Improvement in Pulmonary Function Following Discontinuation of Vaping or E-cigarette Use in Adolescents with EVALI

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Abstract

Introduction: In 2019, an alarming number of cases coined as e-cigarette, or vaping, product use associated lung injury (EVALI) was described in adolescents ranging from mild respiratory distress to fulminant respiratory failure. Limited data has been published on outcomes at short term follow-up. We aimed to describe pulmonary manifestations, function and radiologic findings after corticosteroid therapy in a cohort of adolescent patients. Methods: A retrospective chart review of all patients presenting to our institution between July and December 2019 with EVALI was conducted. Patients who had pulmonary follow-up were included. Spirometry was performed prior to discharge from the hospital and during outpatient follow-up. A paired t-test was used to compare serial spirometry data between visits. Results: Eight patients (6 males) were included. Two patients required intubation with mechanical ventilation, 2 required bilevel positive airway pressure (BPAP), and 3 required oxygen supplementation. All patients received glucocorticoids (3 receiving pulse dosing). Initial spirometry revealed decreased forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) with clinically and statistically significant improvement at follow-up. Diffusing capacity of the lungs for carbon monoxide (DLCO) was decreased in 2/6 patients initially and in 4/5 at follow-up. Radiographic manifestations also improved after vaping was discontinued. Conclusion: In our cohort of patients with EVALI, at short term follow up, all normalized their spirometry parameters. However, most did not normalize their DLCO on follow up, raising concern for risk of developing chronic lung disease later in life.

INTRODUCTION

An epidemic of e-cigarette or vaping product use-associated lung injury (EVALI) has affected thousands of people in the United States (1, 2). Vaping involves the inhalation of concentrated, noxious chemicals mixed with attractive flavorings. It has been increasingly popular with adolescents and young adults as an alternative method of consuming nicotine and non-nicotine products such as tetrahydrocannabinol (THC). The process in which e-cigarette liquid is aerosolized involves heating the liquid using an atomizer made of metal. Another common practice of aerosolization is dabbing, which involves placing concentrated marijuana as wax or hashish onto an extremely hot metallic surface and inhaling the vapor produced. This aerosolization releases toxic chemicals and metallic nanoparticles that deposit into the user's lungs following inhalation and cause lung injury (3).

This disease was initially described in August 2019 with a preliminary report outlining a cluster of patients presenting to hospitals with a recent history of vaping and subsequent pulmonary and constitutional symptoms (1). As of February 18, 2020, the CDC reported 2,807 hospitalized cases in the United States with 68 deaths (2). The initial presenting symptoms of EVALI have now been well characterized by a series of publications describing patients presenting with fever, respiratory distress (cough, dyspnea, tachypnea), nausea, vomiting, malaise and weight loss (1, 2, 4, 5, 6). Characteristic radiographic findings on computerized

tomography (CT) include bilateral consolidation, ground-glass opacities, septal thickening, crazy-paving and lymphadenopathy (7, 8). Patients present with varying degrees of severity ranging from mild symptoms not requiring respiratory support to acute respiratory failure requiring increased respiratory support, mechanical ventilation and in rare cases, leading to death (6). As the number of new cases have declined since August 2019 (2, 6, 9), there have been limited reports describing outcomes and follow-up. There has been subjective data on clinical resolution of symptoms following discontinuation of vaping and e-cigarette use and treatment with corticosteroids. However, data on pulmonary function testing (PFT) on patients diagnosed with EVALI has been limited to outpatient follow up with qualitative reports on spirometry (4, 5, 16). Kalininsky et al. reported resolution in spirometry and radiographic findings in their cohort of patients during follow up (4) and Blagev et al. reported mild abnormalities during follow-up spirometry in 6/9 patients (5). Recently, a report by Carroll et al. described residual abnormalities in pulmonary function testing in 7/11 patients during short-term follow-up (16), and a report by Wang et al from our institution described complete or near-complete resolution of radiographic abnormalities in nearly all cases with a median follow-up period of 114 days (8). In this study, we aim to describe changes over time in quantifiable spirometry values, clinical findings, and radiographic findings in on follow-up in pediatric patients who were hospitalized for EVALI at our medical center.

MATERIALS AND METHODS

Study Design

We performed a retrospective medical records review of patients diagnosed with EVALI admitted to our pediatric tertiary care hospital. Approval for the study was obtained from the Baylor College of Medicine Institutional Review Board (IRB) with a waiver of informed consent.

Study Subjects and Selection Criteria

A retrospective chart review of the electronic medical record in a single pediatric tertiary care hospital was performed for patients that were diagnosed with a confirmed or probable EVALI (1) between August 2019 to February 2020. A confirmed case is described as 1) use of e-cigarettes (vaping) or dabbing within 90 days of symptom onset; 2) pulmonary infiltrate on chest radiograph (CXR) or CT scan; 3) absence of pulmonary infection on initial workup; and 4) no evidence in the medical record of an alternative plausible diagnoses. A probable case would be defined as a patient who fulfills the aforementioned criteria but instead has an identified respiratory infection by polymerase chain reaction or culture and the clinical team caring for the patient does not believe that e-cigarette use was the only etiology for the onset of symptoms (1). Inclusion criteria for our study included: 1) Age 18 years or younger, who were seen at our medical center with a confirmed or probable case of EVALI; and 2) had at least two spirometry tests performed separated by an interval period (mean: 46.5 days) with the first test occurring after diagnosis of EVALI. Details abstracted from the electronic medical record included patient demographic information, e-cigarette and other illicit drug use, duration and frequency of use, clinical symptoms upon presentation, treatment course, clinical progression, spirometry, imaging studies and bronchoalveolar lavage (BAL) results.

Spirometry

Pulmonary function testing was performed on our patients admitted to the hospital prior to discharge upon clinical stabilization (extubated, off supplementary oxygen and hemodynamically and clinically stable to perform appropriate pulmonary function maneuvers). Follow-up pulmonary function testing was obtained during outpatient visits at the pediatric pulmonary clinic separated by an interval period of time following discharge from the hospital. Pulmonary function tests were performed by respiratory therapists using a spirometer adherent to the ATS/ERS standard guidelines (10, 11). Predicted values were based off the European Respiratory Society Global Lung Function Initiative standardization of spirometry based on average multi-racial variability in height, age and gender (12). Diffusion capacity of the lung for carbon monoxide results were corrected for alveolar volume and hemoglobin concentration in the blood (10).

Bronchodilator response was determined by administering four puffs of albuterol (90 mcg/puff) via metered

dose inhaler with a spacer. Spirometry repeated 15 minutes after bronchodilator administration. Differences in pulmonary function test values comparing baseline in hospital to outpatient follow-up was determined using a paired t-test. Statistical significance was accepted as a 2-tailed p-value < 0.05.

Imaging Analysis

CXRs and CT scans were obtained during the patient's hospital course and outpatient follow-up. Available imaging was evaluated independently by two board certified pediatric radiologists who were blinded to demographic information and clinical presentation (8). Inter-observer agreement was analyzed using the chance-correlated index Kleiss' weighted $\varkappa$ (kappa) statistic based on the Landis and Koch benchmarks (13, 14).

RESULTS

Clinical Presentation

We identified 8 patients (6 male, 2 female; mean age 16.25 years old) with a diagnosis of EVALI who were admitted to our hospital and subsequently followed as an outpatient. All 8 patients reported vaping THC containing products, with 5 of the 8 also vaping nicotine containing products. Seven patients also reported smoking marijuana, 1 patient reported use of combustible tobacco, and 1 patient reported other substance abuse. Drug screens were positive for THC on seven patients, and positive for methamphetamine for 2 patients.

Our patients presented with symptoms of fever (8/8), cough (8/8), nausea and vomiting (7/8), weight loss (4/8) and respiratory distress (4/8) (Table 1). Seven patients were hospitalized and placed on respiratory support; one patient was seen in the emergency department without necessitating respiratory support. Two patients were intubated and required ventilatory support, 2 patients needed bilevel positive airway pressure (BPAP), and 3 patients required supplemental oxygen (Table 1). All patients received systemic corticosteroids during their acute illness, with 5 patients receiving methylprednisolone intravenously (IV) and the remaining 3 receiving oral prednisone. Two patients received pulse corticosteroid dosing (1g daily for 3 days) with the rest of the patients receiving regular dosing (maximum of 2mg/kg daily). One patient's course was complicated by hypotensive shock requiring vasopressor support. That patient received a longer course of IV steroids (500 mg for 8 days) with a prolonged taper of oral steroids for 3 more weeks. Upon clinical stabilization and completion of steroid courses, all patients performed pulmonary function testing prior to discharge from the hospital. All patients that were admitted were subsequently discharged with no reported short-term adverse side effects to steroid treatment. During outpatient follow-up, 7 patients reported to have discontinued vaping, while 1 patient reported stopping vaping THC but continued vaping nicotine. One patient reported exercise-induced dyspnea approximately 1 month after discontinuing vaping and the rest of the patients reported complete resolution of initial clinical symptoms such as fever, dyspnea, nausea, vomiting, weight loss and respiratory distress during outpatient follow-up. Patients who endorsed weight loss reported regaining the weight back after discontinuing vaping.

Spirometry

Serial spirometry for each patient was performed and measured between hospital discharge and outpatient follow-up (mean interval 46.5 days). Initial spirometry measurements showed moderately to severely reduced FVC (mean volume 3.46L, 80.2% predicted) and FEV1 (mean volume 2.89L, 76.39% predicted), with all improving to normal range on follow up with FVC (mean volume 4.70L, 108.26% predicted; $p < 0.01$) and FEV1 (mean volume 3.82, 105.7% predicted; $p < 0.01$) (Table 2). Corrected DLCO was measured initially for 6 patients (4/6 normal, 1/6 mildly decreased and 1/6 moderately decreased) and on follow-up, 5 patients underwent DLCO testing (1/5 normal and 4/5 mildly decreased).

Imaging

Chest imaging was performed on each patient during hospitalization and at outpatient follow-up to aid in assessment of severity and progression of the disease. All patients underwent a CXR and 7/8 patients had a

chest CT scan at presentation. Five out of 8 patients had a repeat CXR at follow-up, and 4 out of 7 patients had a repeat chest CT scan. All chest CT scans obtained at presentation were abnormal and 7/8 CXRs at presentation were abnormal. Repeat CXR findings from all 5 patients showed significant improvement or resolution of the initial findings. Chest CT scans revealed bilateral ground-glass opacities, consolidation and mediastinal lymphadenopathy in most patients at presentation. Repeat chest CT findings revealed complete or near complete resolution of the initial chest CT findings (Figure 1) with exception of one patient having widespread CT abnormalities (Figure 1D) related to continued vaping of nicotine products on outpatient follow up. A more detailed description of the imaging findings for 7 of these patients was previously reported in the radiology literature by Wang et al (8).

DISCUSSION

We present a cohort of adolescents diagnosed with EVALI and followed-up in our hospital after clinical resolution of symptoms. All of the adolescents in our cohort describe vaping THC containing products and reported discontinuation of THC containing products on follow up.

We found that spirometry parameters were all moderately to severely abnormal at baseline, and improved to normal range on follow up. There was a decrease in corrected DLCO in most of the patients we tested on follow-up, suggesting interstitial lung changes or damage that could increase risk for future development of chronic lung disease. Our data demonstrates clinically important and statistically significant improvement in spirometry values with respect to FEV1 and FVC. In comparing to previous reports characterizing the symptoms and clinical course of patients affected by EVALI, our patients experienced similar clinical resolution (4, 5, 15, 16). A majority of patients affected by EVALI show significant improvement by clinical (4, 5, 15), radiologic (8) and spirometric assessment (17).

The radiographic findings in our patients closely follow the improvement in the patient's pulmonary function and clinical status following discontinuation of the offending agent, expanding upon the earlier observation reported by Wang et al (8). The one patient with significant abnormalities on follow-up CT scan had continued vaping nicotine (not THC products), suggesting that cessation of all vaping product use is required for optimal resolution of EVALI lung disease. Several of the adolescents in our case series had evidence of other drug abuse, suggesting that assessment for other substance abuse is also an important part of the evaluation of EVALI patients.

In vaping products, THC or nicotine is mixed with flavoring substances and oils like diacetyl, propylene glycol, glycerin, benzaldehyde, vitamin E and other unknown substances (3, 18, 19, 20). These flavored substances are heated up releasing toxic chemicals and potential carcinogens into the alveoli causing lung injury. Previous reports have demonstrated acute and subacute inhalation injury with compounds such as diacetyl causing bronchiolitis obliterans, colloquially known as "popcorn lung" (19). Recently, vitamin E acetate was found in the bronchoalveolar lavage samples of EVALI patients. This was linked as one of the potential toxic agents that led to the acute lung injury in this recent epidemic (18). Currently, there is no evidence on the long-term or subacute effects of vitamin E acetate toxicity in the lungs.

With our available data, we find that patients affected with EVALI have recovered clinically, radiographically and functionally on spirometry with little or no residual disease. Further follow-up will provide additional understanding of the residual effects of acute injury caused by these inhaled toxic vapors.

Limitations

This study is involves a small series of patients who had follow up pulmonary function testing performed at our center as part of their routine clinical care. The chemical(s) used in the vaping products that caused these patients' severe lung disease is not known.

The incidence of EVALI has significantly decreased since February 2020 according to the CDC. Further research is needed to describe long term outcomes of EVALI patients and to identify substances that contribute to the development of EVALI. Although there is good evidence suggesting a role of vitamin-E acetate, other inhaled toxins may also contribute to the development of the severe lung disease observed.

CONCLUSION

Follow-up of patients presenting with severe respiratory disease from EVALI reveals normalization of spirometry parameters in all patients but persisting abnormal DLCO measurement in most patients, raising concern for chronic lung disease. This study further validates previous reports suggesting that EVALI is reversible from a pulmonary and radiographic perspective upon discontinuation of vaping.

FIGURE LEGENDS

Table 1. Demographics, medical and vaping history and clinical course of the adolescents affected with EVALI.

Table 2 . Spirometry measurements including mean FEV1, FVC and FEF 25-75 values, percent predicted and z-scores during hospitalization (Initial) and during outpatient follow-up (FU). Each individual flow-volume loop can be found in the Supplementary Appendix.

Figure 1. Representative chest CT scans of three patients affected by EVALI during hospitalization and outpatient follow-up.**A.** Initial chest CT showed extensive consolidation and ground-glass opacities. **B.** Follow up chest CT of the same patient showed near complete resolution of the prior opacities with residual apical ground-glass opacities. **C.** Initial chest CT showed sharply demarcated ground-glass opacities with areas of subpleural sparing. **D.** Follow-up chest CT showed widespread patchy ground-glass opacities. **E.** Initial chest CT showed bilateral patchy ground-glass opacities **F.** Follow-up chest CT of the same patient showed complete resolution of the previous opacities.

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