



ORIGINAL ARTICLE

# Serum zinc level is associated with liver dysfunction caused by white smoke inhalation

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## Abstract

**Background:** White smoke bomb exposure in the military setting could result in organ injuries, which is uncommon and has been rarely described in previous studies. The aim of this study is to observe whether serum zinc levels are associated with liver function after white smoke inhalation.

**Methods:** Fifteen patients with white smoke exposure were the subjects in this study. The clinical manifestations, liver function tests and the serum zinc levels were analysed.

**Results:** The level of serum zinc was increased in the moderate or severe group ( $n = 4$ ) compared with that in the mild group ( $n = 11$ ). The four cases in the moderate or severe group had delayed impairment of liver function with an elevation of alanine transaminase. Additionally, increased blood concentrations of hyaluronic acid were found in three patients in the moderate or severe group. But no hexachloroethane or trichloropropane was detected.

**Conclusion:** This study suggested that serum zinc levels may be associated with the severity of liver injuries after white smoke inhalation.

**Key words:** Zinc chloride; smoke inhalation injury; liver function

## Introduction

White smoke bombs are used extensively in battles, military drills and fire-fighting training. The major ingredients in smoke from smoke bombs are fine particles of zinc chloride, hexachlorohexane and various other chemical compounds. Given that zinc chloride aerosols are extremely hygroscopic to the respiratory tract, both the inhalation of the smoke and the instillation of zinc chloride 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 [1, 2]. Although a series of case studies have reported on various types of lung damage by the inhalation of white smoke, few studies have reported other organ injuries [3–5]. Loh *et al.* reported that white smoke inhalation induced acute, dose-

dependent hepatic injury in 20 cases [3, 6]. Huang *et al.* also reported cases with transient impairment of liver function after white smoke inhalation [5]. Though limited case reports and descriptive studies have provided data liver injuries after white smoke inhalation, no clinical evidence has identified the association between halogenated organic compounds (HC)/zinc chloride smoke inhalation and liver function.

The level of serum zinc has been recommended as an appropriate biochemical indicator [7]. The serum concentration is affected by factors such as age, dietary intake and infections. Since patients were exposed to an amount of zinc chloride fumes in this study, whether inhalation of zinc chloride and zinc oxide changes the serum zinc level remains elusive. Here, we hypothesized that serum zinc might be used as a prognostic

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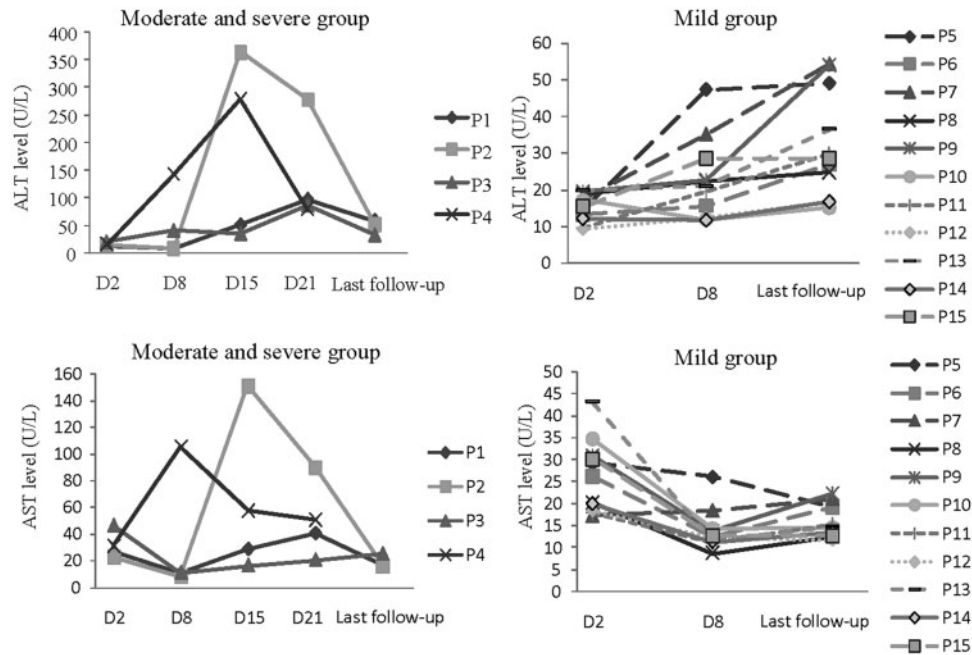


Figure 1. The change in liver function after white smoke inhalation. ALT, alanine aminotransferase; AST, aspartate transaminase.

marker for the severity of liver injury by HC/zinc chloride smoke.

## Methods

### Subjects

Fifteen soldiers with HC/zinc chloride-related conditions during military drills were enrolled. They had experienced smoke bomb inhalation in a tunnel with respiratory protection for about 1–5 minutes. Patients were divided into two groups according to their clinical conditions: those who recovered without intensive care unit (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).

### Data collection

The clinical parameters including age, height, weight, past and personal history, drug history, symptomatology, complete blood counts and C-reaction protein (CRP) were collected. The whole blood samples were taken from patients 4 days after smoke inhalation (the acute stage). The level of serum zinc was determined by direct aspiration of the analytical dissolution into the flame of the atomic absorption spectrometer (MB5, Puyi technology, Beijing). Liver functions were measured using patient serum. Measured liver enzymes included alanine transaminase (ALT) and aspartate transaminase (AST).

### Statistical analysis

Data are presented as frequencies or mean  $\pm$  standard deviation (SD). Comparison of continuous variables was by t-test or Whitney U-test where appropriate. All statistical analyses were

performed with SPSS statistical software version 19.0 (SPSS, Germany). A  $p$ -value of  $<0.05$  was accepted as significant.

## Results

### Patient demographics

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

### Hematogram and serum zinc

At hospital admission, the white blood cell (WBC) counts of the moderate or severe group were significantly higher than those of the mild group ( $19.74 \pm 5.46/\mu\text{L}$  vs  $12.03 \pm 3.73/\mu\text{L}$ ,  $p=0.008$ ). The percentages of neutrophils in the moderate or severe group were similar to those in the mild group ( $80.3 \pm 9.9\%$  vs  $86.6 \pm 7.5\%$ ,  $p=0.276$ ). The CRPs of the moderate or severe group were significantly increased compared with those of the mild group ( $4.64 \pm 0.89\%$  vs  $1.97 \pm 1.56\%$ ,  $P=0.007$ ). The moderate or severe group had higher serum zinc levels in comparison with the mild group ( $215.2 \pm 17.7 \mu\text{mol/L}$  vs  $145.3 \pm 32.1 \mu\text{mol/L}$ ,  $p=0.001$ ). The serum zinc levels in the moderate or severe group were all above the normal range ( $76.5\text{--}150 \mu\text{mol/L}$ ).

### Liver function tests

Patients in the moderate or severe group were administered liver function tests on the first to 42nd days after the white smoke inhalation, while others in the mild group were administered on the first to the 12th day (Figure 1). On the second day (acute phase), all of the patients had normal liver function. On the eighth day, only one patient with severe clinical

manifestations had abnormal liver dysfunction, whose ALT was 142.1 U/L, AST was 105.1 U/L and ALT/AST was 1.35. The liver functions of patients in the mild group were normal in the last follow-up (day 12). On day 15, however, two patients in the moderate or 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, ALT/AST was 2.41 and 4.82, respectively. On day 21, all the patients in the moderate and severe group had abnormal liver dysfunction. In the moderate or severe group, one patient died and the other three patients did not recover within the normal 2 months.

### Levels of hyaluronic acid, hexachloroethane and trichloropropane

Increased blood concentrations of hyaluronic acid were found in three patients in the moderate or severe group (115, 103, 600 ng/ml, respectively) (normal range: 26–70 ng/ml). However, no hexachloroethane and trichloropropane were detected in the serum in this study.

### Discussion

For the majority of patients with white smoke inhalation, acute lung injury has been considered the most common form of organ injury [2, 5, 8]. Limited clinical observation reported certain patients had liver dysfunction or other complications due to white smoke inhalation [3, 5, 6, 9]. Here, we reported small numbers of the population with liver dysfunction induced by HC/zinc chloride smoke inhalation and found serum Zn levels were associated with liver function.

The major compounds of HC/zinc chloride smoke are a mixture of the chemicals of zinc chloride, zinc oxide (ZnO) and hexachloroethane. Traditionally, zinc is considered relatively non-toxic and has antioxidative defense [10, 11]. However, recent studies have reported that excessive free ionic zinc accumulation is toxic biologically in cells and tissues [12, 13]. Excess zinc intake can lead to cardiac dysfunction, including premature atrial beats, hypovolemic shock and hypertension [12]. Inhalation of 20 µg/mL zinc oxide nanoparticles (ZnO NPs) could induce increased IL-8 release and excessive reactive oxygen species (ROS) production in lung epithelial cells (A549) [14, 15]. And intranasal instillation of ZnO NPs could also cause pulmonary inflammation in mice [13, 14]. In our previous study, HC/zinc chloride smoke inhalation rapidly caused acute manifestations of serum Zn levels and restrictive ventilation impairments in the pulmonary function tests [4]. The serum zinc levels were increased in the severely affected patients and restrictive ventilation impairments were significantly reduced.

An in-vivo study revealed ZnO NPs caused oxidative damage and oxidative stress to livers in zebrafish, by increasing the activity of catalase and superoxide dismutase, up-regulating lipid peroxidation, triggering an excessive production of ROS and activating cell apoptosis [16, 17]. Kong et al. reported that orally administered 50-nm ZnO NPs might target the liver, kidney, lung and pancrea for subchronic and chronic toxicity in mice [18]. Furthermore, ZnO NPs exposure induces direct injury to hepatic (HepG2) cell lines, as well as A549, through apoptosis and autophagy pathways [19].

In this study, patients in the moderate or severe group had elevated levels of ALT and AST after 1 week of HC/zinc chloride smoke inhalation. Additionally, increased blood concentrations of hyaluronic acid were found in three patients in the moderate or severe group. The patients with moderate and severe clinical

manifestations were the soldiers who entered the tunnel earliest, so they were exposed to more and higher concentrations of smoke than the others. The features of high incidence and a dose-dependent gradient indicated that the mechanism of injury is toxic to the liver.

In conclusion, serum zinc levels were elevated in patients with moderate and severe HC/zinc chloride-related conditions after exposure to smoke bombs, which is a potential biomarker for delayed liver impairment of HC/zinc chloride smoke inhalation. Further studies on the mechanism of HC/zinc chloride smoke-induced hepatotoxicity needed to be elaborated on.

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*Conflict of interest statement:* none declared.

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