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

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ABSTRACT

Emerging evidence suggests that vaping can significantly impede wound healing, with prevalence rates of current e-cigarette use varying between 3.3% and 11.8%. This study aims to investigate the impact of vaping on wound healing, particularly in acute wounds encountered in plastic surgery settings. Electronic cigarettes (e-cigarettes), comprising a rechargeable battery and an atomizer or heating element, typically contain flavored liquids with or without nicotine as humectants. Skin wounds heal through overlapping inflammatory, proliferative, and remodeling phases. Chemical constituents of e-cigarettes, including propylene glycol (PG), vegetable glycerin (VG), nicotine, flavoring agents, and contaminants, hinder wound healing by inducing osmotic effects, cellular toxicity, vasoconstriction, reduced oxygen supply, impaired angiogenesis, cytotoxicity, and modulation of inflammatory responses. Similar to conventional cigarettes, e-cigarettes may compromise wound healing through a multifaceted mechanism, although they may offer a comparatively less harmful alternative.

KEYWORDS: E-cigarettes, acute wound, wound healing, cigarette smoking, nicotine

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INTRODUCTION

The act of burning tobacco and inhaling the smoke, the activity widely known as tobacco smoking, will cause the related substances enter the bloodstream. Approximately 23% of people worldwide smoke cigarettes.[1] Smoking cigarettes has several detrimental effects on the healing of wounds. Since the 1940s, there has been mounting evidence that smoking impairs tissue repair and wound healing. Smoking has also been connected to longer-term consequences like fistulas and incisional hernias. According to numerous studies, smokers experience more postoperative problems than non-smokers.[2]

Electronic nicotine dispensing systems (ENDS), also referred to as electronic cigarettes or e-cigarettes, have gained widespread acceptance as a less dangerous option to traditional cigarette smoking since they initially hit the market more than ten years ago. There is a prevalent belief that using e-cigarettes, or "vaping," is safer than smoking traditional cigarettes since they don't require combustion and because most of the negative consequences of tobacco are caused by this reaction.[3] The prevalence of current e-cigarette uses ranges from 3.3% to 11.8%.[4] Evidence of the negative effects of using e-cigarettes is beginning to emerge, indicating that vaping may do significant harm to wound healing and may cause some of the same physiological changes as smoking regular cigarettes.[5] This study aims to explore how vaping may impact wound healing, particularly in the context of acute wounds in plastic surgery.

OVERVIEW OF VAPING DEVICES AND CHEMICAL COMPOSITION

Electronic cigarettes (e-cigarettes) are electronic devices that basically consist of a rechargeable battery, an atomizer or heating element to heat the electronic cigarette liquid (e-liquid) and produce a vapour that may be breathed through a mouthpiece, and a cartridge filled with e-liquid (see **Figure 1**).[5]

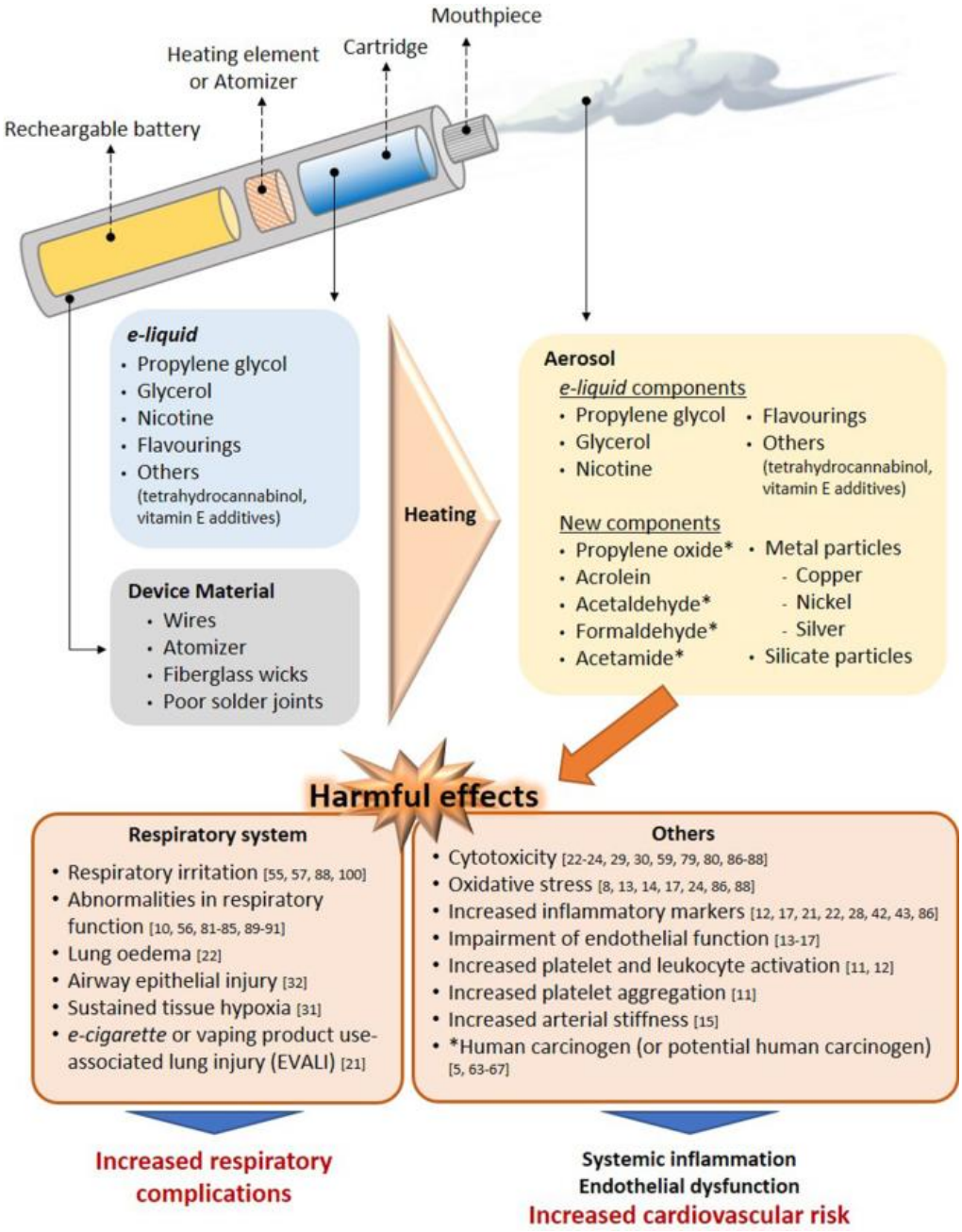

Figure 1. Effect of the heating process on aerosol composition[6]

Typically, e-liquids contain flavorings and humectants, either with or without nicotine. When the atomizer produces vapour, the aerosol produces a sensation similar to smoking tobacco, but supposedly without any negative effects.[7,8] The study claimed that users of e-cigarettes exhaled higher amounts of nitrous oxide (NO) and experienced more severe airway inflammation due to the nicotine in the devices; however, there were no differences in the amounts of carbon monoxide (CO), a marker of oxidative stress, exhaled before and after using an e-cigarette.[9] In a more recent human study, the urine of adolescents who used both e-cigarettes and traditional tobacco was found to contain much higher levels of metabolites of dangerous substances like benzene, ethylene oxide, acrylonitrile, acrolein, and acrylamide than that of adolescents who used e-cigarettes exclusively. Additionally, e-cigarette only users had urine levels of metabolites of acrylonitrile, acrolein, propylene oxide, acrylamide, and crotonaldehyde that were up to twice as high as those of non-smoker subjects. All of these metabolites are harmful to human health.[10]

The main addictive ingredient in tobacco, nicotine, can also be found in different concentrations in the commercially available e-liquids; nicotine-free versions are also offered.[8,11] For example, discrepancies in the amount of nicotine compared to the manufacturer's claim were found using gas chromatography with a flame ionization detector (GC-FID) (average of 22 ± 0.8 mg/mL vs. 18 mg/mL).[9] This means that the content is approximately 22% greater than what is stated on the product label.[12] Glycerol, also known as glycerine (propane-1,2,3-triol), and propylene glycol (PG, or 1,2-propanediol), are the most prevalent and important ingredients in e-liquids. Both kinds of chemicals are categorized and put into "*generally recognized as safe*"

(GRAS) list by the Food and Drug Administration (FDA) and are utilized as humectants to keep the e-liquid from drying out. Other substances found in aerosols include certain aldehydes and acetamide, a possible human carcinogen. However, these compounds were found in very little amounts.[12]

An increasing number of people are concerned about their health and are drawn to e-cigarettes due to the wide variety of flavors that are available to consumers.[13] Although they are typically not listed on product labels, the long-term effects of all 15,000+ flavor compounds utilized by this sector are yet unclear. Moreover, there is no assurance of safety as they might include potentially harmful or irritating properties.[12] A few studies have addressed the material of the electronic device and its potential consequences—specifically, the potential presence of metals such as copper, nickel or silver particles in e-liquids and aerosols originating from the filaments and wires and the atomiser.[14]

PATHOPHYSIOLOGY OF WOUND HEALING

A skin wound results from the breakdown of the epidermal layer integrity. Any tissue injury with anatomical integrity disruption with functional loss can be described as a wound. Wound healing mostly means healing of the skin, begins immediately after an injury to the epidermal layer and might take years. This dynamic process includes the highly organized cellular, humoral, and molecular mechanisms. Wound healing has 3 overlapping phases which are inflammation, proliferation, and remodeling.[15]

1. Inflammation

   During this stage, inflammation and hemostasis manifest. Upon skin injury, clotting cascades activate immediately, temporarily sealing the wound with a fibrin blood clot. Simultaneously, the wounded area undergoes a brief period of vasoconstriction, lasting 5-10 minutes, to safeguard the wound and halt further bleeding. Furthermore, the fibrin plug generated serves as a temporary matrix, facilitating subsequent healing processes by facilitating the migration of endothelial cells, fibroblasts, leukocytes, and keratinocytes, and serving as a reservoir of growth factors. Subsequent to this transient vasoconstriction response, localized hyperemia and edema occur due to vasodilation. The initiation of inflammation and the completion of hemostasis are mediated by the secretion of chemotactic and growth factors. Neutrophils are recruited to the injured site within the initial 24 hours and persist for 2 to 5 days, initiating phagocytosis, subsequently continued by macrophages. These phagocytic cells release reactive oxygen species (ROS) and proteases to eliminate local bacteria and debride necrotic tissues. Additionally, neutrophils serve as chemoattractants for other cells, augmenting the inflammatory response by releasing various pro-inflammatory cytokines. Macrophages typically arrive around 3 days post-injury, similarly releasing numerous growth factors, chemokines, and cytokines that foster cell proliferation and the synthesis of extracellular matrix (ECM) molecules.[15,16]

2. Proliferation

   During the proliferative phase, granulation tissue forms and the vascular network restores, commencing approximately 3 to 10 days post-injury and continuing for days or weeks. Various cytokines and growth factors, including members of the transforming growth factor-beta family (TGF-β1, TGF- β2, and TGF- β3), interleukins (ILs), and angiogenesis factors, play roles in this phase. Fibroblasts and endothelial cells are the predominant proliferating cells, while angiogenesis and vasculogenesis mechanisms initiate vessel formation. Endothelial progenitor cell (EPC) recruitment into circulation begins post-injury, facilitated by nitric oxide (NO), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs), particularly MMP-9. Stromal derived factor 1-alpha (SDF1-alpha) acts as the main homing signal guiding EPCs to ischemic areas, where they contribute to new vascular network formation, facilitating nutrient delivery and gas exchange. Concurrently, epithelization is stimulated by inflammatory cytokines and growth factors following injury. Local keratinocytes at the wound edge and epithelial stem cells in hair follicle bulbs and apocrine glands participate in epithelization. Stem cells differentiate into keratinocytes, which migrate over the wound edge until contact with neighboring keratinocytes inhibits further migration. The final step of the proliferative phase involves granulation tissue formation, as fibroblasts migrate to the wound site, proliferate, and synthesize a provisional matrix containing collagen type III, glycosaminoglycans, and fibronectin.[16-18]

3. Remodeling

   Remodeling is the last phase of the wound healing, begins from day 21 and continues up to 1 year. During the remodeling phase, the granulation tissue formation ends, and the maturation of the wound begins. ECM components exposed to some certain modifications to form a stronger and organized ECM. Remaining cells of the previous phases undergo apoptosis.[18] additionally, wound contraction begins. TGF-beta1 stimulates the fibroblasts to differentiate into myofibroblasts. Besides synthesizing major ECM proteins such as collagen types I to VI and XVIII, glycoproteins and proteoglycans, myofibroblasts participate in wound contraction. Finally, angiogenic responses cease, the blood flow diminishes. Acute metabolic activity in the wound ends.[19]

IMPACT OF VAPING ON WOUND HEALING

The general consensus maintains that propylene glycol (PG) is deemed "practically non-toxic," a viewpoint consistent with its inclusion by the FDA in the GRAS list. Although most of the studies supporting this assertion were conducted decades ago and may not align with current "*good laboratory*

practices" standards, their use of large doses, combined with the consistent absence of evidence indicating organ system effects or reproductive or developmental toxicity, strongly supports the overall lack of toxic effects associated with PG exposure in humans, whether through diet or occupation. However, limited yet consistent evidence from case reports suggests that extremely high doses of orally or intravenously administered PG to humans can result in toxic effects, likely attributed to changes in blood osmolality and the formation of lactic acid as a result of PG metabolism.[20]

Smoking is particularly harmful to the healing process as it impacts blood flow and oxygenation. The byproducts of smoking include nicotine, carbon monoxide and hydrogen cyanide. Nicotine causes the arteries to spasm and become narrow. When an artery that sends blood to the skin is narrow, it is not able to bring blood and nutrients to a wound which are needed for healing. It may also prevent the delivery of medicine used to treat surgical site infection. Smoking and nicotine use also impacts the immune system. The immune system is critical to the healing of the surgical site as it is required to fight illness and infection. As a result of smoking, the cells and antibodies that protect the body and wound against bacteria become weak. This makes it easier for the growth of bacteria and biofilm within the wound, increasing the risk of infection and delays wound healing.[20]

While the Flavor and Extracts Manufacturers Association deems many flavors as GRAS in food products; however, when aerosolized and inhaled, these chemicals may pose harm, as safety testing typically focuses on ingestion. Flavoring in tobacco products entices users and may prompt experimentation or initiation of tobacco use. Reactive oxygen species (ROS), including free radicals, arise from normal biological processes and external sources like tobacco smoke, inducing oxidative stress that impairs cellular processes and health. E-cigarette users may encounter both highly reactive and stable ROS during device operation, as heating elements activate and aerosolize e-liquids, generating ROS.[22]

CLINICAL EVIDENCE

Alanazi and colleagues conducted a study wherein they collected biopsies of healthy gingival connective tissue and exposed them to e-liquid vapor and cigarette smoke. The study revealed that both types of vapor condensate negatively affect gingival fibroblast migration, proliferation, and wound healing.[23] Shaikh and colleagues investigated the effects of e-cigarettes on normal and cancerous monolayer and 3D models of human oral mucosa, as well as oral wound healing, after short-term (3 days) and medium-term (7 days) exposure. Their findings indicated that medium-term exposure to high concentrations of e-liquid (10%) prolonged wound healing in normal human oral fibroblasts, oral keratinocytes, and oral mucosa cells.[24]

Various studies examined by Ralho and colleagues in a systematic review revealed an increase in bleeding on probing among nonsmokers compared to both conventional cigarette smokers and e-cigarette users, with no discernible differences between the latter two groups. This phenomenon might arise from the presence of nicotine, eliciting vasoconstriction in gingival blood vessels, thereby diminishing hemorrhage, impeding cellular healing, and suppressing early gingivitis signs and symptoms.[25] In vitro investigation by Willershausen and colleagues underscored the potential harm certain e-cigarette additives pose to cell proliferation. While flavors like lime or hazelnut appeared innocuous to cell viability and proliferation, menthol e-liquid formulations significantly compromised fibroblast function.[26]

There is a severe paucity of data on the impact of e-cigarette use on surgical outcomes and wound healing. One such study examined skin flap survival using a rat model exposed to e-cigarettes in a smoking chamber, where nicotine containing e-cigarettes were found to negatively impact skin flap survival and tissue perfusion.[27] When compared to controls, significantly higher rates of dorsal skin flap necrosis were found in rats exposed to nicotine containing e-cigarettes and tobacco cigarettes. Of note, clinicians found similar rates of dorsal skin flap toxicity and necrosis between e-cigarette and tobacco smoke exposed groups, illustrating the deleterious effects of nicotine exposure on wound healing. Tissue hypoxia was also significantly higher in e-cigarette and tobacco cigarette exposed groups compared to non-exposed control.[28]

An intriguing finding from a systematic review indicates that while nicotine seems to negatively impact inflammation in wound models, there is insufficient evidence to confirm any adverse or favorable effects on postoperative wound or tissue healing outcomes.[29] Remarkably, no substantial studies have reported adverse effects of e-cigarette usage on wound healing, cardiovascular incidents, or respiratory complications in human subjects. Upon conducting an extensive literature review, the examination of surgical outcomes linked with e-cigarette usage remains confined to a small collection of case reports. For instance, one case report portrays a woman with a 25-pack-year history of tobacco smoking who transitioned to e-cigarettes three months before surgery, encountering notable skin flap necrosis and unsuccessful breast reconstruction following bilateral mastectomy with immediate tissue expander reconstruction for breast cancer.[5] Another case study associates perioperative e-cigarette utilization with postoperative vasospasm. In this instance, a woman undergoing bilateral mastectomy with transverse rectus abdominis musculocutaneous (TRAM) flap reconstruction for intraductal carcinoma suffered recurrent episodes of postoperative vasospasm, necessitating a return to the operating theater for surgical exploration of the anastomosis.[5] Additionally, a study revealed that e-cigarettes containing nicotine compromised microcirculation compared to non-smokers and nicotine-free e-cigarettes.[30] Moreover, nicotine seems to detrimentally impact tissue perfusion; however,

further large-scale investigations are imperative to fully comprehend the vascular ramifications of e-cigarette utilization.

DISCUSSION

Comparing the medium-content and high-nicotine e-cigarette exposure groups to the tobacco cigarette exposure group, the study discovered that both groups exhibited comparable levels of flap necrosis and hypoxia. Consequently, it seems that both smoking and vaping have an identical negative impact on wound healing and are linked to a statistically significant rise in flap necrosis ($p<0.05$) when compared to the unexposed group.[27] Based on the findings, it appears that vaping is not a better option than smoking cigarettes when it comes to wound healing, and it is not a recommendation that should be made.[28]

The absence of carbon monoxide generated by e-cigarettes suggests that users will undergo enhanced tissue oxygenation post-surgery. However, human research indicates that e-cigarette users encounter akin adverse impacts on skin oxygenation and related factors as conventional cigarette smokers. This phenomenon may stem from evidence illustrating that e-cigarette vapor modifies neutrophils, macrophages, and keratinocytes, along with other immune cell types. These modifications lead to altered production of pro-inflammatory cytokines and subsequent suppression of defenses against bacteria and viruses, potentially increasing the risk of hospital-acquired infections such as Methicillin-resistant Staphylococcus aureus (MRSA). Consequently, disturbances in skin and bone growth commonly occur. These effects arise from humectants (glycerine and glycerol), assorted flavorings, and additional ingredients present in e-cigarettes, which have been shown to induce inflammation and free radical assault, alongside nicotine's effects. The adverse impacts of e-cigarette vapor on respiratory and cardiovascular physiology may also be partially elucidated by these immunological effects.[32]

The limitations of this study include the absence of extended-term investigations, the diversity in e-cigarette merchandise and usage habits, and the difficulties in segregating the impacts of singular constituents. Our proposed strategies for forthcoming research involve employing standardized methodologies and conducting investigations that concentrate on particular components and their biological repercussions.

CONCLUSION

Current research indicates that e-cigarettes may have a similar detrimental effect on wound healing as regular cigarettes, most likely through a multifactorial mechanism in which nicotine-induced vasoconstriction and the ensuing creation of a hypoxic tissue environment are involved. With less adverse effects than traditional tobacco cigarettes, e-cigarettes may be a good alternative. Nevertheless, further toxicological research, particularly studies on the long-term consequences of e-cigarettes, is necessary, as well as stronger regulations governing the industry and sales practices.

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