Arch Bronconeumol. 2014;50(8):362–367

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Special article

The Electronic Cigarette. Official Statement of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) on the Efficacy, Safety and Regulation of Electronic Cigarettes☆

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ARTICLE INFO

Article history:
Received 14 December 2013
Accepted 7 February 2014
Available online 1 July 2014

Keywords:
Electronic cigarette
Efficacy
Safety
E-cigarette regulations

ABSTRACT

The electronic cigarette (EC) is a device formed by 3 basic elements: battery, atomizer and cartridge. When assembled, it looks like a cigarette. The cartridge contains different substances: propylene glycol, glycerine and, sometimes, nicotine. When the user "vapes", the battery is activated, the atomizer is heated and the liquid is drawn in and vaporized. The smoker inhales the mist produced. Various substances have been detected in this mist: formaldehyde, acetaldehyde and acrolein and some heavy metals. Although these are found in lower concentrations than in cigarettes, they may still be harmful for the human body. Several surveys show that 3%–10% of smokers regularly use e-cigarettes. A randomized study has shown that the efficacy of e-cigarettes for helping smokers to quit is similar to nicotine patches. Nevertheless, the study has relevant methodological limitations and reliable conclusions cannot be deduced. This report sets down the Position Statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) on the efficacy and safety of e-cigarettes. This statement declares that e-cigarettes should be regulated as medicinal products.

El cigarrillo electrónico. Declaración oficial de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) sobre la eficacia, seguridad y regulación de los cigarrillos electrónicos

Palabras clave:
Cigarrillo electrónico
Eficacia
Seguridad
Regulación de los cigarrillos electrónicos

RESUMEN

El cigarrillo electrónico (CE) es un dispositivo que está constituido básicamente por tres elementos: la batería, el atomizador y el cartucho. Estos tres elementos se ensamblan unos con otros y forman un dispositivo que tiene el aspecto de un cigarrillo. El cartucho está cargado con líquido que puede contener diferentes sustancias: propilenglicol, glicerina y, en ocasiones, nicotina. Cuando el sujeto «vapea» y la batería entra en funcionamiento, se calienta el atomizador y el líquido se vierte en el interior del mismo y se convierte en vapor. Este vapor es el que es inhalado por el consumidor. Diferentes sustancias se han detectado en el mismo: formaldehido, acetaldehído, acroleína y diversos metales pesados. Estas sustancias aunque se encuentran en cantidades más bajas de las que se detectan en los cigarrillos habituales, tienen capacidad para producir patología en humanos. Diversas encuestas muestran que entre un 3 y un 10% de los fumadores de todo el mundo son consumidores habituales de este tipo de productos. Un estudio aleatorizado ha mostrado que la eficacia de los CE para dejar de fumar pudiera ser similar a la

☆ Please cite this article as: Jimenez Ruiz CA, Solano Reina S, de Granda Orive JI, Signes-Costa Minaya J, de Higes Martinez E, Riesco Miranda JA, et al. El cigarrillo electrónico. Declaración oficial de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) sobre la eficacia, seguridad y regulación de los cigarrillos electrónicos. Arch Bronconeumol. 2014;50:362–367.

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1579-2129/$ – see front matter

de los parches de nicotina. No obstante, tiene importantes deficiencias metodológicas que no permiten obtener conclusiones fiables. En este artículo se muestra la Declaración Oficial de la Sociedad Española de Neumología y Cirugía Torácica sobre eficacia y seguridad del CE. En ella se recoge la solicitud de expertos de dicha sociedad de que el CE debería ser regulado como un producto medicinal.

Introduction

Since they first appeared in China in 2003, patented by pharmacist Hon Lik, electronic cigarettes (EC) have burst onto the world market. The number of consumers, known as "vapers", is increasing daily, and sales by companies that market them are expanding year by year.[1]

The use of ECs is not without its controversy, not only among users of the product, but also among various groups of healthcare professionals.

Below, a group of experts on smoking from the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), made up of members from both the SEPAR Smoking Area and the Integrated Program for Research on Smoking, present a review of various aspects of this new device for nicotine inhalation.

What Is an Electronic Cigarette? Types of Electronic Cigarette

An EC is a battery-operated device that releases a vapor or mist (which may contain nicotine) that can be inhaled by the user.

It consists basically of 3 elements: a battery, atomizer and cartridge. When assembled, it looks like a cigarette. The cartridge may contain different substances: propylene glycol, glycerine and, sometimes, nicotine. When the user "vapes", the battery is activated, the atomizer is heated and the liquid is drawn in and vaporized. The smoker inhales the mist produced. Since their introduction in 2009, the design of these devices has become more sophisticated, but while their outer appearance has changed, becoming more attractive and available in different shapes and colors, they remain essentially the same. The battery lasts longer and the cartridge can be filled with a liquid that is sold separately and comes in small containers. These liquids can have different doses of nicotine. It is worth noting that there are currently numerous patents for EC –up to 19 in Europe, of which 14 are registered in the United Kingdom.

The cartridge of the EC is filled with liquid, an essential part of the device. It contains 95% propylene glycol and vegetable glycerine, which produce the mist. The liquid in almost all brands of EC also contains nicotine in various concentrations, ranging from 0 to 36 mg/ml. Other components include flavorings, such as: tobacco, mint, cinnamon, fruit, etc. Some additives are also added to lessen the irritating action on the oropharynx.

Studies on the Use of Electronic Cigarettes

ECs are used mainly by smokers who want to quit or cut down on smoking, or by former smokers. However, some surveys have shown that a small number of non-smokers also use these products.

Recent Eurobarometer data show that 7% of smokers from 27 European countries have occasionally used ECs: 5% have used them once or twice, 1% use them occasionally, and 1% use them regularly.[2]

Data from the International Tobacco Control Four-Country Survey show that 7.6% of smokers in these countries have used ECs occasionally, and that 2.9% were regular "vapers" at the time of the survey.[3,4]

As far as the authors are aware, there are no reliable studies in Spain from representative surveys that show data on the prevalence of EC use.

The latest data on EC use are possibly those published in the *Smoking Toolkit Study*. This is a monthly Internet survey carried out in England[5] with data on EC use from the second quarter of 2011. The figures show that at present (third quarter of 2013), 16% of English smokers have used an EC occasionally, and 10% do so regularly. It is notable that during the second quarter of 2011, only 2% used EC regularly or had tried them.[5]

The most representative data on EC use in young people comes from 2 studies: one is a study conducted in Poland on a sample of 13,250 subjects aged between 15 and 24 years, of whom 20% had tried ECs, and up to 7% had done so in the last month. Significantly, 3.2% of those who had used them were non-smokers.[6] This figure approaches the 4.9% reported by Sutfin et al.[7] in their study on students. According to data from the *Global Youth Tobacco Survey* (GYTS), in 2012 in Hungary 13% of children aged between 13 and 15 years had tried ECs in the last month. Worryingly, up to 4.7% of young non-smokers had tried the device,[8,9] suggesting that in some individuals ECs could be a precursor to smoking manufactured cigarettes.

The Electronic Cigarette Market

Eurobarometer data from 2012 indicate that 69% of Europeans have heard of ECs.[2] Data from English-speaking countries show that 73% and 54% of American and British people, respectively, are familiar with ECs, while awareness of these devices is lower than 35% among Canadian and Australian citizens.[3] It is worth noting that the sale and distribution of ECs are banned in both these countries.

In the United States, sales of ECs and refills increased 9- and 14-fold from 2010 to 2012, respectively.[10] The circulation and marketing of these products in the United States have been spectacular. Suffice to say that during the Grammy awards ceremony in 2010, ECs were given as a gift to attendees, and have even been promoted in some American films.[11]

EC sales have also risen exponentially in the United Kingdom, going from a few thousand in 2006 to 600,000 in 2012, an annual increase of 500%.[12] In some countries, this increase in sales has not been sustained over time. In Italy, for example, sales of ECs increased for one year, before gradually falling.

The EC market in Europe is very fragmented and is led by small firms,[13] although large tobacco companies are very interested in this product. In 2012, the American tobacco company Lorillard bought one of the top EC companies in America (*Blu e-Cigs*).[14,15] At present, other major tobacco companies, such as Reynolds

American Inc., BAT and Philip Morris, are researching and developing new EC-type products.[16–18]

Chemical Substances Present in Electronic Cigarettes. Safety of Use

Two aspects must be considered with respect to the chemical substances present in ECs: on one side, the substances contained in the liquid with which the EC is filled; on the other, those produced as a result of heating the aforementioned liquids, and which are then carried in the mist emitted by the EC.

The liquid with which ECs are filled contains the following substances: propylene glycol, glycerine, nicotine, flavorings (tobacco, mint, fruit, cinnamon, etc.) and other additives.

Propylene glycol is the fundamental component of the liquid, and is considered safe for use as an ingested substance.[19] However, there is little data on its safety when inhaled using products such as ECs. Some studies have shown that prolonged inhalation may cause irritation of eyes, throat and airways, as well as asthma in children.[20–22] It should be assumed that EC users would be exposed to inhalation of this substance throughout the day over a more or less prolonged period of use. This could be particularly dangerous for subjects with underlying respiratory problems. In fact, some EC manufacturers warn about this aspect in their product literature.[23]

Glycerine is another of the basic components of EC liquids. This substance is considered safe when consumed orally, but its effects when inhaled are unknown. A recent article presented the case of a 42-year-old woman who had been using ECs for 7 months, and who had developed sub-acute symptoms of fever, cough and dyspnea. Analysis of sputum and bronchoalveolar wash samples revealed lipid-laden macrophages. The patient was diagnosed with lipoid pneumonia. Quitting EC use resulted in improvement and disappearance of her condition.[24]

The liquid in EC contains nicotine in doses ranging between 0 and 36 mg/ml. The main problem it can cause is that, due to manipulation of the liquid to insert it into the atomizer, part of this nicotine may come into contact with the skin and cause irritation or may be ingested accidentally by children. It is known that ingestion of only 6 mg can be lethal for this group.[19]

Small quantities of nitrosamines and diethylene glycol have also been found in the liquids of some brands of EC.[25–27]

The mist emitted by ECs is also full of chemical substances that may pose a health risk, among them formaldehyde, acetaldehyde and acroleins, although these are found in lower concentrations than in cigarette smoke.[28,29] Metals such as nickel, chromium and lead have also been found in EC mist, and it is believed that they are produced by the atomizers. It is notable that nickel levels in the mist of ECs are higher than those detected in cigarette smoke.[30] The *International Agency for Research on Cancer* classifies all these substances as carcinogenic, with no safety threshold for their consumption.[31,32]

One study analyzed the acute effects on the respiratory tract of inhalation of an EC for 5 min in 30 healthy smokers. The study showed that this did not affect basic lung parameters such as the FEV_1, FVC, PEF and $MEF_{50\%–75\%}$, although it did reduce exhaled nitric oxide levels and increase peripheral airway resistance and impedance. Although both the reduction in the nitric oxide levels (by 2.14 ppb, p=.005) and the increase in the resistance (β: 0.042 kPa/[l/s]; p=.024) and impedance (by 0.04 kPa/(l/s), p=.003) were significant, they were not accompanied by acute clinical manifestation. However, their long-term clinical significance could not be evaluated or entirely ruled out.[33] At present, there is a significant lack of serious studies evaluating the possible short-, mid- and long-term effects of the use of ECs on lung function.

ECs emit substances into the environment, including propylene glycol and nicotine as well as liquid particles smaller than 2.5 μm in diameter (PM 2.5). These particles can permeate the lungs and cause damage associated with passive consumption of ECs in "non-vapers". A study measuring the particles released into the environment by ECs and conventional cigarettes found that the quantity emitted by the latter far outweighed that of ECs (901 $\mu g/m^3$ for conventional cigarettes vs 43 $\mu g/m^3$ for ECs). It should be noted that the safety threshold issued by the WHO for these types of substances[34] is slightly below 43 $\mu g/m^3$.

Studies on the Use of the Electronic Cigarette as a Smoking Cessation Aid

This section will analyze studies conducted to assess the efficacy of the EC as a device to aid smoking cessation.

These studies can be roughly divided into those that assess the efficacy of ECs in controlling withdrawal syndrome symptoms, and those designed to evaluate the efficacy of the product in achieving complete cessation.

Some studies have found that ECs are effective in controlling cravings and other withdrawal syndrome symptoms. A study by Bullen et al.[35] showed that the use of an EC with 16 mg of nicotine for one hour by a group of 40 smokers resulted in a significant reduction in cravings compared to a group using placebo (p=.006). A more recent study by Vansickel and Eissenberg analyzing a small group of regular "vapers", found that inhaling ECs with nicotine significantly reduced different symptoms of abstinence syndrome.[36]

Another important aspect that requires analysis is whether ECs are effective in releasing sufficient quantities of nicotine to warrant their use in nicotine replacement therapy. A recent study has shown that in order to obtain sufficient nicotine levels using an EC, it is essential to use the correct "vaping" technique.[37] Subjects who "vape" correctly can quickly absorb up to 25 ng/ml, while those who do not only absorb up to 3 ng/ml.[37]

To date, only two randomized, placebo-controlled studies have been conducted to evaluate the efficacy and safety of ECs in smoking cessation treatment: the ECLAT study[38] and the study by Bullen et al.[39]

The ECLAT study was a prospective, 12-month randomized study that evaluated the efficacy of EC in achieving abstinence or reduction in a group of 300 smokers who did not wish to quit.[38] One group of subjects received ECs containing 7.2 mg of nicotine for 12 weeks, another received the same dose followed by a further 6 weeks with an EC containing 5.4 mg of nicotine, and a third group received a nicotine-free EC for 12 weeks. The results showed a decline in the number of cigarettes smoked per day in all groups, and smoking reduction was observed in 22.3% and 10.3% of subjects after 12 and 52 weeks of follow-up, respectively. Complete abstinence was documented in 10.7% and 8.7% of subjects at 12 and 52 weeks of follow-up, respectively. Acceptance of ECs by the study participants was satisfactory.[38]

In the study by Bullen et al.,[39] the authors randomized a group of 657 smokers who wanted to quit smoking to 3 treatment arms: (a) EC with 16 mg nicotine; (b) 21 mg nicotine patches, and (c) nicotine-free EC. The subjects used treatment from one week before and 12 weeks after quit day. The results showed that after 6 months of follow-up, the abstinence rate for the group who used nicotine ECs was 7.3%, 5.8% for patches, and 4.1% for nicotine-free ECs. The authors explained that the study did not have sufficient statistical power to conclude that nicotine ECs are

more effective than nicotine patches. Nevertheless, they reported that the efficacy of nicotine ECs as a smoking cessation aid was similar to that of patches. Furthermore, they did not find that use of nicotine ECs was accompanied by more frequent or serious adverse effects than those associated with the nicotine patch treatment.[39]

These studies appear to show promising results. However, they suffer from major methodological flaws, and as such their conclusions cannot be definitive. Neither study included a blind arm, nor all subjects using the EC knew that it was a new form of treatment that could give them a better chance of success than subjects randomized to the nicotine patch group, some of whom had previously used them unsuccessfully. Additionally, the number of subjects who dropped out or were lost to follow-up was higher in the groups that used patches compared to those that used EC.

Regulation of Electronic Cigarettes

There are 3 possible categories for the regulation of ECs: a medicinal product; a tobacco product; or a consumer product. The most rational option is for ECs to be regulated as a medicinal product.

There are 2 fundamental reasons for regulating ECs as a medicinal product: presentation and function. ECs are usually presented as products that not only help quit smoking, but also to reduce the number of cigarettes smoked, and even alleviate withdrawal syndrome symptoms. The presentation of ECs in different nicotine doses further strengthens the opinion that these devices should be regulated as a medicinal product. Moreover, from a functional point of view, ECs containing nicotine, regardless of the amount, require regulation as medicinal products. Nicotine produces pharmacological and toxic effects on the body. The amount of nicotine contained in these devices is not only capable of causing pharmacological effects on users, but also toxic effects if they are not used in accordance with certain instructions.

The regulation of ECs as a medicinal product would facilitate the scientific evaluation of their efficacy and safety for treating withdrawal syndrome. It would also force manufacturers to adopt more stringent quality control strategies, and limit the current indiscriminate access to the product, especially among young people who may use them as a gateway to smoking. Following this, ECs should be regulated according to European Union Directive 2001/83/EC relating to medicinal products for human use.

It is important to note that regulation of ECs as medicinal products should be accompanied by adequate legislation to control not only the use of these devices in public places, but also advertising, promotion, distribution and sale. This may mitigate the gradual retreat from regarding smoking in public places as unacceptable, an attitude initially achieved by anti-smoking regulations.

Up to 12 countries in the European Union support the regulation of ECs as medicinal products: Austria, Denmark, Estonia, Finland, Germany, Hungary, Holland, Portugal, Romania, Slovenia, Sweden and France. A large number of scientific institutions are also in favor of this type of classification. Among these are the British Medicines and Healthcare Products Regulatory Agency (MHRA), which plans to regulate ECs as medicinal products in the United Kingdom from 2016[40]; the International Union against Tuberculosis and Lung Diseases (IUTLD)[41]; the German Cancer Research Center[42]; the WHO working group on tobacco product regulation,[43] and some pharmaceutical companies.[44]

In Spain, the Minister for Health, Social Affairs and Equality has announced that the use and sale of these products will shortly be regulated.

Official Statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) on the Efficacy, Safety and Regulation of Electronic Cigarettes

1. Electronic cigarettes (ECs) are devices used to vaporize a liquid composed of a mixture of chemical substances that are deposited in the user's lungs on inhalation.
2. The substances most frequently found in the liquid of ECs are propylene glycol, glycerine and nicotine, although some brands do not contain nicotine. Propylene glycol and glycerine have been shown to be harmless when used orally. However, when inhaled, as in the case of ECs, their safety has not been clearly demonstrated.
3. Various substances have been detected in the mist released by ECs: formaldehyde, acetaldehyde and acroleins. These substances are also present in the smoke of manufactured cigarettes, although in higher quantities than in ECs. Formaldehyde and acrolein are formed as a result of heating the glycerine. Metals such as nickel, chromium and lead have also been found in EC mist. It is notable that nickel levels found in the mist of ECs are higher than those detected in cigarette smoke. The International Agency for Research on Cancer classifies all these substances as carcinogenic, and no safety thresholds have been determined for their consumption. Furthermore, some of these substances can damage the pulmonary interstitium.
4. One study found that the mist produced by ECs contains PM 2.5 particles which, in addition to being harmful for active EC users, may also be damaging for passive smokers of these types of products.
5. At present, most of the general population has heard of ECs: between 30% and 90%, depending on the country. It is notable that between 1% and 10% of smokers in the United States and in various European countries are regular EC smokers. It is of concern that ECs have been used occasionally by 20% of young people, and that between 3% and 5% of young non-smokers have used them at some time.
6. Some studies have found that ECs, both with and without nicotine, may help control withdrawal syndrome symptoms. However, these studies had very small samples and major methodological flaws, and as such cannot be used to support the recommendation that these devices be used to alleviate withdrawal syndrome symptoms in smokers.
7. To date, only two randomized clinical studies designed to evaluate the efficacy and safety of ECs to help smokers quit or reduce the number of cigarettes smoked have been conducted. Both studies have shown promising results. However, they have major methodological flaws that do not allow reliable, definitive conclusions to be drawn about the efficacy and safety of ECs as smoking cessation treatment or to reduce the number of cigarettes smoked.
8. ECs should be regulated as medicinal products. This will control their use, enable compliance with manufacturing and distribution quality standards to be monitored, and facilitate scientific and medical research on this device.

In view of the above, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) considers it necessary and urgent that:

A. The Spanish health authorities regulate ECs and their accessories as medication. This would control their current indiscriminate use, which is not only a threat to public health, but may

encourage young people to start smoking. Moreover, it damages the process of "de-normalization" of smoking in public places resulting from current smoke-free laws. Furthermore, the regulation of these devices as medication would also help to ensure that their production and distribution conform to the quality and safety standards required for products for pharmaceutical use. This type of regulation would also facilitate scientific and medical research into these devices.

B. National and international scientific communities set up extensive, quality clinical studies without the methodological flaws present in those conducted to date, which can be used to reliably determine the efficacy and safety of use of ECs not only as a smoking cessation aid, but also as a mechanism for helping to reduce the number of cigarettes smoked.

Likewise, SEPAR would like to use the dissemination of this document on ECs to encourage all smokers in the general population to quit smoking. To that end, we recommend that they see a healthcare professional who will give them support and advice, and who can prescribe medicinal treatments that have been shown to be effective and safe as smoking cessation aids: nicotine replacement therapy, varenicline and bupropion.

Conflict of Interests

None of the authors report any conflict of interests.

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