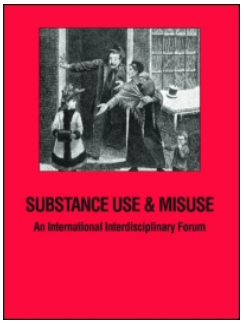

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ORIGINAL ARTICLE

Comparison of End Tidal Carbon Monoxide Levels between Conventional Cigarette, Electronic Cigarette and Heated Tobacco Product among Asiatic Smokers

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ABSTRACT

Background: Electronic nicotine delivery systems (ENDS) and heated tobacco products (HTPs) are noncombustible tobacco products which have been found to generate aerosols containing lower levels of Harmful and Potentially Harmful Constituents (HPHCs) in comparison to conventional cigarettes. *Objective:* This quasi experimental study measured and compared the end tidal carbon monoxide (eCO) levels of participants after use of ENDS, HTPs and conventional cigarettes. *Methods:* In total 45 smokers, each smoking at least 10 conventional cigarettes per day for 5 years participated in the study. Based on their preference, participants used only one of the tobacco products (ENDS, HTPs, or conventional cigarette) and were briefed about the product use based on manufacturer's instructions. The eCO levels were obtained at baseline, followed by 5, 10, 15, 30 and 45 min respectively after the product use. *Results:* There was significant increase in eCO levels for conventional cigarettes as compared to other modes. Peak eCO levels of 20.2 ± 0.86 ppm, 8.8 ± 1.56 ppm and 6.0 ± 1.36 ppm was achieved at 30 min, 15 min and 10 min for conventional cigarettes, ENDS and HTPs respectively. However, the levels were significantly lower in ENDS and HTPs. *Conclusion:* Even though ENDS and HTPs may have produced significantly lower eCO than conventional cigarettes, the significantly increasing levels over time from baseline which was not shown before is a cause of concern. As of now, their use as an alternate to cigarettes needs to be considered under regulatory framework.

KEYWORDS

Electronic nicotine delivery systems; heated tobacco products; conventional cigarettes; noncombustible tobacco products; Carbon monoxide

Introduction

Smoking is the chief preventable cause of premature death worldwide, resulting in more than 7 million deaths per year (Centers for Disease Control and Prevention (CDC), n.d.; Jha et al., 2013; Jha, 2009; World Health Organization (WHO), 2017). It has been associated with numerous severe medical conditions including cardiovascular disease (CVD), pulmonary disease and cancer (WHO, 2019). In year 2012, U.S. Food and Drug Administration (FDA) published a preliminary list of 93 Harmful and Potentially Harmful Constituents (HPHCs), which were identified in tobacco products and tobacco smoke, many of which have been recognized to play a role in the detrimental effects of smoking.

Hence, with the aim of reducing the health burden of cigarette smoking, there has been great interest in tobacco harm reduction (THR), leading to development of less harmful alternatives, such as electronic nicotine delivery systems (ENDS) and heated tobacco products (HTPs) (Britton et al., 2016; Eaton et al., 2018; Notley et al., 2018; Schorp et al., 2012). When compared to conventional cigarettes, both of these tobacco products do not involve combustion to deliver nicotine, hence less HPHCs, including carbon monoxide (CO) are released (Polosa et al., 2013).

HTPs are new electronic devices that heat tobacco up to temperatures (≤350 °C) sufficient to aerosolise nicotine, but not high enough to combust the tobacco. This limits the emission of HPHCs, reducing the risk of smoking-related diseases (Jaccard et al., 2017; Kogel et al., 2016; Pratte et al., 2017; Rodu, 2011; Simonavicius et al., 2018; Smith et al., 2017; WHO, 2019). A number of HTPs which are commercially available include iQOS from Philip Morris International, Glo from British American Tobacco, Ploom TECH from Japan Tobacco International, and PAX from PAX Lab. They generally consist of a holder which heats tobacco sticks, plugs or capsules, mimicking the smoking experience (Rodu, 2011; Smith et al., 2017; WHO, 2019).

ENDS are also known as "electronic cigarettes," "e-cigs," "e-hookahs," "mods," "vapes" and "tank systems." It is defined as an electrical device that generates aerosol by heating a liquid containing propylene glycol, nicotine, and other chemicals. Although not risk-free - key literature reviews have acknowledged that electronic cigarettes release much lower

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toxic emissions compared to tobacco cigarettes (Farsalinos & Polosa, 2014; McNeill et al., 2018; Daynard, 2018).

To our knowledge, there are only two independent studies that investigated on eCO levels between HTPs and conventional cigarettes (Adriaens et al., 2018; Caponnetto et al., 2018). However, given that both studies were conducted in Caucasians, we seek to obtain data from an Asiatic population.

This quasi experimental study aimed to bridge the gap that was observed in the previous studies. This would also provide further insight that whether ENDS and HTPs could be better alternatives to cigarette smoking or could contribute toward THR. Through this study, we aimed to measure and compare the end tidal carbon monoxide (eCO) levels of participants after use of HTPs, ENDS and conventional cigarettes.

Materials and methods

In this quasi experimental study, a total of 45 smokers were recruited at International Medical University, Kuala Lumpur based on non-probability convenience sampling. These included either staff, supporting staff or patients visiting the Oral Health Center, International Medical University (OHC-IMU). Eligibility criteria for this study included smokers who were smoking at least 10 conventional cigarettes per day (cig/day) for ≥5 years and provided a baseline eCO ≥10 ppm on screening. The participation was voluntary, they were ensured anonymity and written consent was sought at recruitment.

End tidal carbon monoxide levels was used as a marker of combustion products as its measurement is rapid, noninvasive and inexpensive (Akhter et al., 2014). Besides, previous studies revealed that eCO is closely correlated with both carboxyhemoglobin levels in blood and the intensity of tobacco smoke (Deveci et al., 2004; Irving et al., 1988; Wald et al., 1981). The eCO levels are expressed in part per million (ppm) and is categorized in different ranges (0–6: non smoker; 7–10: light smoker, non smoker breathing in poor air quality, passive smoker; 11–20: smoker; >20: heavy smoker) (Adriaens et al., 2018; CoVita & LLC, 2019). A hand-held eCO meter (piCO^{TM} Smokerlyzer; Bedfont Scientific Ltd., UK) was used to measure eCO levels based on the manufacturer's recommendations and was standardized throughout the study. Participants were asked to inhale deeply, hold their breath for 15 s, and then slowly but forcefully blow into the mouth piece, with the aim to empty the lungs completely (Bedfont, 2017; Kumar et al., 2010).

The products used in this study were (i) conventional cigarettes, where participants were requested to use their own preferred brand (ii) ENDS, where Aspire AVP AIO Kit 700 mAh battery having a 1.2 Ω coil with e-liquid "Liquideo Evolution" containing a propylene glycol/vegetable glycerin (PG/VG) ratio of 70/30, 10 mg/ml nicotine with a tobacco flavor was used (iii) heated tobacco product, where iQOS device, Philip Morris International with Marlboro Heat Sticks was used.

Data collection was carried out in two planned visits. During the first visit, baseline data (eCO levels) was collected within the first hour after the use of conventional cigarettes to ensure that the participants are eligible for the study (≥10ppm). Participants also completed a questionnaire which had three sections: (i) demographic information, (ii) smoking history (iii) Fagerstrom test for nicotine dependence (Heatherton et al., 1991).

After the questionnaires were completed, each participant was briefed on the study course and the 3 types of tobacco products (HTPs, ENDS or conventional cigarettes) used in this study. They were allowed to choose either one of three tobacco products based on individual preference, making this a quasi-experimental study as no randomization was performed. Subjects were consecutively recruited in three groups (conventional cigarettes, ENDS and HTPs) based on personal preferences until a maximum of 15 smokers per group was reached. A one-to-one training for at least 30 min was provided, focusing on safety and correct usage of the tobacco product chosen (except for those choosing conventional cigarettes) according to manufacturers' recommendations.

Participants were instructed to remain abstinent from cigarette smoking for at least 12 h prior to the 2nd visit. Upon arrival, eCO levels was measured to verify no recent cigarette use (≤10 ppm). The ENDS and HTPs were ensured to be fully charged before each study sessions. After the baseline value was obtained, depending on which tobacco product was chosen, participants were instructed to take the first round of 10 puffs with a 30 s inter-puff interval, followed by an identical second round after a 5 min pause in between rounds as described by Vansickel et al. (2010). Next, eCO was recorded at 5, 10, 15, 30, and 45 min after the first puff of the first round respectively. The detailed flow of the study methodology are simplified in Figure 1.

Statistical Package for the Social Science (SPSS) v.22.0 software was used for all statistical analysis. Descriptive statistics was used to analyze the socio demographic details and Fagerstrom test for nicotine dependence. Comparison between all the variables (eCO levels, time points and tobacco products) was tested using repeated-measures ANOVA. The differences were deemed statistically significant at the $p < 0.05$.

Ethics approval was sought by the Research and Ethics Joint Committee of International Medical University BDen Project 4.13/JCM-177/2019.

Results

A total of 45 conventional cigarette smokers (39 Males, 6 Females; mean age of 43.6 years) were enrolled. Majority of the smokers belonged to the Chinese ethnicity (51.1%), out of which 69% of the subjects were married while 87% of smokers were employed. The demographic details of participants are summarized in Table 1.

The time trends of eCO levels for each tobacco product is shown in Figure 2. Baseline eCO levels were below 5 ppm for each participant in the 2nd visit. Three components were evaluated by using repeated-measures ANOVA post-hoc comparisons.

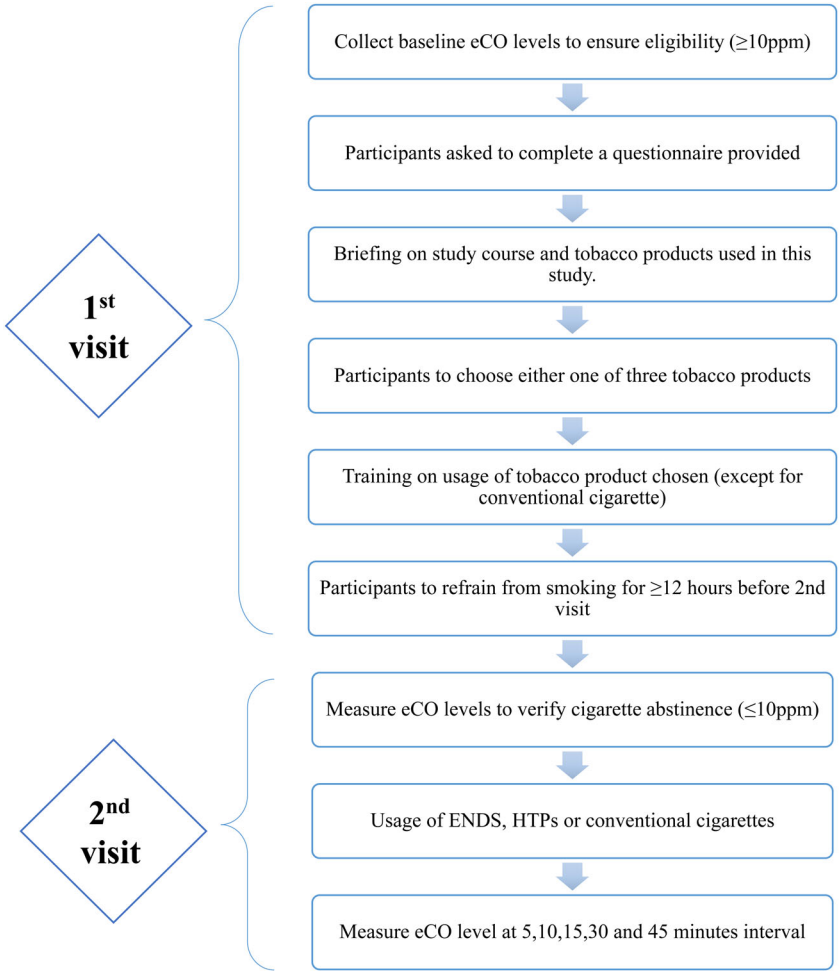

Figure 1. Methodology of this study.

Table 1. Demographic profile of subjects.

Demographic profile		Smokers (%)
Gender	Male	86.7
	Female	13.3
Ethnic	Chinese	51.1
	Malay	22.2
	Indian	20.0
	Others	6.7
Marital status	Married	68.8
	Not married	31.1
Employment status	Employed	86.7
	Not employed	13.3
Number of cigarette per day	10 or less	8.9
	11–20	68.9
	21–30	13.3
	31 or more	8.9
Previous quit attempt	No attempt	62.2
	Multiple unsuccessful attempts	28.9
	1–3 successful attempts	6.7
	>3 successful attempts	2.2
Total Fagerstrom score	0-3 (low)	20.0
	4-5 (medium)	64.4
	6-10 (high)	15.5

i. Within-product effect (i.e. time, $p \leq 0.001$)
Significant difference in eCO levels between the different time points within the same tobacco product was noted ($p < 0.001$).

ii. Between product effect
Significant differences were noted between-tobacco products effect (HTPs/ENDS vs conventional cigarette; $p < 0.001$; HTPs vs ENDS; $p < 0.001$).

iii. Time × product effect
Significant difference in the change of eCO levels with time between different tobacco products were noted ($p < 0.001$).

Time trends of eCO levels measured at baseline, and at 5, 10, 15, 30 and 45 min after use of conventional cigarettes (blue), ENDS (orange) and HTPs (green). Repeated-measures ANOVA was conducted, having tobacco product and time points as main effects. The within-product effect was significant for all three tobacco products ($p < 0.001$). Significant difference was observed in the between-product effect for all three tobacco products ($p < 0.001$).

Minimal changes in eCO levels were noted after use of HTPs and ENDS as compared to conventional cigarettes. The mean eCO level (95%CI) for ENDS and HTPs reached a maximum peak at 15 min with 8.8 ± 1.56 ppm and at 10 min with 6.0 ± 1.36 ppm respectively, after which the levels gradually started to decline. Even though an increase of eCO levels were noted for both ENDS and HTPs, it was below 10 ppm (eCO levels in blood specified for light smokers, passive smokers or nonsmokers breathing in poor air quality). However, for conventional cigarettes, the maximum peak was 20.2 ppm ± 0.86 at 30 min, which was much higher

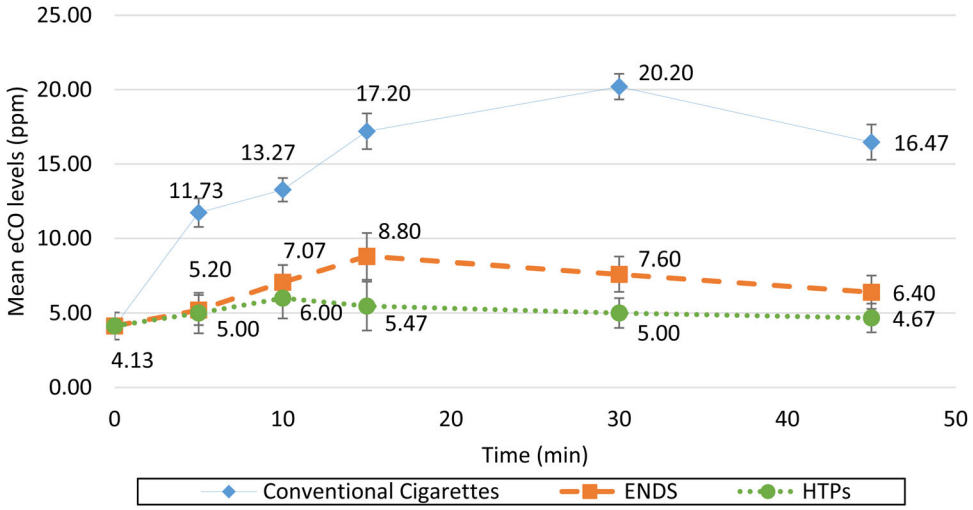

Figure 2. Time trends of eCO levels for each tobacco product.
Time trends of eCO levels measured at baseline, and at 5, 10, 15, 30 and 45 minutes after use of conventional cigarettes (blue), ENDS (orange) and HTPs (green). Repeated-measures ANOVA was conducted, having tobacco product and time points as main effects. The within-product effect was significant for all three tobacco products ($p < 0.001$). Significant difference was observed in the between-product effect for all three tobacco products ($p < 0.001$).

Table 2. Repeated-measures ANOVA summary table for eCO levels.

Effect	F	*p* value	Partial Eta Squared
Between products	428.048	<0.001	0.983
Within products (Time)	363.272	<0.001	0.985
Time × Tobacco product	23.848	<0.001	0.754

than 10 ppm (unsafe eCO level in blood specified for regular smokers). The details are summarized in Table 2.

Discussion

In this independent quasi experimental study, we measured and compared the eCO levels after use of HTPs, ENDS and conventional cigarettes. Quasi experimental study design was selected as randomization in this study would be unethical. It is also inexpensive, less time consuming and have good external validity. However, since no randomization is done in these study designs, we take that as a limitation, as the ability to conclude a causal association between an intervention and outcome is limited (Schweizer et al., 2016). The inclusion of participants was based on the baseline smoking status and their compliance to the abstinence rule during the second visit. The eCO levels were all comparable and below 5 ppm for all the participants which reflected on the internal validity of this study.

When interpreting the study findings, caution should be applied due to certain limitations. First, although this study was conducted on a small sample, based on the sample size calculation, it was more than sufficient to minimize the play of chance. However, our study was adequately powered, with a power of 80% to detect eCO differences between the use of three different tobacco products, indicated by the power analysis of the collected data. Secondly, our study did not include data concerning craving and subjective experiences, which will further show whether HTPs and ENDS can act as an alternative to conventional cigarettes. Third, we only used one specific type of ENDS and HTPs for an acute period of time. A diversity of types of ENDS with various nicotine concentration and flavors of e-liquids exists, which could affect the eCO levels studied here meanwhile the availability of different HTPs products is somewhat limited. Hence, the results of this study do not represent same products under investigation after prolonged use or to the other types of HTPs and ENDS. Finally, despite our findings seem to support the tobacco industry data, it should be noted that the focus of this study was not to advocate smoking. It was rather geared toward the emerging challenges faced by tobacco control authorities due to increasing prevalence of the new tobacco products in the market.

From this study, the eCO elevations after use of HTPs was deemed to be significant. Despite this, the increase in eCO levels were minimal and correlates with the findings of a study conducted by Adriaens and colleagues (2018). Their randomized, cross-over study investigated on the effects of using HTPs, ENDS and conventional cigarettes in overnight-abstinent regular smokers. A similar pattern was also observed in their study as eCO levels increased significantly until a certain time point, after which the levels decreased slowly. However, these results appear to contradict with the study conducted by Caponnetto et al. (2018), where the elevation of eCO levels after use of two HTPs were not significant. The most probable reason for the insignificant increase in eCO levels observed in Caponnetto's study (2018) was the lack of statistical power (small sample size). The findings by Caponnetto correlated with previous studies conducted by tobacco industries which shows that CO present in the aerosol of iQOS was negligible (0.436 mg/stick). This was only 1.4% of CO contained in the aerosol of reference cigarettes (30.2 mg/stick) (Forster et al., 2018; Haziza et al., 2016; Jaccard et al., 2017). Nonetheless, we can conclude that HTPs, in terms of eCO levels generated is much lower than conventional cigarettes as no combustion is taking place. Further studies should be conducted to evaluate the HPHCs generated through pyrolysis in aerosol of HTPs and

its effect on human health before concluding it is a safer product than conventional cigarettes.

Another finding observed was that after the use of ENDS, a slight increase in eCO levels was detected that showed statistical significance. This finding differed from previous studies, where they revealed minimal insignificant change in eCO levels after use of ENDS (Adriaens et al., 2018; Farsalinos et al., 2013; Van et al., 2013; Vansickel et al., 2010). However, this elevation does not have clinical significance as the increase in eCO levels noted for ENDS is below 10 ppm. To our knowledge, this is a new finding compared to other studies and this change in eCO levels may differ with varying nicotine concentrations in ENDS and the type of ENDS used. Also possible reason can be supported by several previous studies, that have shown inhalation effects associated with certain factors such as socio-demographics (age, sex, health status), climate condition, room ventilation, number of users in the specific location, battery voltage and puff duration (Etter et al., 2011). Thus, further long term studies are required to investigate on the prolonged effects of HTPs and ENDS to ultimately determine their safety for use as replacement therapy.

As tobacco industries are good in promotional skills, online advertisements of ENDS and HTPs can readily be found and often deliver deceptive information about health benefits and safety. Some policy makers and researchers debate about these alternatives as harm reduction agents as compared to conventional cigarettes (Hart et al., 2018).

Conclusion

Moving toward the tobacco 'endgame', that aims beyond tobacco control measures and focuses toward a tobacco-free future (Malone, 2013; Thomson et al., 2012). This targets either the use of commercial tobacco products be eliminated or their availability significantly restricted. Thus, for many low and middle-income countries the 5% endgame scenario may seem impossible (Hammond, 2000; Smith, 2013; Van der Eijk, 2013). One of the main reasons is that the industry will argue on the proposed strategies and simultaneously enforce marketing of all these new tobacco products. We conclude, that even though ENDS and HTPs may have significantly few harmful effects as compared to conventional cigarettes as of now. Their use as an alternate to cigarette needs to be considered under regulatory framework.

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Declaration of interest

The authors declare no conflict of interest.

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