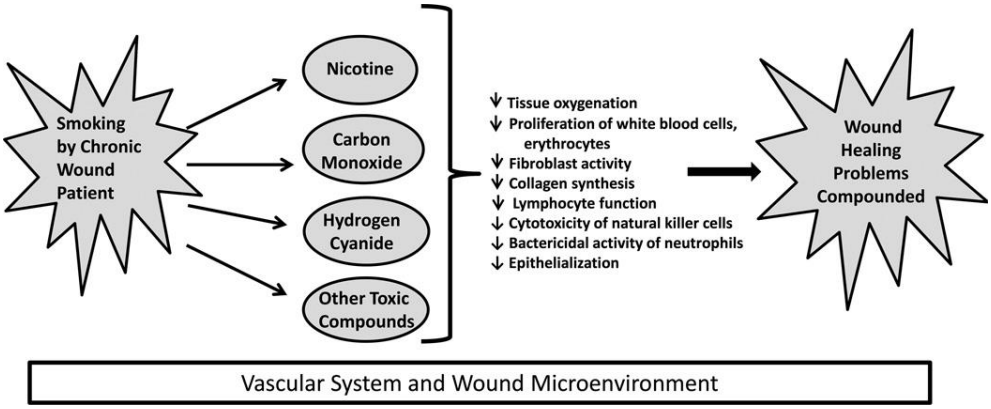

Figure 2. Detrimental effects of smoking on healing chronic wounds[22]

CONCLUSION

Data suggests that e-cigarettes could potentially impede wound healing comparably to traditional cigarettes. This is likely attributed to a multifaceted mechanism involving nicotine-induced vasoconstriction, leading to the development of a hypoxic tissue milieu. Despite yielding fewer side effects compared to conventional tobacco cigarettes, e-cigarettes are posited as a plausible alternative. However, the influence of smoking on chronic wound healing remains inadequately understood. Additional investigation is imperative to elucidate the precise impact of smoking on the healing dynamics of chronic wounds. Such research could provide valuable insights into optimizing wound management strategies for individuals with a history of smoking.

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