Evaluating Nicotine Abstinence, Smoking Cessation, Reduction and its Relapsed Among Electronic Cigarettes Single and Dual Malaysian Users: A One Year Observational Study

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ABSTRACT--Purpose: Evidence for the complete nicotine cessation is inadequate among electronic cigarettes (ECs) single users (SUs, use only ECs), and dual users (DUs, use both ECs and conventional cigarettes (CCs). The primary aim of this study was to evaluate the nicotine cessation among SUs and DUs who used ECs over one year. **Methods:** We observed 70 SUs and 148 DUs for 52 weeks and tested their exhaled carbon monoxide and saliva cotinine to confirm their complete nicotine cessation status through cotinine in saliva. Safety issues were to be identified through self-report. Smoking cessation, CCs reduction of ≥ 50%, and relapsed to CCs smoking and safety issues were also documented. **Results:** The nicotine cessation rate was higher in SUs then DUs (15.9% vs. 6.8%; P = 0.048; 95% CI (2.328-0.902). A similar result for smoking cessation (34.8% SUs vs. 17.1% DUs; P = 0.005; 95% CI: 2.031-0.787), whereas CCs ≥ 50% reduction was 23.3% DUs vs 21.7% SUs (P = 0.863; 95% CI :1.020-0.964). Relapse to CC smoking was 47.3% in DUs versus 30.4% in SUs (P = 0.026; 95% CI: 1.555-0.757). The adverse effects reported were coughing and breathing problems, whereas craving smoking was documented as a major withdrawal symptom. Smoking-related diseases were also identified, five in DUs and two in SUs, during the one-year study period. **Conclusions:** Study showed SUs achieved higher complete nicotine and smoking cessation rates as compared to DUs. However, the rates of reduced CC use were not different between both the groups. No serious adverse effects related to the sole use of ECs were detected. However, the safety of the sole use of ECs in absolute terms needs to be further validated in different populations.

Introduction

Electronic cigarettes (ECs) are gaining recognition and their use has increased in the last few years [1]. The use of ECs is increasing as a substitute for smoking conventional cigarettes (CCs) among existing smokers. According to a recent public health report in England (2018), nearly 32,000 kinds of ECs and e-liquids are available in the United Kingdom [2]. The EC was developed to mimic the act of smoking by way of nicotine supply but without the deleterious effects of smoke generated by the CCs use [2,3]. ECs is relatively novel and their consumption spreading as an electronic nicotine delivery system worldwide. Smokers use ECs that produce vapours that resemble smoke. Some executive health care services have stated that the smoke released by CC is primarily responsible for inducing many cardiovascular, respiratory and cancers type ailments in human beings [4].

ECs are battery-controlled gadgets available in numerous shapes and sizes, such as conventional cigarettes, pens, USB and various box shapes [2,3]. ECs do not release smoke but vaporise e-liquids (also called e-juice) that EC users (also called vapers) inhale. The chief constituents of EC liquids are nicotine, propylene glycol, glycerine, and some flavouring ingredients [2,3]. Due to consumer demand and to make vaping as enjoyable as smoking, there has been a notable expansion in the technology of EC devices.

ABBREVIATION. CC: Conventional cigarettes; CO: Carbon monoxide; DU: Dual users; EC: Electronic cigarettes; IIUM: International Islamic University of Malaysia; IREC: International Islamic University of Malaysia Research Ethics Committee; ITT: Intention to Treat; NMRR: National Medical Research Registration; NRT: Nicotine; Replacement Therapy; PPM: Parts Per Million; RCTs: Randomised Clinical Trials; SPSS: Statistical Package for Social Sciences

As per the National Academies of Sciences, Engineering, and Medicine report specified that only a few randomized controlled trials (RCTs) [6-9] are available. The report further stated that there is inadequate data to indicate that ECs helps smokers to quit cessation and might act as a gateway to CCs among youth [1]. In addition, there is uncertainty regarding ECs since their use may renormalize smoking in ex-smokers, could fascinate youngsters due to the availability of nicotine e-liquids with various flavours [5]. Inadequate information regarding the long-term health effects of ECs has become a significant issue in the use of ECs worldwide, including Malaysia [5].

The existing trials are limited to demonstrate the complete nicotine and smoking cessation among single users (SUs, use only EC) and dual EC users (DUs, use both EC and CC). Both SUs and DUs represent the real-world population of the vaping community. Presently in Malaysia, ECs are not banned per se regulated but nicotine-free e-liquids are permitted for sale [12]. In Malaysia, the nicotine in e-liquids should be sold by the registered medical pharmacist as per the control of drugs and cosmetics act regulations (1952) [12]. According to the Malaysian National EC Survey (2016), the prevalence of EC users among Malaysian adults aged ≥ 18 years was 3.2% (3.3%; urban users and 2.9% as rural users). The survey further stated that the prevalence of DUs was 2.3%, while that of SUs was < 1% [13]. ECs studies in Malaysia and elsewhere have insufficient data to reveal whether sole EC use, or dual use of ECs is connected to complete nicotine cessation or increased nicotine dependency by inducing both practices in vapers. The primary aim of this study was to evaluate the nicotine cessation in both SUs and DUs who used ECs over one year. Smoking cessation, CCs reduction ≥ 50%, and its relapse, as well as safety issues related to EC, were also identified.

METHODS

Study Design

A one-year prospective observational cohort study was designed to assess the objectives of the study in a naturalistic setting. In our earlier 6-month studies, only 3.3% of study participants in both the groups reported complete nicotine cessation [14]. In the present study, the researcher extended preceding studies and explored the complete nicotine abstinence, smoking cessation, reduction and its relapse in the same cohorts for up to 1 year. Figure 1 shows a flow chart of the recruitment process and follow-up of subjects during the study period. The final data was collected from 82% (176) of the study participants.

Sample size

To observe a smoking cessation rate in combined SUs and DUs with 80% power, 200 participants were required for the study [15]. The 10% smoking cessation rate was selected for the whole group based on some previous RCTs [6-8]. The study was designed to register 200 samples. However, 220 subjects were initially obtained with the consideration that 10% may withdraw from the study. Therefore, registration of 220 participants was adequate to ensure that 200 subjects will complete the study. In Malaysia, approximately two-thirds of vapers are DUs, whereas the remaining one-third are SUs. Therefore, the participants were selected in the ratio of 2:1; i.e., 148 DUs and 70 SUs [13].

According to standard practice in tobacco research, intention to treat (ITT) analysis was applied for the study outcomes [16]. Missing subjects were included in the analysis to evaluate smoking cessation at the final stage of the study. All subjects who visited at least once during follow-up visits were included in the study. The participants were allowed a maximum of two missing visits to be included in the final analysis. Subjects who were lost to follow-up were excluded from the study.

Study questionnaire

A pre-validated interview administered in English was used to collect the data. The instrument was developed and piloted among Malaysian SUs and DUs vapers [17]. The questionnaire consisted of queries regarding the demographic characteristics of the participants and queries to evaluate the effectiveness and safety of ECs.

Inclusion and exclusion criteria

The inclusion criteria included existing SUs and DUs using ECs for at least the previous month, age 18–65 years, with good self-reported health conditions and agreed to sign a consent form. The investigator recruited healthy subjects for the study because the participants who suffer from health issues will be more influenced to quit CCs smoking as compared to healthy users. This creates biased in the study results since these subjects will quit CCs due to health issues, not due to the competency of ECs. Exclusion criteria comprised of the use of any smoking cessation medicines, such as nicotine

replacement therapy (NRT) or varenicline currently or within the last year. Participants who were dependent on any illicit drugs were also omitted through self-reporting.

Settings and screening

Study subjects were enrolled from the semi-urban districts of Kuantan and Pekan, state of Pahang, Malaysia and the data was collected between March 2015 and June 2016. As per the National Health and Morbidity Survey 2015, the smoking prevalence in the state of Pahang was 25.5%, more than the national smoking prevalence rate of 22.8% [18]. The above-mentioned locations were chosen due to the feasibility of the research site related to time and funding constraints. Further, it appeared to be more balanced in terms of accessibility of EC users. Applicants were informed that there would be no monetary compensation for enrollment in the study, but reimbursement would be provided for food and transportation expenses. More than 90% of the subjects understood and spoke English, but for those subjects who were not familiar with the English language, a Bahasa Malay to English professional translator was used. The translator was equally proficient in both languages. The same professional translator was used in all the visits to avoid any bias and inconsistencies related to documentation.

The participants who committed to the study and signed the consent form were screened for inclusion and exclusion criteria. The participants who met the eligibility criteria were selected for enrolment in the study. Then, users were screened for their self-reported health status as per the validated questionnaire, which was documented by the researcher. The same researcher screened all the subjects to maintain uniformity and to avoid obscurity in the recruitment process. Subjects were then separated into two groups based on 7 Days point prevalence abstinence rate**.** Means SUs, who self-reported that they had quit at least CCs in the past 7 days and using only EC confirmed by an exhaled carbon monoxide (CO) level of < 8 ppm. Whereas DUs, who used both ECs and CCs inveterate by a CO level of ≥ 8 ppm.

Data verification

At baseline and the end of the study, both groups were tested for exhaled CO level by $PiCO^{+}$ Smokerlyzer® to measure the 7 days point prevalence abstinence rate. In addition, for self-reported complete nicotine abstinence, a saliva cotinine NicAlert test [19] was performed. Participants were considered to have quit CCs when the estimated CO value was < 8 ppm with zero levels (0-10 ng/ml) on saliva cotinine strips. Measuring CO level alone is insufficient to confirm complete nicotine abstinence, as CO test results can produce inappropriate outcomes. The Preceding studies have revealed that the specificity of a CO test is 89% and the sensitivity is 90%. While cotinine in saliva has a sensitivity of 96–97% and specificity of 99–100% [20].

Data analysis

Categorical variables were summarised as frequencies and percentages. Continuous variables were calculated as medians since medians are less sensitive to extreme values. Statistical analysis was performed based on ITT. Chi-square test was applied for categorical variables. Independent Student's t-tests was used to compare the mean differences between the groups. Mann–Whitney U test was used to compare nonparametric data between groups. However, the Wilcoxon signed ranks test was applied within the same group. Statistical methods were two-tailed and a P-value of less than 0.05 was considered significant. The analysis was performed using the Statistical Package for Social Sciences (IBM®, SPSS® Inc., Chicago, IL, USA) for Windows version 21.

Ethical approval

The study questionnaire, protocols, consent forms, participant information sheet and study-related flyer to recruit the study subjects were approved by the Research Ethics Committee (IREC) of Kulliyyah of Medicine, International Islamic University Malaysia (IIUM), Kuantan on 9th October 2014, IREC no. 302. The study was also registered at the National Medical Research Registration (NMRR.NO:15–180-24,825). Written consent was obtained from all the participants before enrolment in the study.

RESULTS

Baseline characteristics of participants

There were no statistically significant differences in the demographic characteristics of the subjects of the two groups. In both groups, the median age was 23 years and almost 98% were male. The majority of DUs were unmarried at the time of recruitment. There was no significant difference in race between groups (P = 0.632). However, more than 80% of the study participants were Malays compared to Chinese (11.9%) and Indians (1.8%). Approximately 73% of users were either studying

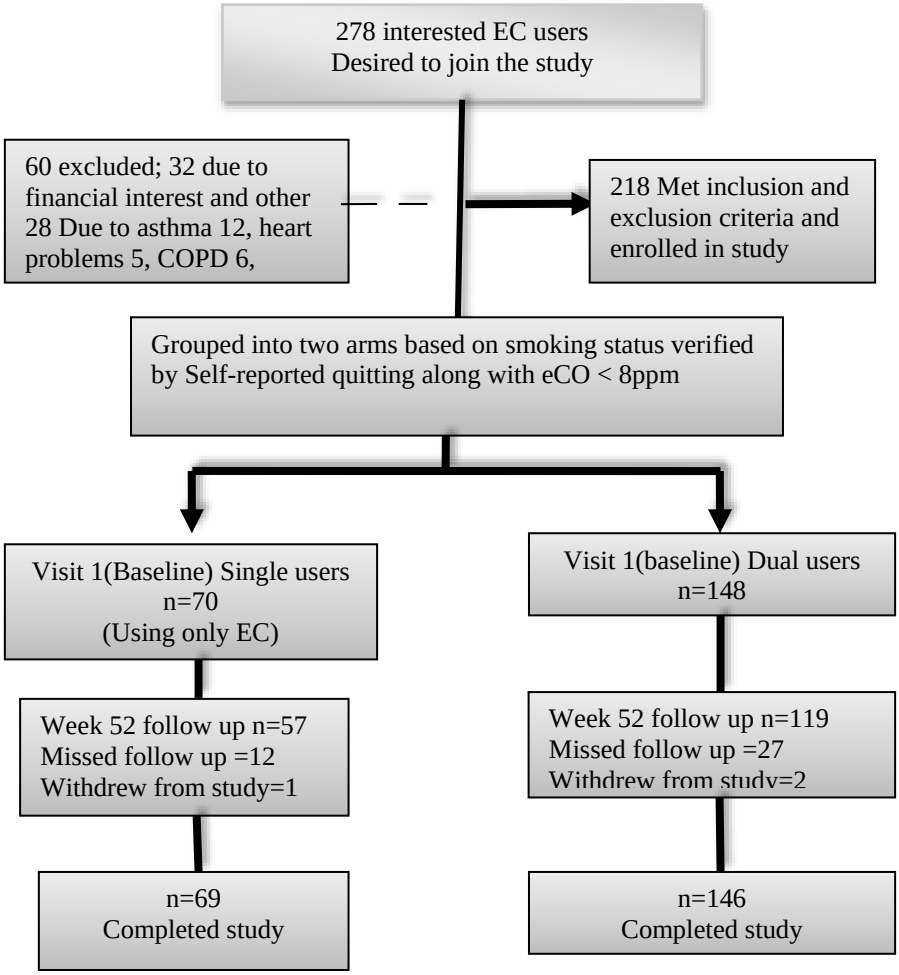

FIGURE 1. number of particpants at baseline and at week 52 among the single and dual vaper users. COPD: Chronic Obstructive Pulmonary Disease; eCO: Exhaled Carbon Monoxide; EC: Electronic cigarette; CC: Conventional Cigarette

or held a diploma or degree. Regarding profession and income, there was no statistical difference between the groups. More than 95% of the users in both the groups were using third-generation EC models i.e. Mods EC and the remaining participants reported using second-generation EC vape pens. Most of the participants of both groups used ECs daily, and only 1.4% used them occasionally (P = 1.000). The difference was insignificant. All participants reported using nicotine ECs at concentrations ranging from 6 to 18 mg/ml.

Evaluation of ECs effectiveness on nicotine abstinence and smoking cessation

The median intake of CCs in both the groups before EC use was 20 CCs per day. The nicotine cessation rate among SUs was high and significant as compared to DUs; i.e., 15.9% versus 6.8% (P = 0.048; 95% CI (2.328-0.902) (Table 1). Likewise, for smoking cessation, more SUs remained abstinent from smoking as compared to DUs, and this result was statistically significant, i.e., 34.8% versus 17.1% (P = 0.005; 95% CI: 2.031-0.787). The reduction in ≥ 50% of CCs consumption at week 52 was compared with CCs use prior to the starting the use of ECs. The consumption of CC among SUs who shifted to smoking again after 52 weeks was measured. A similar number of participants in both groups showed ≥ 50% reduction in CCs, i.e., 23.3% DUs versus 21.7% SUs (P = 0.863; 95% CI :1.020-0.964) and there was no significant difference after the 1-year follow-up period. At the end of the study, 47.3% of DUs relapsed to smoking as compared to 30.4% of SUs (P = 0.026; 95% CI: 1.555-0.757), this result was statistically significant. The overall EC status of both groups at baseline and week 52 is shown in Figures 2.

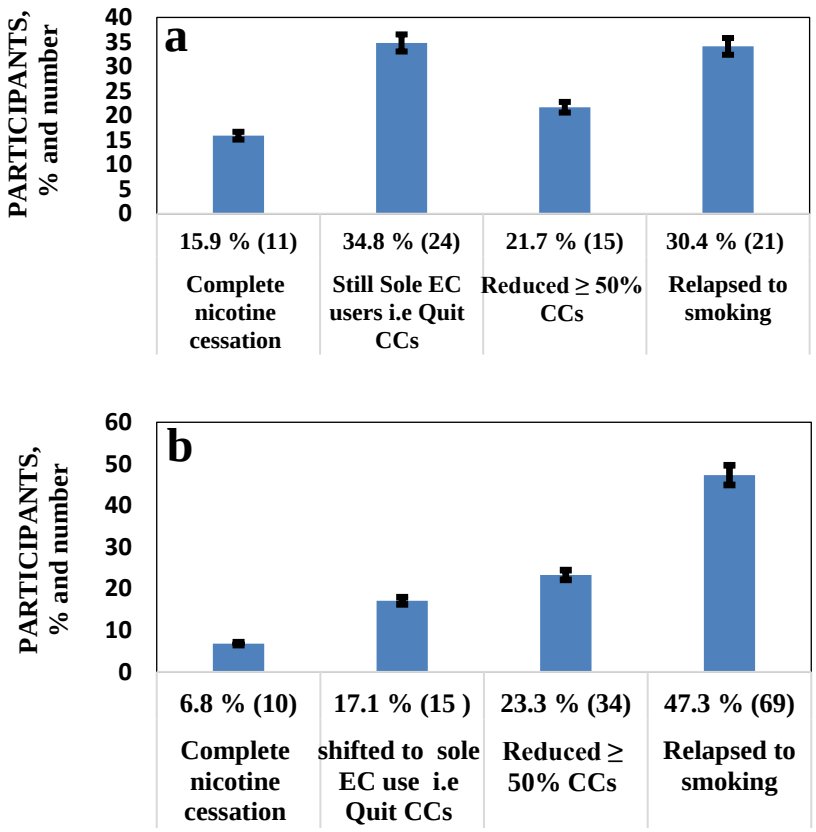

Figure 2. (a). Single Users Electronic Cigarette Status at Week 52. n=69; (b) Dual users electronic cigarette status at week 52 n=146. Error bars represent standard deviations. Keys: EC: electronic cigarette; CCs: conventional cigarettes

Evaluation of EC safety

Table 2 depicts possible EC adverse events among both the groups at baseline and week 52. The most resilient adverse effect reported by nearly 50% of participants in both groups at baseline was dry mouth. However, it was not statistically significant between the groups at both visits ($p > 0.05$). However, some noticeable adverse effects, such as cough and breathing problems, were common among DUs and significant during the entire study ($P < 0.05$) compared with SUs. Additionally, seven possible smoking-related diseases were recognised during the entire study period. The five smoking-related diseases recognised in DUs were chronic obstructive pulmonary disease [COPD], angina, diabetes, two cases of hypertension whereas in SUs each case of hypertension and diabetes were reported.

DISCUSSION

The current study not only evaluated the smoking cessation but also measured the complete nicotine abstinence rate. Tobacco expert authorities recommend that smoking cessation studies not only aim for smoking cessation but complete abstinence from nicotine should be the ultimate goal [1-3]. A 1-year follow up showed that nearly 10% of the study participants had completely stopped the nicotine intake. However, the nicotine cessation rate was two times higher in SUs as compared with DUs.

The smoking cessation rate in this study was found to be higher than some earlier studies like Caponnetto et al [7] and Bullen et al [6]. However, the current study smoking cessation results were comparable to Adriaens et al [8], Manzoli et al [9] and the recent Hajek et al [10]. Earlier studies

Table 1. Participants' status at week

NICOTINE ABSTINENCE AT WEEK 52 (INTENTION-TO-TREAT ANALYSIS)			
	7 Days Point Prevalence Abstinence Rate at Week 52; Testified by CO < 8 ppm + Zero level on saliva cotinine strips; n (%)	**OR (95% CI)**	***p* (2T)**
Single users	11 out 69 (15.9)	2.57 (2.328-0.902)	
Dual Users	10 out 146 (6.8)		0.048
The complete nicotine abstinence means stopped using any form of nicotine, confirmed by measuring CO level of < 8 ppm and zero level on saliva cotinine strips. Intention-to-treat analysis applied where all participants included except three subjects who were lost to follow-up.			
SMOKING CESSATION AT WEEK 52 (ITT)			
	7 Days Point Prevalence Smoking Cessation Rate at Week 52 Testified by CO < 8 ppm; n(%)		
Single users (remained as ECs users)	24 out 69 (34.8)	2.581 (2.031-0.787)	0.005
Dual Users	25 out 146 (17.1)		
The smoking cessation rate confirmed by measuring CO level of < 8 ppm. Dual users confirmed through who stopped CC use. Single user confirmed who retained to EC use only.			
SMOKING REDUCTION ≥ 50 % AT WEK 52			
	By calculating baseline conventional cigarettes consumption with Week 52		
Single User	15 out 69 (21.7)	1.092 (1.020-0. 964)	0.863
Dual User	34 out 146 (23.3)		
Reduction in ≥ 50% confirmed in dual users by comparing conventional cigarettes use prior to ECs use and at week 52. In single users by comparing use of conventional cigarettes prior to ECs us and after shifted to smoking at 52 weeks.			
RELAPSED TO SMOKING AT WEEK 52 (ITT)			
	7 Days Point Prevalence relapsed to smoking at Week 52 Testified by CO > 8 ppm: n (%)		
Single Users	21 out 69 (30.4)	2.055 (1.5559-0.7571)	0.026
Dual Users	69 out 146 (47.3)		
Relapsed to smoking confirmed by measuring CO level of > 8 ppm among both the group participants who relapsed to conventional cigarettes only at week 52. Keys: CC, conventional cigarette; EC=electronic cigarette; ITT, Intention to Treat; Odd ratio (OR); 95% Confidence Interval (95%CI).			

studies have indicated also that the sole, regular use of ECs (without the use of CCs) resulted in better smoking cessation rates compared with dual use [9,11, 21]. The reasons for the inconsistency in the results compared to certain RCTs may be that the current study participants were more confident to quit smoking compared to the subjects in the RCTs. Hence, care should be taken when comparing these results with other population studies. Another possibility is the use of distinct EC models and diverse topography features among the study participants. Previous studies revealed that newer EC models and distinctive topography between the users affect vaper fulfilment and satisfying their craving for smoking [23-24]. This study also evaluated the smoking cessation rate at week 52. At the final visit, smoking abstinence was evaluated regardless of their self-reported smoking status. As per the $PiCO^{+}$ Smokerlyzer® manual, a value of 0–6 ppm represents a non-smoker and a value of 7–10 ppm represents the danger zone, which indicates a low or passive smoker. In the present study, a cut-off value of < 8 ppm was used to discriminate EC and CC users based on previous studies [20,22].

The current study revealed a good rate of smoking cessation but showed a moderate nicotine cessation rate, which occurred in 10% of the study population at the 1-year mark. This indicated that participants who used ECs, even for an extended period, were unable to break their nicotine addiction, and it may be possible that many of the study participants were using ECs as an alternative device for nicotine. This notion is further supported by the fact that all the study participants were using nicotine ECs. Thus, nicotine plays a vital role in the success of ECs as a smoking cessation aid. Therefore, EC users may require more time to break their nicotine addiction as compared with other conventional FDA approved therapies. RCTs assessing the use of NRT, bupropion, and varenicline revealed nicotine abstinence rates in the range of 20 % to 35% in a period of 26 to 40 weeks [25,26]. Nevertheless, the above factors

make the role of ECs in smoking cessation control unclear. There is a likelihood that vaping may uphold nicotine addiction and could renormalize the smoking habit for ex-smokers and may disrupt a smoker's drive to quit. Besides, ECs may attract non-smokers, youngsters, and women to vaping. Moreover, the availability of ECs in several flavours may lead to nicotine addiction among non-nicotine users. [18]

Throughout this study, no mortality was reported. Most of the subjects experienced at least one side effect during the study period. The long-lasting adverse effect reported by more than half of the study population was dry mouth. This side effect could be triggered by the vegetable glycerine content of the e-liquid, which acts as a humectant, i.e., absorbs moisture. The adverse effects reported by the participants of this study were also reported in previous studies [14, 28-30]. However, certain adverse effects such as coughing and breathing problems were common among DUs, and the occurrence of these effects was significant as compared to SUs.

Previous studies have revealed that the above adverse effects are due to the contents of the e-liquids. The e-liquid ingredients, such as propylene glycol, when heated at a high temperature usually above 3 volts, are oxidised to many carcinogenic carbonyl compounds such as formaldehyde, acetaldehyde glyoxal, and methylglyoxal, whereas glycerol is oxidised to acrolein [31-33]. In reply to the formation of these harmful substances at high voltage, some authors have clarified that this high temperature generates a harsh taste termed as 'dry puff' in the vaping community, which EC users have realised and try to avoid [33].

The chief withdrawal symptoms, which were recognised in nearly two-thirds of the study population, was craving smoking, although this was primarily reported in DUs compared to SUs. The reason for craving smoking might be due to the inappropriate selection of nicotine concentrations in the e-liquids. Most of the current study participants were used a low nicotine concentration, i.e., 6 mg/ml [34], which usually does not deliver the required level of nicotine in the blood. Studies have shown that an e-liquid nicotine concentration of 18–24 mg/ml can give a plasma nicotine concentration of 8–16 ng/ml for inexperienced users within 5 min of vaping. This is roughly like the plasma nicotine concentration produced by CCs in smokers after 5 min of smoking [35]. Therefore, an appropriate selection of nicotine concentration in the e-liquids of ECs can help vapers to combat the urge to smoke.

Table 2. Adverse events and withdrawal symptoms experienced by both group users at baseline and week 52.

Adverse Events	Groups	Baseline			At Week 52		
		Total n (%)	Mean*	*p* 2-tailed	Total n (%)	Mean*	*p* 2-tailed
Dry Mouth	Dual user	82 (55.4)	1.23	0.062	14 (11.8)	0.12	0.552
	Single user	30 (42.9)	0.90		5 (8.8)	0.09	
Sore throat	Dual user	32 (21.6)	0.40	0.250	7 (5.9)	0.07	0.472
	Single user	9 (12.9)	0.27		4 (7)	0.11	
Cough	Dual user	34 (23)	0.55	<0.001	23 (19.3)	0.32	0.034
	Single user	8 (11.4)	0.16		8 (14)	0.14	
Anxiety	Dual user	0 (0)	0.00	0.321	nd	nd	nd
	Single user	1 (1.4)	0.03				
Stomach disturbances	Dual user	2 (1.4)	0.27	0.158	nd	nd	nd
	Single user	0 (0)	0.00				
Nausea	Dual user	nd	nd	nd	2 (1.7)	0.02	0.449
	Single user				2 (3.5)	0.04	
Vomiting	Dual user	0 (0)	0.00	0.033	4 (3.4)	0.05	0.713
	Single user	5 (7.1)	0.16		2 (3.5)	0.04	
Headache	Dual user	14 (9.5)	0.15	0.764	2 (1.7)	0.02	0.972
	Single user	6 (9.2)	1.13		1 (1.8)	0.02	
Breathing Problem	Dual user	27 (18.8)	0.32	<0.001	12 (10.1)	0.17	0.043
	Single user	2 (2.8)	0.04		3 (5.3)	0.05	

*, Mean of the severity on a o-4 scale; nd, not determined.

The safety of ECs was further assessed by documenting smoking-related diseases among study participants. The diseases recognised in the DUs were each case of COPD, angina, and diabetes and two cases of hypertension. Whereas in SUs, one each case of hypertension and diabetes were reported. As per smoking history data, all the disease affecting subjects were heavy smokers in smokers in the past and their average CC pack/year was 24.33 (± 8.89). The probable reason for smoking-related diseases among these seven participants might be due to their past smoking behaviours and not attributed to ECs use. However, tobacco experts consider ECs as a tobacco harm reduction (THR) device rather than an effective smoking cessation aid because it consists of nicotine but without smoke [3]. The THR policy aims to provide nicotine to tobacco users but deprive them of smoke. Some advisory groups have suggested that the THR strategy can be used in health care and in social policy to reduce damage to individuals or populations from the harmful effects of CCs use that cannot be entirely avoided or prohibited [3]

Nevertheless, ECs are not completely risk-free, and some health risks are associated with their use. Current studies have shown that ECs release a low level of toxicants [1,3,8]. However, the effects of inhalation of such a low level of toxicants over long periods have yet to be determined. Therefore, as per the available studies, the level of risk from ECs is low compared to CCs. However, with 1 year of observational data, it is not possible to compute the extended health hazards of ECs as compared with CCs. Therefore, longer studies are required to explore the harmful effects of compounds released from the EC e-liquids to guide existing vapers and policymakers to regulate their use.

Limitations of the study

There were some limitations of the study because it included mostly middle-aged Malay males with less Chinese and Indians from the Kuantan and Pekan districts of Malaysia. Additionally, due to constraints of funds and time, the investigator recruited participants from only two geographic regions in Malaysia. However, the current study participants baseline characteristics and EC use pattern were not significantly diverse from EC users of other geographical provinces of Malaysia. The demographic characteristics of the participants were compared with those from the two national EC surveys [11,16]. The researcher compiled the reported adverse events and smoking-related diseases for up to 1-year in a small sample size. However, with the 1-year observation period and small sample size, it is not possible to determine the health hazards of ECs. Therefore, for a thorough evaluation of safety, a period longer than 1-year and the larger sample size is required to explore the harmful effects of ECs in both SUs and DUs. Further, the severity of adverse events and the appearance of smoking-related diseases during the study period were based on subjects' own experience.

CONCLUSIONS

As per the current study results, the SUs are 2.57 times more likely to achieve complete nicotine-free status and smoking cessation rates as compared to DUs. However, the use of electronic cigarette reduced the use of CCs equally in both groups. This study did not find any serious adverse events related to the use of ECs. But electronic cigarette SUs showed fewer side effects than DUs. However, we are unable to conclude that the sole use of ECs is safe in absolute terms. Therefore, extended studies are required to confirm ECs safety amongst different populations.

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AVAILABILITY OF DATA AND MATERIALS. The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

COMPETING INTERESTS. The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS. MH and AR were responsible for the study concept, preparation of the questionnaire, data analysis and result interpretation. MH and AR prepared the manuscript. AR and SM were responsible for data collection. All the authors read and approved the final manuscript.

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