Observational Study

Medicine®

OPEN

Prognostic value of serum zinc levels in patients with acute HC/zinc chloride smoke inhalation

Fei Xie, MD, Xingang Zhang, MM, Lixin Xie, MD*

Abstract

Hexachloroethane (HC)/zinc chloride (ZnCl, smoke bomb) exposure in the military setting results in lung injury which is uncommon and has been rarely described in previous studies. The aim of this study is to investigate the correlation between the serum zinc in patients with HC/ZnCl smoke inhalation lung injury and disease severity. A total of 15 patients with HC/ZnCl-related conditions were recruited in this study. The serum zinc level and the pulmonary function tests and liver function tests including total lung capacity (TLC), forced vital capacity (FVC), forced expiratory pressure in 1 second (FEV1), alanine aminotransferase (ALT), and aspartate transaminase (AST) were analyzed. Eleven cases had mild clinical manifestations. Four cases rapidly developed features typical of severe adult respiratory distress syndrome. The level of serum zinc was increased, but FVC, FEV1, and TLC was decreased significantly in the moderate and severe cases. In addition, the serum zinc level correlated well with the TLC, FVC, and FEV1 ($r = -0.587$, -0.626, -0.617, respectively; $P = .027$, .017, .019, respectively). The 4 cases in moderate and severe group had delayed impairment of liver functions after the accident. This study suggested that the serum zinc level may be associated with the severity of lung and liver injuries after HC/ZnCl smoke inhalation.

Abbreviations: ALT = alanine aminotransferase, ARDS = acute respiratory distress syndrome, AST = aspartate transaminase, FEV1 = forced expiratory pressure in 1 second, FVC = forced vital capacity, HC = hexachloroethane, TLC = total lung capacity, ZnCl = zinc chloride, ZnO = zinc oxide.

Keywords: pulmonary function test, serum, smoke inhalation injury, zinc, zinc chloride

1. Introduction

Hexachloroethane (HC)/zinc chloride (ZnCl, smoke bombs) are used extensively in battles, military drills, and fire-fighting training.[1,2] The major ingredients in smoke from smoke bombs are fine particles of ZnCl, HC, and various other chemical compounds. Given that ZnCl aerosols are extremely hygroscopic in the respiratory tract, both the inhalation of the smoke and instillation of ZnCl cause pulmonary edema, alveolitis in the early phase, some pulmonary fibrosis at a later phase, and often fatal acute respiratory distress syndrome (ARDS) in confined spaces.[3–5] Although a series of case reports have been reported on various lung damage by inhalation of ZnCl from a smoke bomb, little effective protocol is available for the treatment of lung damaged, especially the ARDS.[6,7] Subsequent oxygen administration had little effect on the development or progression of the pathological changes.

Measuring the serum zinc level has been recommended as an appropriate biomarker.[8] The serum concentration is affected by factors such as age, dietary intake, and infections. Since patients were exposed to amount of ZnCl fume in this study, whether inhalation of ZnCl and zinc oxide (ZnO) change the serum zinc level remains elusive. Here, we hypothesized that the serum zinc might be used as a prognostic marker for the severity of injury by HC/ZnCl smoke. To answer this question, we correlated findings from serum zinc and the results of pulmonary function and liver function tests in patients.

2. Methods

2.1. Subjects

The records of soldiers with HC/ZnCl-related conditions during military drills were recruited. All patients were transferred to the respiratory department at People's Liberation Army General Hospital and admitted immediately. They had smoke bombs inhalation in a tunnel with respiratory protection for about 1 to 5 minutes. Fifteen patients were divided into 2 groups according to their clinical conditions: those who recovered without ICU (mild) and those who required ICU admission (moderate or severe). The use of human clinical materials in this study was approved by the Ethical Committee of the General Hospital of the People's Liberation Army. All patients or their caregivers have provided written informed consent approved by the ethics committee of the Chinese PLA General Hospital (S2014-011-01).

2.2. Data collection

The clinical parameters including age, height, weight, past and personal history, drug history, and symptomatology were

Editor: Jian Liu.

XF and ZX contributed equally to this work.

Funding/support: This study was funded by the Clinical research funding of Chinese People's Liberation Army General Hospital to Xie Lixin.

The authors have no conflicts of interest to disclose.

Department of Pulmonary and Critical Care Medicine, Chinese PLA General Hospital, Beijing, China.

* Correspondence: Lixin Xie, Department of Pulmonary and Critical Care Medicine, Chinese PLA General Hospital, Beijing 100853, China (e-mail: vorbeiflug@126.com).

Medicine (2017) 96:39(e8156)

Received: 9 April 2017 / Received in final form: 18 June 2017 / Accepted: 2 September 2017

http://dx.doi.org/10.1097/MD.0000000000008156

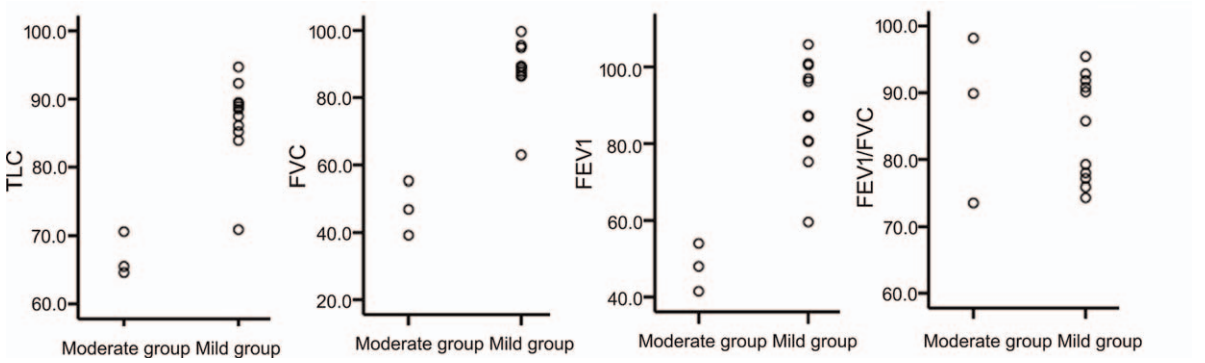

Figure 1. Comparison of TLC, FVC, FEV1, and FEV1/FVC in 14 patients with smoke inhalation. The patient with severe injuries did not undergo testing. FEV1 = forced expiratory pressure in 1 second, FVC = forced vital capacity, TLC = total lung capacity.

collected. The whole blood samples were taken from patients 4 days after smoke inhalation (the acute stage). The level of serum zinc concentration was determined by direct aspiration of the analytical dissolution into the flame of the atomic absorption spectrometer (MB5, Puyi technology, Beijing). The flexible bronchoscopy was scheduled individually.

The pulmonary function tests including total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory pressure in 1 second (FEV1) were performed using Mater Screen Diffusion (Ms-PET, Jaeger, Germany) according to the standard protocol.

2.3. Statistical analysis

Data are presented as frequencies or mean ± standard deviation. Comparison of continuous variables was by *t* test or Mann–Whitney *U* test where appropriate. For correlation analyses, Person correlation was used for normally distributed variables. All statistical analyses were performed with SPSS statistical software version 19.0 (SPSS, Germany), *P*-value <.05 was accepted as significant.

3. Results

3.1. Patient demographics

Fifteen patients were included in this study, of which 11 had mild clinical manifestations, 3 had moderate, and one had severe required ICU admission within 48 hours. All patients initially presented with symptoms of chest tightness and intractable cough. Of the ICU patients, 1 patient (6.7%) developed rapidly to ARDS, pulmonary fibrosis with small airway trapped, and liver failure after 24 hours, and leading to death from and multiorgan failure.

3.2. Hematogram and serum zinc

At hospital admission, white blood cells count of moderate and severe group was significantly higher than that of mild group (19.74 ± 5.46 vs 12.03 ± 3.73/μL, $P = .008$). Neutrophils in moderate and severe group were similar to that in mild group (80.3% ± 9.9% vs 86.6% ± 7.5%, $P = .276$). C-creation protein of moderate and severe group was significantly increased than that of mild group (4.64% ± 0.89% vs 1.97% ± 1.56%, $P = .007$). And moderate and severe group had a higher serum zinc level in comparison with mild group (215.2 ± 17.7 vs 145.3 ± 32.1 μmol/L, $P = .001$). The serum zinc levels in moderate and severe group were all above the normal range (76.5–150 μmol/L).

3.3. Pulmonary functions

In the moderate and severe group, 1 patient with ARDS could not undergo pulmonary function tests because of receiving mechanical ventilation. Other 3 patients had mild restrictive ventilation impairment (TLC ≥ 60%–<80% of predicted) (Fig. 1). Of the 11 patients in mild group, 1 patient (9%) had mild restrictive ventilation, and 10 (91%) patients had normal ventilation function. Moreover, the 3 patients in the moderate and severe group showed a significant reduction of FVC (47.1% ± 8.1% vs 88.1% ± 9.4%, $P < .001$) and FEV1 (47.8% ± 6.3% vs 88.3% ± 13.7%, $P < .001$), but normal FEV1/FVC ratio values (Fig. 1).

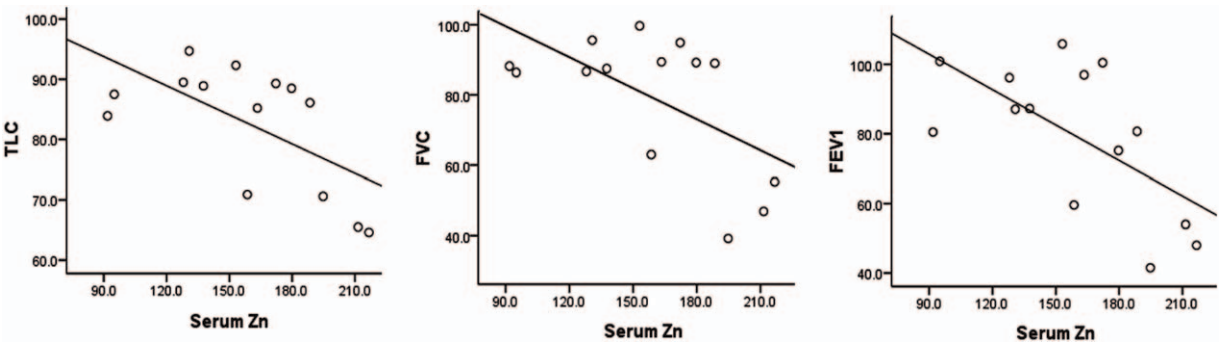

Figure 2. Scatterplot of correlation between pulmonary functions and serum zinc level. The levels of serum zinc were negatively correlated with TLC, FVC, and FEV1 on day 4 (n = 14). FEV1 = forced expiratory pressure in 1 second, FVC = forced vital capacity, TLC = total lung capacity.

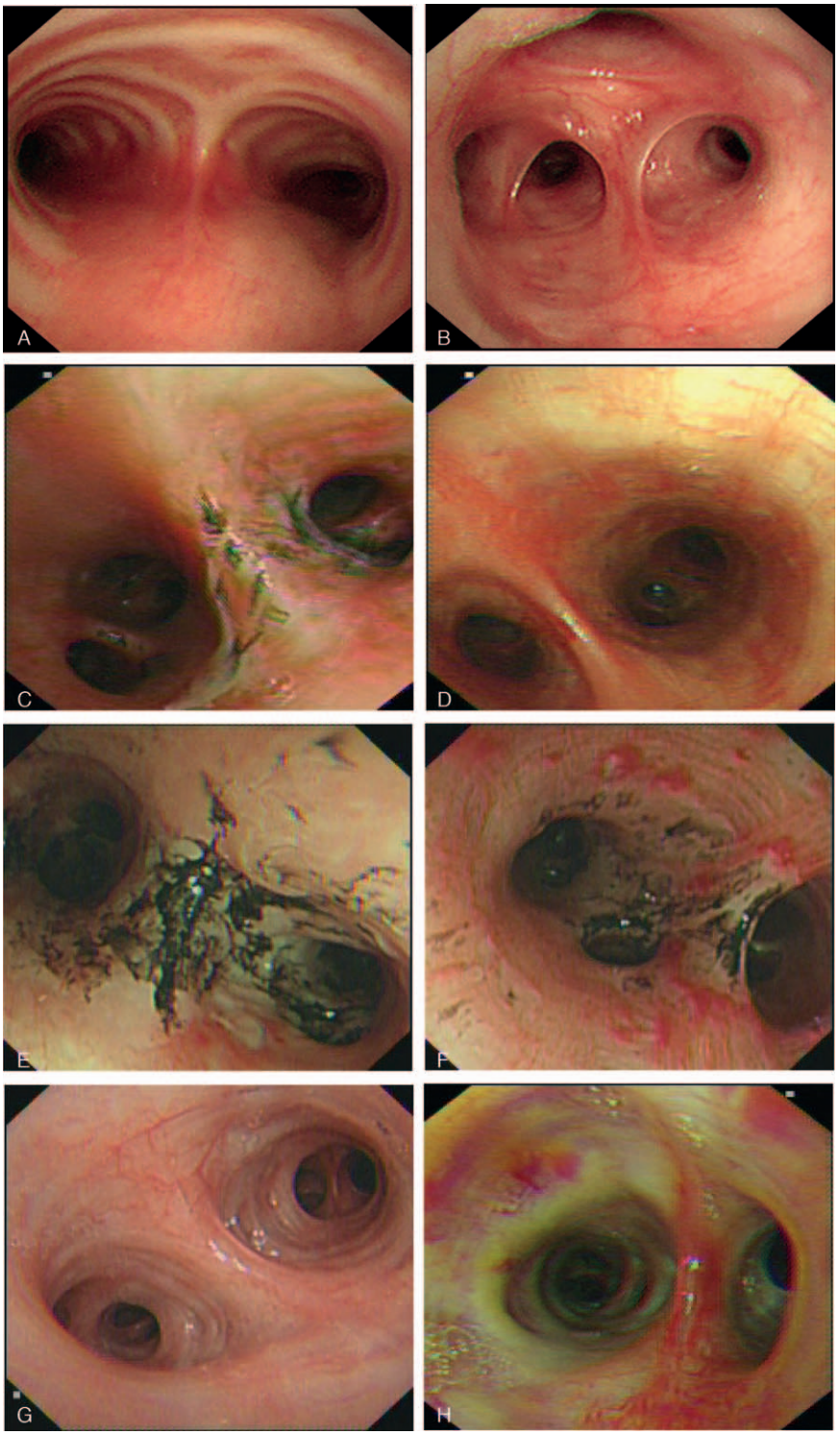

Figure 3. Representative bronchoscopic findings in 3 patients after smoke inhalation. (A, B) A patient in mild group; (C, D, and G) a patient in moderate group; and (E, F, and H) a patient in severe group. (A–F) On day 1; (G, H) on day 4 and 17, respectively.

3.4. Relationship between serum zinc level and pulmonary functions

In order to assess the serum zinc level associated with pulmonary functions, TLC, FVC, and FEV1 were analyzed across serum Zn level. Bivariate Pearson correlation analysis showed TLC, FVC, and FEV1 had significantly negative correlation with serum zinc level and ($r = -0.587$, -0.626, and -0.617, respectively; $P = .027$, .017, and .019, respectively; Fig. 2).

3.5. Bronchoscope findings

Smoke contains particulate matter which is formed from incomplete combustion of an organic material. The respiratory

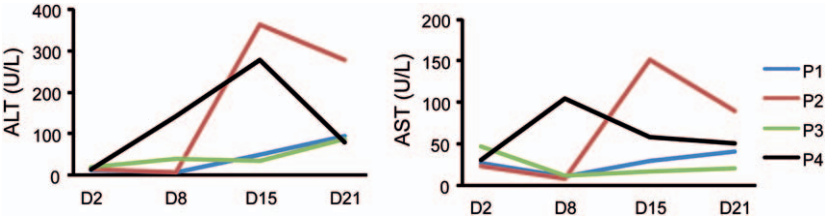

Figure 4. Liver function in patients with moderate and severe symptoms after smoke inhlation. P1 to 3: patients with moderate symptoms; P4: the patient with severe symptoms.

tracts were affected by the combustible dust in moderate and severe group, but normal in the mild group (Fig. 3). Bronchoscopy revealed carbonaceous endobronchial debris, erythema, or ulceration airway burns in the acute stage (Fig. 3C–F). The lesions recovered to normal within 1 week in moderate group (Fig. 3G), whereas the severe patient had diffuse congestion of the bronchial mucosa (Fig. 3H).

3.6. Liver functions

Patients in the moderate and severe group were administered liver function tests on the 1st to 42th days after smoke inhalation, while others in the mild group were administered on 1st to 12th day. On the 2nd day, all of the patients had normal liver function (Fig. 3). On the 8th day, only 1 patient with severe clinical manifestations had abnormal liver function, whose alanine aminotransferase (ALT) was 142.1 U/L, aspartate transaminase (AST) was 105.1 U/L, and ALT/AST = 1.35. On the 15th day, the liver functions of patients in the mild group were normal. However, 2 patients in the moderate and severe group had abnormal liver dysfunction, whose ALT was 364.4 and 278.3 U/L, AST was 151.1 and 57.7 U/L, and ALT/AST > 2.41 and 4.82. On the 21th day, all the patients in the moderate and severe group had abnormal liver dysfunction (Fig. 4). The 3 patients in moderate group did not recover to normal until 2 months.

4. Discussion

Here, we assessed serum Zn level and its association with pulmonary function and liver function in patients who had HC/ZnCl smoke inhalation during military training. Zinc is a key element involved in biological functions including multiple enzymes/proteins and antioxidative defense.[9,10] Traditionally, zinc is considered as relatively nontoxic. However, several researches have been reported that excessive free ionic zinc accumulation is toxic in cells such as neurons and glia.[11] Excess zinc intake can lead to cardiac dysfunction including premature atrial beats, hypovolemic shock, and hypertension.[12] These studies indicate free zinc ion may be much more toxic biologically than generally realized.

Smoke bomb (HC/ZnCl smoke) consists of a mixture of chemicals of ZnCl, ZnO, and HC are major compounds which are harmful may cause acute lung injury in humans. In previous observations, ZnCl inhalation may cause acute lung injury, a syndrome known as metal fume fever, or even death.[5,6,13,14]

In our study, HC/ZnCl smoke inhalation caused acute manifestations of serum Zn level and restrictive ventilation impairments on the pulmonary function tests rapidly. The serum zinc level was increased in the severely affected patients, and restrictive ventilation impairments were significantly reduced. Sporadic cases reported in all the literatures had ARDS, with poor treatment outcomes. In this study, the patient who had the highest level of serum zinc (237.8 μmol/L) developed too rapidly to ARDS, pulmonary fibrosis with small airway trapped, and liver failure after 24 hours, and leading to death from and multiorgan failure. Moreover, our clinical observation, together with previous report on pulmonary function test findings in the same population, suggested that patients with excessive zinc accumulation appeared to have worse restrictive ventilation impairments.[15]

A recent study has reported inhalation of 20 μg/mL ZnO nanoparticles (ZnO NPs) could induce increased IL-8 release and excessive ROS production in lung epithelial cells (A549).[16,17] It was also reported intranasal instillation of ZnO NPs could cause pulmonary inflammation in mice.[16,17] Therefore, this study was set forth to validate our clinical observations.

HC, one main compound in smoke bomb, has not been reported to cause lung damage, while it has been reported to induce fatty change and liver toxicity.[18–20] Increased ALT was found to follow HC inhalation.[18,19] In this study, all 4 patients in the moderate and severe group also had an elevation of ALT. Additionally, increased blood concentrations of hyaluronic acid were found in 3 patients in the moderate and severe group (115, 103, and 600 ng/mL, respectively) (normal range: 26–70 ng/mL). However, no HC and trichloropropane were detected in the serum in this study. The present study has some limitations: due to the special causes, the retrospective study only had small sample size. Therefore, it might not be the proper way to confirm examined relationships. And cases of smoke bomb inhalation are unusual, so our findings may not be applicable in other settings.

In conclusion, serum zinc level was elevated in patients with severe HC/ZnCl-related conditions after exposed to smoke bomb. Higher serum zinc was correlated negatively with pulmonary functions and delayed liver functions. These results suggest that serum zinc is a potential biomarker for restrictive ventilation impairments and liver dysfunction after HC/ZnCl smoke inhalation.

Acknowledgments

The authors thank all members of the Pulmonary and Critical Care Medicine Department of the General Hospital of the People's Liberation Army for valuable comments on this study and helpful suggestions, and technicians in Pulmonary Function Testing Room of Chinese People's Liberation Army General Hospital for their contribution to this study. The authors also thank the Clinical research funding of Chinese People's Liberation Army General Hospital for the support to XL.

References

[1] Greenfield RA, Brown BR, Hutchins JB, et al. Microbiological, biological, and chemical weapons of warfare and terrorism. Am J Med Sci 2002;323:326–40.

[2] Matarese SL, Matthews JI. Zinc chloride (smoke bomb) inhalational lung injury. Chest 1986;89:308–9.

[3] Hsu HH, Tzao C, Chang WC, et al. Zinc chloride (smoke bomb) inhalation lung injury: clinical presentations, high-resolution CT findings, and pulmonary function test results. Chest 2005;127:2064–71.

[4] Brown RF, Marrs TC, Rice P, et al. The histopathology of rat lung following exposure to zinc oxide/hexachloroethane smoke or installation with zinc chloride followed by treatment with 70% oxygen. Environ Health Perspect 1990;85:81–8.

[5] Homma S, Jones R, Qvist J, et al. Pulmonary vascular lesions in the adult respiratory distress syndrome caused by inhalation of zinc chloride smoke: a morphometric study. Hum Pathol 1992;23:45–50.

[6] Gil F, Pla A, Hernández AF, et al. A fatal case following exposure to zinc chloride and hexachloroethane from a smoke bomb in a fire simulation at a school. Clin Toxicol (Phila) 2008;46:563–5.

[7] Pettilä V, Takkunen O, Tukiainen P. Zinc chloride smoke inhalation: a rare cause of severe acute respiratory distress syndrome. Intensive Care Med 2000;26:215–7.

[8] De Benoist B, Darnton-Hill I, Davidsson L, et al. Conclusions of the Joint WHO/UNICEF/IAEA/IZiNCG Interagency meeting on zinc status indicators. Food Nutr Bull 2007;28:S480–4.

[9] Vallee BL, Auld DS. Zinc coordination, function, and structure of zinc enzymes and other proteins. Biochemistry 1990;29:5647–59.

[10] Cruz KJ, de Oliveira AR, Marreiro Ddo N. Antioxidant role of zinc in diabetes mellitus. World J Diabetes 2015;6:333–7.

[11] Frederickson CJ, Koh JY, Bush AI. The neurobiology of zinc in health and disease. Nat Rev Neurosci 2005;6:449–62.

[12] Expert Group on Vitamins and Minerals (EVM), Committee on Toxicity. Safe Upper levels for vitamins and minerals. London: Food Standards Agency Publication; 2003.

[13] Plum LM, Rink L, Haase H. The essential toxin: impact of zinc on human health. Int J Environ Res Public Health 2010;7:1342–65.

[14] Vogelmeier C, Konig G, Bencze K, et al. Pulmonary involvement in zinc fume fever. Chest 1987;92:946–8.

[15] Cao L, Zhang XG, Wang JG, et al. Pulmonary function test findings in patients with acute inhalation injury caused by smoke bombs. J Thorac Dis 2016;8:3160–7.

[16] Saptarshi SR, Feltis BN, Wright PF, et al. Investigating the immunomodulatory nature of zinc oxide nanoparticles at sub-cytotoxic levels in vitro and after intranasal instillation in vivo. J Nanobiotechnol 2015;13:6.

[17] Fukui H, Horie M, Endoh S. Association of zinc ion release and oxidative stress induced by intratracheal instillation of ZnO nanoparticles to rat lung. Chem Biol Interact 2012;198:29–37.

[18] Loh CH, Liou SH, Chang YW, et al. Hepatic injuries of hexachloroethane smoke inhalation: the first analytical epidemiological study. Toxicology 2008;247:119–22.

[19] Loh CH, Chang YW, Liou SH, et al. Case report: hexachloroethane smoke inhalation: a rare cause of severe hepatic injuries. Environ Health Perspect 2006;114:763–5.

[20] Seldén A, Nygren M, Kvarnlöf A, et al. Biological monitoring of hexachloroethane. Int Arch Environ Health 1993;65(1 Suppl): SU1-S114.