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Association of high-level humidifier disinfectant exposure with lung injury in preschool children

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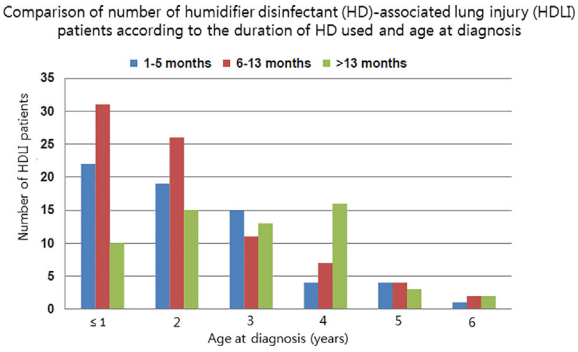
HIGHLIGHTS

- Risk of humidifier disinfectant-associated lung injury (HDLI) increased in a dose-dependent manner.
- Risk of HDLI increased ≥ two-fold in the lower duration of usage.
- Exposure to high levels of HD within a short period in early life affected HDLI in preschool children.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Children aged ≤6 years reportedly account for 52% of victims of humidifier disinfectant-associated lung injuries.
Objectives: To evaluate the association of humidifier disinfectants with lung injury risk among children aged ≤6 years.
Methods: Patients with humidifier disinfectant-associated lung injuries (n = 214) who were clinically evaluated to have a definite (n = 108), probable (n = 49), or possible (n = 57) association with humidifier disinfectants as well as control patients (n = 123) with lung injury deemed unlikely to be associated with humidifier disinfectant use were evaluated to determine factors associated with increased risk of humidifier disinfectant-associated lung injury using unconditional multiple logistic regression analysis.
Results: For estimated airborne humidifier disinfectant concentrations, risk of humidifier disinfectant-associated lung injury increased ≥two-fold in a dose-dependent manner in the highest quartile (Q4, 135–1443 μg/m^3) compared with that in the lowest quartile (Q1, ≤33 μg/m^3). Registered patients using more than two humidifier disinfectant brands were at an increased risk of humidifier disinfectant-associated lung injury (adjusted OR, 2.2; 95% confidence interval, 1.3–3.8) compared with those using only one brand. With respect to the duration of humidifier disinfectant use, risk of humidifier disinfectant-associated lung injury increased ≥two-fold in the lowest

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quartile (≤5 months) compared with that in the highest quartile (≥14 months; adjusted OR 0.3; 95% confidence interval, 0.2–0.6).
Conclusions: Younger children are more vulnerable to HDLI when exposed to HD chemicals within short period in early life.

1. Introduction

In 2006, an unidentified fatal interstitial lung disease was observed among children in South Korea (Cheon et al., 2008; Kim et al., 2009). Affected patients complained of rapidly progressing respiratory difficulty, which was associated with high mortality (Lee et al., 2013). Subsequent comprehensive epidemiological and experimental studies have demonstrated chemical disinfectants in humidifiers as the cause of this disease in both children and adults (Deterding and White, 2014; Yang et al., 2013). To our knowledge, no similar fatal health problem due to the use of household products, especially among children, has been reported.

Several types of chemical disinfectants were widely used in humidifiers since 1994 to prevent microbial contamination; they remained in use until 2011 when certain humidifier disinfectant (HD) brands were banned because of an outbreak of HD-associated lung injury (HDLI) (Korean Society of Environmental Health, 2012). In South Korea, a Humidifier-associated with Lung Injury Investigation and Decision Committee (HLIIDC) has been operational since July 2011 to clinically evaluate registered patients with lung injuries who were predicted to have developed lung injuries due to HD use as well as to determine whether the injuries were clinically associated with HD use (Korean Centers for Disease Control and Prevention, 2011b; Park et al., 2017). HDLI patients who were clinically confirmed to be affected by HD use included victims from all age groups, ranging from fetuses, preschool children, pregnant women, and elderly patients aged >80 years. The third round of the investigation covering the period from September 2015 to August 2017 is currently underway to identify and collect data on HDLI victims.

A previous study has revealed that 75.6% of HDLI patients use humidifiers and that 31.1% of them are children (Jeon and Park, 2012). In that study, although the percentage of patients using HDs was high, only a subset exhibited signs of HDLI based on pathological evaluation, chest imaging studies, or clinical manifestations. Differences in HDLI susceptibility or other currently undetermined factors might impact HDLI development. Since the reporting of the first fatal HDLI case, no study has examined HD use characteristics that might affect HDLI risk.

This study aimed to determine HD exposure-related risk factors for HDLI among children aged ≤6 years.

2. Methods

2.1. Study subjects

In total, 699 patients registered in the third round of the HLIIDC (361, 169, and 169 subjects in the first, second, and third rounds, respectively) were clinically evaluated to assess associations between HD use and lung injury. HD exposure assessment and clinical examination of registered subjects were conducted in a blinded and independent fashion. In this study, among 343 identified children aged ≤6 years, 337 were selected after excluding six children, including those with indeterminate diagnosis due to lack of clinical information (n = 4), premature birth (n = 1), and fetal death (n = 1). Children aged ≤6 years (n = 343) were included in this study as they accounted for 52% of the main cohort (n = 699) who were included in all three rounds of the national program conducted from July 2013 to July 2016 and as their sensitivity to HDs was assumed to be comparable to that of other age groups. Study flow chart showing the selection of study subjects aged ≤6 years (n = 337) is shown in Fig. 1.

2.2. Field investigation into HD use

Methods employed to evaluate HD use characteristics, which were based on personal interviews and home investigations, have been described elsewhere (Park et al., 2015a; Park et al., 2015b). We developed a systematic and transparent approach to assess potential HD exposure, which was consistently followed through all three phases of the national program. Trained environmental health scientists visited the residences of registered subjects to complete detailed questionnaires and checklists and recorded the following information related to HD use: type of HD brand/s used; HD volume added to the humidifier, frequency of HD addition, and time spent in room/s with the humidifier; duration of HD use in the household in average months/year, weeks/month, and days/week; average sleeping hours in a room with an operating humidifier containing a disinfectant; number of HD brands used and type of HD; average distance of the bed from the humidifier in meters.

HD brands that were determined to cause lung injury included polyhexamethylene guanidine phosphate (PHMG, CAS # 89697-78-9), oligo(2-(2-ethoxy)ethoxyethyl guanidinium (PGH, CAS # 374572-91-5), and a mixture of chloromethylisothiazolinone (CMIT, CAS # 26172-55-4) and methylisothiazolinone (MIT, CAS # 2682-20-4). The exposure assessment team was blinded to the clinical diagnostic information related to the lung injury in study subjects.

2.3. Clinical examination

All registered subjects were clinically examined by a committee comprising two pediatric pulmonologists, two adult pulmonologists, two pediatric radiologists, two chest radiologists, and two pathologists to diagnose and confirm HDLI and determine its severity. Clinical confirmation of HDLI was based on a combination of clinical manifestations, natural disease course, and radiological and pathological findings in subjects whose lung specimens were available (Kim K.W. et al., 2014; Lee et al., 2013). Registered lung injury cases were classified into five groups, including definite, probable, possible, unlikely, and indeterminate. Cases were considered definite when all of the following criteria were met: 1) typical symptoms of HDLI, such as cough, dyspnea, and chest wall retraction, followed by rapidly progressive respiratory distress; 2) focal patchy consolidation with subpleural sparing in early phase and diffuse centrilobular nodules with ground glass opacities in combination with air leak syndrome on chest computed tomography; 3) centrilobular distribution of diffuse alveolar damage in early phase and/or diffuse alveolar damage in the later phase of disease in subjects whose biopsy specimens were available; and 4) absence of other factors that might cause lung injury. Probable cases included subjects with the abovementioned symptoms and chest computed tomography and/or pathologic findings compatible with HDLI in whom infectious, autoimmune, and/or other interstitial lung diseases could not be ruled out. Subjects with strong infectious, autoimmune, and/or other features of interstitial lung disease and those with weak or incomplete clinical features and radiological and pathological findings of HDLI were classified as possible HDLI cases and were recommended to undergo clinical examination for further assessment of HD use as an etiology. The final group, classified as unlikely to have developed lung injury due to HDs,

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