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Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes

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ABSTRACT

The development of electronic cigarettes (e-cigs) has the potential to offer a less harmful alternative for tobacco users. This clinical study was designed to characterize e-cig users' exposure to nicotine, and to investigate the acute effects of e-cigs on the hemodynamic measurements (blood pressure and heart rate) in comparison with the effects of regular smoking. Five e-cigs and one Marlboro® cigarette were randomized for twenty-three participants under two exposure scenarios from Day 1 to Day 11: half-hour controlled administration and one hour *ad lib* use. The nicotine plasma concentrations after 1.5 h of product use (C_{90}) were significantly lower in the users of e-cigs than of Marlboro® cigarettes. The combination of glycerin and propylene glycol as the vehicle facilitated delivery of more nicotine than glycerin alone. The heart rate, systolic and diastolic blood pressure were significantly elevated after use of Marlboro® cigarettes, but the elevation was less after use of most of the e-cigs. Use of e-cigs had no impact on the exhaled CO levels, whereas the Marlboro® cigarette significantly increased the exhaled CO more than 8 times above the baseline. In conclusion, e-cigs could be a less harmful alternative for tobacco users.

1. Introduction

Cigarette smoking is a major health hazard, and contributes significantly to cardiovascular morbidity and mortality (Ambrose and Barua, 2004). According to the World Health Organization (WHO), smoking is the most preventable risk factor for cardiac and lung disease and is expected to cause 1 billion deaths during the 21st century. Studies have shown that acute smoking inhalation has significant adverse effects on left ventricular function in healthy smokers (Lichodziejewska et al., 2007). Smoking inhalation increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol that contributes to the cardiovascular dysfunction, such as defects in myocardial function (Farsalinos et al., 2013). Smoking also increases the risk of developing atherosclerosis, a disease which can cause heart attacks, strokes, and can even lead to death. The mechanisms by which cigarette smoking contributes to acute cardiovascular effects include (1) induction of a hypercoagulable state; (2) increased myocardial work; (3) CO mediated reduction in the oxygen-carrying capacity of the blood; (4) induction of endothelial dysfunction; (5) coronary vasoconstriction; and (6) catecholamine (Benowitz and Gourlay, 1997; Benowitz et al., 2002). There are many toxicants in cigarette smoke, such as CO, α, β-unsaturated aldehydes, superoxide, N_2O, and other oxidant gases, which could contribute to heart disease. Heart disease is the main cause of morbidity and mortality in smokers, with 40% of deaths in smokers due to coronary artery disease alone (Deanfield et al., 1986).

Thus, Tobacco Harm Reduction strategies and products have been developed to reduce the amount of toxic substances that a smoker is exposed to while smoking. As an alternative for smokers, e-cigs are rapidly growing worldwide and are gaining significant attention as potentially reduced exposure products and smoking cessation products (Etter and Bullen, 2013; Polosa et al., 2011; Farsalinos and Polosa, 2014). Though only developed and marketed in recent years, e-cigs are already used by several millions of people worldwide. The device consists of a battery, a cartridge containing liquid and a heating element which is heated by the battery and evaporates the liquid. The liquid usually contains water, nicotine, glycerin, propylene glycol, and a variety of flavors. E-cigs simulate the effect of smoking by producing an inhaled aerosol and satisfy the behavioral aspects associated with smoking. Because e-cigs does not involve the combustion of the chemical components commonly found in tobacco cigarettes, it is expected that user exposure to the toxicants may be less so use of e-cigs could avoid many of the detrimental health effects attributed to cigarette smoking. Laboratory analyses of the e-liquids show that there are less harmful and potentially harmful constituents (HPHCs) than regular cigarettes (Burstyn, 2013). Most studies have found no

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nitrosamines in the vapor, but even in studies where nitrosamines were found, the levels detected were 500–1400 times less than the amount present in one tobacco cigarette (Cobb et al., 2010; Burstyn, 2013; Goniewicz et al., 2013; Kim and Shin, 2013).

As an emerging product developed recently, public health concerns have been raised globally about using of this smoking alternative. To date, there is little objective data that provide sound information on e-cigs toxicant content, the toxicant exposure level and the potential health effects to end users. Studies provided mixed data on plasma nicotine levels after use of e-cigs. One study found that in contrast to use of usual-brand cigarettes, use of e-cigs containing 16–18 mg/mL of nicotine did not increase nicotine plasma concentrations significantly from baseline (Vansickel et al., 2010). Other studies reported significant increases from baseline in nicotine plasma concentration after use of the usual-brand electronic devices (containing 9–24 mg/mL of nicotine), similar to conventional cigarette smoking (Vansickel and Eissenberg, 2013; Dawkins et al., 2013). These mixed results may reflect the differences in study design, or device characteristics, or suggest an acclimation to the product for new users.

Extremely limited studies have evaluated the effects of e-cigs on the hematology and cardiovascular system in relation to nicotine delivery. A study evaluated the acute effects of e-cigs and cigarette smoking on complete blood count markers in 30 human subjects and found cigarette smoking increased white blood cell, lymphocyte, and granulocyte counts for at least 1 h in smokers and never smokers, but the e-cigs smoking did not influence the complete blood count (Flouris et al., 2012). A clinical study examined the acute effects of e-cigs and regular cigarettes on nicotine delivery profile and cardiovascular function. It was observed that regular cigarettes significantly increased the plasma nicotine and CO concentration and heart rate within the first 5 min of administration, whereas e-cigs did not (Vansickel et al., 2014). Farsalinos et al. (2014) found that smoking one tobacco cigarette led to significant acute myocardial dysfunction but e-cigs had no acute adverse effects on cardiac function. The researchers reported that smoking a tobacco cigarette had important hemodynamic consequences, with significant increases in heart rate, systolic and diastolic blood pressure. In contrast, e-cigs produced only a slight elevation in diastolic blood pressure. The nicotine level in the e-cigs reported in the Farsalinos study was 1.1% in the liquid. The authors concluded nicotine in e-cigs was absorbed at a lower rate compared to regular cigarette smoking and e-cigs did not show to have adverse effects on the heart (Farsalinos et al., 2014).

The nicotine concentrations tested in above studies, were relatively considered to be "low-medium", with short duration of exposure. Given the fact that there is wide range of nicotine concentrations in the e-liquid of currently marketed e-cigs, and the amount of regular and electronic cigarettes consumed can be very different from smoker to smoker and from day to day, this clinical study was designed to characterize blu e-cigs users' nicotine exposure, and to investigate the acute effects of blu e-cigs with higher nicotine level (up to 2.4% in the e-liquid) and longer duration (up to 1.5 h) on the hemodynamic effects (blood pressure and heart rate) in relation to internal nicotine dose, compared to the adverse effects of regular smoking.

2. Methods

2.1. Participants

The study was approved by the Institutional Review Board (IRB) of Chesapeake Research Review Inc. (CRRI, Columbia, MD). Thirty-eight subjects underwent the screening procedures to ensure that they met the requirements for inclusion within 28 days prior to participation in the study. The IRB-approved informed consent form (ICF) was collected from all participants prior to completion of the screening or other study procedures. Fourteen subjects withdrew from the study. The remaining 23 participants (11 male and 12 female) properly completed the study and were included in the analyses. All participants were between 21 and 65 years of age, smoked an average of 10 or more manufactured cigarettes per day for at least 12 months prior to the study. All provided positive urine cotinine at screening ($\geqslant$500 ng/mL). Exclusion criteria included self-reported history of any chronic mental or physical health condition, pregnancy or breastfeeding, systolic blood pressure > 150 mmHg, diastolic blood pressure > 95 mmHg, or heart rate > 99 bpm at screening, use of tobacco or nicotine-containing products other than manufactured cigarettes and e-cigs, and use of any prescription smoking cessation treatments within 3 months prior to Day 1 product administration and throughout the study, use of prescription anti-diabetic medication and/or insulin therapy within 12 months of Day 1 product administration, and use of medications known to interact with cytochrome P450 2A6 within 3 months prior to Day 1 product administration.

2.2. Test articles

The blu e-cigs are currently sold in retail outlets across the United States (US) in both disposable and re-useable forms. The blu e-cigs prepared for use in the current study were 2 commercial products (Product D and E) that contain 16 mg/mL (1.6%) nicotine (USP grade), and 3 non-commercial products (Product A, B and C) that contain 24 mg/mL (2.4%) nicotine (USP grade), in the cartomizer device format attached to rechargeable batteries. In comparison, the nicotine yield of the market-leading conventional cigarette (Marlboro® Gold King Size) is approximately 0.8 mg per cigarette (FTC 2007). As the blu e-cigs may yield from 250 to 400 puffs per cartridge, a single cartridge may equate to approximately 1–2 packs of conventional cigarettes.

The following investigational and comparator product designations were used in this study.

Product A:	Classic Tobacco e-cigarette in rechargeable cartomizer (2.4% nicotine, ~75% glycerin vehicle), or Product A Classic e-cig (2.4% Nic in Gly)
Product B:	Classic Tobacco e-cigarette in rechargeable cartomizer(2.4% nicotine, ~50% glycerin/ ~20% propylene glycol vehicle), or Product B Classic e-cig (2.4% Nic in Gly/PG)
Product C:	Magnificent Menthol e-cigarette in rechargeable cartomizer (2.4% nicotine, ~75% glycerin vehicle), or Product C Menthol e-cig (2.4% Nic in Gly)
Product D:	Classic Tobacco e-cigarette in rechargeable cartomizer (1.6% nicotine, ~75% glycerin vehicle), or Product D Classic e-cig (1.6% Nic in Gly)
Product E:	Classic Tobacco e-cigarette in rechargeable cartomizer (1.6% nicotine, ~50% glycerin/ ~20% propylene glycol vehicle), or Product E Classic e-cig (1.6% Nic in Gly/PG)
Product F:	Marlboro® Gold King Size, or Product F Marlboro® cigarette

In addition to nicotine, the blu e-cigs prepared for use in this study contain vegetable glycerin, natural and artificial flavors, distilled water, citric acid, and propylene glycol.