Histopathological Study of Short and Long-Term Pulmonary Effects of Nebulized Sodium Bicarbonate Treatment in Chlorine Gas Exposured Rats

Klor Gazı Zehirlenmesi Oluşturulan Ratlarda Nebülize Sodyum Bikarbonat Tedavisinin Akciğerlerdeki Erken ve Geç Dönem Etkilerinin Histopatolojik Olarak Araştırılması

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Geliş Tarihi/*Received:* 07.09.2008
Kabul Tarihi/*Accepted:* 18.03.2009

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ABSTRACT Objective: Sodium hypochlorite (known as bleach) and hydrochloric acid are traditionally used as cleaning materials. Mixture of these two liquids yields chlorine gas. Chlorine gas exposure is a frequent reason for emergency consultations. There is no accepted specific treatment for reduction of the pulmonary injury. In our study, we have investigated histopathologically the effect of nebulized sodium bicarbonate, the use of which is also controversial in the literature, in the treatment of pulmonary injury caused by chlorine gas inhalation. **Material and Methods:** Forty-eight rats were used. Rats were randomly distributed into five groups. Rats in Group 1 (n= 8) were kept untreated throughout the study. Rats in Group 2 (n= 8), Group 3 (n= 8), Group 4 (n= 12), and Group 5 (n= 12) were exposed to 155 ppm chlorine gas inhalation for five minutes. Rats in Group 3 and 5 were additionally given nebulized sodium bicarbonate following chlorine gas inhalation. Rats in Group 2 and 3 were sacrificed 30 minutes after the chlorine inhalation, and rats in Group 4 and 5 were sacrificed 45 days after the inhalation for histopathological examinations. Pulmonary injury grade was determined and the results were compared between groups. Statistical analysis was performed using the SSPS 13.0 software. **Results:** Histopathological examination of the lungs of rats in Group 2 and 3 showed acute injury. There was no injury in Group 1. All of the rats in Group 2 had Grade 1 injury. In Group 3, 50% of rats had Grade 1 and 50% had Grade 2 injuries. Some of the rats in Group 4 and Group 5 showed similar interstitial fibrosis and alveolar emphysematous alterations. Grade 3 injury was not determined in any groups. **Conclusion:** We concluded that nebulized sodium bicarbonate increases the severity of pulmonary injury in the short-term. It has no effects on the injury in the long-term.

Key Words: Inhalation exposure; sodium bicarbonate

ÖZET Amaç: Halk arasında çamaşır suyu ve tuz ruhu olarak bilinen sodyum hipoklorit ve hidroklorik asit, geleneksel olarak temizlik amacı ile kullanılırlar. Bu iki sıvının karıştırılması sonucu klor gazı ortaya çıkar. Klor gazı zehirlenmeleri acil servise sık başvuru nedenlerinden birisidir. Bu hastaların tedavisinde ana yaklaşım semptomatik ve destekleyici tedavidir. Ortaya çıkan akciğer hasarını azaltmaya yönelik kabul görmüş spesifik bir tedavi yaklaşımı yoktur. Çalışmamızda, klor gazı inhalasyonu ile oluşturulan akciğer hasarının tedavisinde, kullanımı literatürde de tartışmalı olan, nebülize sodyum bikarbonatın etkisini histopatolojik olarak araştırdık. **Gereç ve Yöntemler:** Toplam 48 adet rat kullanıldı. Ratlar randomize olarak beş gruba ayrıldı. Grup 1 (n= 8) ratlara deney süresince hiçbir şey verilmedi. Grup 2 (n= 8), Grup 3 (n= 8), Grup 4 (n= 12), ve Grup 5 (n= 12)'teki ratlara beş dakika süreyle 155 ppm klor gazı inhale ettirildi. Grup 3 ve Grup 5'teki ratlara ek olarak klor gazı inhalasyonu sonrası nebülize sodyum bikarbonat verildi. Grup 2 ve Grup 3'teki ratlar klor gazı inhalasyonundan 30 dakika sonra, Grup 4 ve Grup 5'teki ratlar inhalasyondan 45 gün sonra histopatolojik değerlendirilme için sakrifiye edildiler. Pulmoner hasar skorlaması yapıldı ve sonuçlar gruplar arasında karşılaştırıldı. SSPS 13.0 yazılım programı kullanılarak istatistiksel analizler yapıldı. **Bulgular:** Akciğerlerin histopatolojik değerlendirilmesinde Grup 2 ve Grup 3'teki ratlarda akut zararlanma görüldü. Grup 1'de hiçbir ratta zararlanma yoktu. Grup 2'deki ratların hepsinde Grade 1 zararlanma vardı. Grup 3'teki ratların %50'sinde Grade 1, %50'sinde de Grade 2 zararlanma vardı. Grup 4 ve Grup 5'te benzer olarak ratların bazılarında interstisyel fibrozis ve alveolar amfizematöz değişiklikler görüldü. Grade 3 zararlanma hiçbir grupta tespit edilmedi. **Sonuç:** Nebülize sodyum bikarbonat erken dönemde akciğer hasarını arttırır. Geç dönemde ise hasar üzerine herhangi bir etkisi yoktur.

Anahtar Kelimeler: Solunumla maruz kalmak; sodyum bikarbonat

Turkiye Klinikleri J Med Sci 2010;30(2):650-8

Inhalation of chlorine vapor arising from inappropriate mixture of bleach water (sodium hypochlorite), one of the cleaning agent used in the household, with other acidic products, can result in chlorine gas exposure.[1] The most common non-professional exposure is the inappropriate combination of the cleaning agents.[2] Sodium hypochlorite (NaOCl) and hydrochloric acid (HCl) are effective and cheap solutions used for cleaning of porcelain, marble and ceramic surfaces. Combination of NaOCl and HCl produces large amounts of bubbles and chlorine gas.[3] Chlorine gas is a pulmonary irritant gas with intermediate water solubility that causes acute injury in the lower and upper respiratory tracts. This gas has a yellowish-green color and a bitter odor. The density of this gas is two times greater than that of air. In addition, it is non-combustible in room temperature and at normal atmospheric pressure.[4,5] The severity of the toxicity depends on the solubility within tissues and is dependent on dose, which is a function of concentration, minute ventilation and duration of exposure.[5] The most important result of chlorine gas exposure is that it produces irritant effects when it comes into contact with important mucosal membranes within the respiratory tract.[6] HCl and oxygen radicals O^- are responsible for chlorine gas toxicity.[1-3]

Decrease in ventilated air, non-allergic hypersensitivity, mucosal inflammation in lymphocytes, and epithelial basal membrane thickening have been reported following the acute exposure to high doses of chlorine gas.[7]

Some clinical studies mention that use of nebulized sodium bicarbonate (NSB) in emergency patients exposed to chlorine gas has beneficial effects in treating the respiratory problems. No clinical regression has been reported in patients given nebulized sodium bicarbonate.[1,8,9] However, the use of nebulized sodium bicarbonate is yet controversial.[10] In chlorine gas exposure, rapid sodium bicarbonate administration has been suggested to neutralize the HCl arising from the reaction of chlorine gas with the water in the mucosal membranes of the respiratory tract. The combination of sodium bicarbonate and HCl can yield heat, causing additional damage in the respiratory tract.

In this study, we aimed to investigate histopathologically the effect of nebulized sodium bicarbonate in pulmonary damage that was induced by chlorine gas inhalation.

MATERIAL AND METHODS

This experimental study has been carried out at the Animal Laboratory, Pathology and Physiology Departments of the Faculty of Medicine, Gaziantep University, following the approval of the Ethical Committee (Date:14.05.2007; number: 2007/4). The protocol was kept in accordance to the Helsinki Declaration. Forty eight Male Wistar Albino rats weighing 250-300 grams, raised in the Animal Laboratory of the Faculty of Medicine, Gaziantep University, were used in the study.

PREPARATION OF SUBJECTS

The animals were fed with the standard ration prior to and during the study. The rats were randomly distributed into five groups. Group 1 (control group): Eight rats were used. They were neither exposed to chlorine gas, nor they were given nebulized sodium bicarbonate. Tissue samples were obtained for comparison with the other groups. The rats in Group 2 (eight rats) were treated with 155 ppm chlorine gas for 5 minutes; they were sacrificed 30 minutes after the treatment for tissue sampling. The rats in Group 3 (eight rats) were treated with 155 ppm chlorine gas for five minutes: They were then given nebulized sodium bicarbonate for 30 minutes and sacrificed for tissue sampling. The rats in Group 4 (12 rats) were treated with 155 ppm chlorine gas for five minutes, and were then sacrificed after 45 days for tissue sampling. The rats in Group 5 (12 rats) were treated with 155 ppm chlorine gas for five minutes, and were then given nebulized sodium bicarbonate for 30 minutes and sacrificed 45 days after the treatment for tissue sampling.

EXPERIMENTAL DESIGN AND CHLORINE GAS PRODUCTION

Two transparent plastic anesthesia chambers of cubic shape and 25 x 25 cm size were placed one above the

other. The rats were placed in the lower chamber and a steel grid was placed between the chambers to allow gas diffusion. A Petri dish was placed on the steel grid. A plastic pipette was introduced into the Petri dish through the hole on the side of the upper chamber. 10 ml of sodium hypochlorite (Koruma, Istanbul, Turkey) was poured onto the Petri dish using a 50 ml injector. 10 ml hydrochloric acid (Koruma, Istanbul, Turkey) was added to the plate through the same way. An immediate reaction occurred from the combination of these solutions and a gas appeared which was supposed to be the chlorine gas.

Chlorine gas production occurs following reactions below:[2]

a. Chlorine gas formation from HCl and HOCl

$HCl + HOCl \leftrightarrow Cl_2 + H_2O$

b. Chlorine gas formation from HCl and NaOCl

$HCl + NaOCl \leftrightarrow Cl_2 + NaOH$

c. HOCl and HCl formation from Cl_2 gas

$Cl_2 + H_2O \leftrightarrow HCl + HOCl$

d. HCl and $\{O^-\}$ formation as a result of the reaction of chlorine gas with water in the respiratory tract

$Cl_2 + H_2O \leftrightarrow 2HCl + \{O^-\}$

e. HCl ve $\{O^-\}$ formation from HOCl

$HOCl \leftrightarrow HCl + \{O^-\}$

This chlorine gas diffused to the lower chamber due to the fact that it was heavier than air. Rats in Group 2, Group 3, Group 4, and Group 5 were exposed to chlorine gas inhalation. Rats in the Group 1 were also placed in the anesthesia chambers, but kept unexposed to the gas inhalation. Thereafter, rats were removed. Four rats were placed in the anesthesia chamber each time. One liter of 20% NaOH (Merck, Germany) was introduced in a glass container in the lower chamber to measure the chlorine gas.

Protective masks, gloves and aprons were used during the experiment.

MEASUREMENT OF THE CHLORINE GAS LEVEL

The solution absorbing the chlorine gas was measured at the Quality Control Laboratory of the Faculty of Food Engineering. Chlorine gas was measured under normal barometric pressure and room temperature. Hydrogen chloride and potassium iodide were added to the NaOH solution which had absorbed the chlorine gas. The quantity of chlorine gas was measured by titration with 0.01 mol/L sodium thiosulfate. The quantity of chlorine gas was determined as 155 ppm.[4] This method is routinely used for chlorine measurement in the laboratory tap water, industrial tanks and swimming pools.

NEBULIZED SODIUM BICARBONATE ADMINISTRATION

Two ml of 8.4% $NaHCO_3$ was mixed with 2 ml of physiological saline, yielding 4 ml of 4.2% $NaHCO_3$. Rats in Group 3 and 5 were placed in the transparent anesthesia chambers of 25 x 25 cm. Nebulized sodium bicarbonate was administered to the rats for 30 minutes through the hole on the side of the anesthesia chamber, by means of a transparent pipe connected to the nebulizer (Mod. Air 3000 plus, Norditalia Elettromedicalis, Brescia-Italy). Rats in Group 1, Group 2 and Group 4 were placed in the same chamber, inhalating air instead of nebulized sodium bicarbonate.

HISTOPATHOLOGICAL EVALUATION

Rats were sacrificed and their chests were opened following anesthesia induced with 120 mg/kg intraperitoneal thiopental administration. The lungs and the hearts were removed completely. Routine tissue fixation procedures were followed and all tissues were blocked with paraffin and sections of 5-8 microns were prepared. All tissues were stained with hematoxylin-eosin (HE) and evaluated by light microscopy. Staining was performed with the HE stain. Stained preparations were evaluated under the light microscope.

The microscopic evaluations were made by the same person who did not have any knowledge about groups. Pulmonary injury scoring was done (Table 1) and the results were compared between groups.

The severity of pathological findings and injury grade was determined according to Broccard and his colleagues' criteria.[11]

STATISTICAL ANALYSIS

The Simplex Fisher's Exact test in the SPSS 13 program and the Chi-square test were used for the sta-

TABLE 1: Histopathological classification of short and long term pulmonary findings.[11]

Grades	Histopathological classification of short term pulmonary findings	Histopathological classifications of long term pulmonary findings
Grade 0	No Injury	No Injury
Grade 1	Mild injury; mild congestion, interstitial edema, few neutrophils and erythrocytes in the alveoli associated with interstitial neutrphil infiltration	Mild injury; slight interstitial fibrosis and mild alveolar emphysematous alteration
Grade 2	Moderate injury; moderate congestion, interstitial edema and partial alveolar neutrophil infiltration	Moderate injury; moderate interstitial fibrosis and moderate alveolar emphysematous alteration
Grade 3	Severe injury; marked congestion, interstitial edema and almost complete alveolar neutrophil infiltration	Severe injury; severe interstitial fibrosis and alveolar emphysematous alteration

tistical analyses between the groups. In the result of the comparison between the groups, p values of < 0.05 were accepted as significant.

RESULTS

In this experimental study, we obtained the following findings from the histopathological examination of pulmonary tissues of the rats in Group 1, Group 2, Group 3, Group 4 and Group 5.

No injury was found in the pulmonary tissues of rats in Group 1 (Figure 1). Histopathological examination of the pulmonary tissues of the eight rats (100%) in Group 2 showed mild congestion, interstitial and alveolar edema, a mild injury associated with interstitial neutrophil infiltration, in addition to neutrophil and erythrocyte-filled alveoli (grade 1) (Figure 2). The difference between Group 1 and Group 2 was statistically significant (p< 0.001). Histopathological examination of the pulmonary tissues of the rats in Group 3 showed that there was a mild injury in four rats (50%), and a moderate injury associated with moderate congestion, interstitial edema and alveolar edema in four rats (50%) (Figure 3). The difference between Group 1 and Group 3 was statistically significant (p< 0.001). The pulmonary injury in rats in Group 3 was more serious, compared to Group 2. The difference in inflammation grade between Group 2 and Group 3 was statistically significant (p= 0.038). Histopathological classification of rats in Group 1, Group 2 and Group 3 was demonstrated in the Table 2. In the histopathological examination of the pulmonary tissues of the rats in Group 4, we observed normal pulmonary tissues in five rats (41.7%), mild interstitial fibrosis and emphysematous alterations in the lungs of four rats (33.3%) and moderate interstitial fibrosis and emphysematous alterations in three rats (25%) (Figure 4). In the histopathological examination of the pulmonary tissues of the rats in Group 5, we found normal pulmonary tissues in six rats (50%), mild interstitial fibrosis and emphysematous alterations in five rats (41.7%) and moderate interstitial fibrosis and emphysematous alterations in one rat (8.1%) (Figure 5, 6). There was no significant difference in inflammation between Group 4 and Group 5 (p= 0.548). Histopathological classification of rats in Group 1, Group 4 and Group 5 was presented in the Table 2.

DISCUSSION

Chlorine gas is a pulmonary irritant gas with intermediate water solubility that causes acute injury in the lower and upper respiratory tracts.[5] The mechanism of chlorine gas toxicity has been suggested to be due to HCl and $\{O^-\}$ arising from the reaction between chlorine gas and water on the moist surface of the airways following the inhalation. These two agents have been reported to be responsible for the pulmonary injury.[1-3] Today, as there is no specific treatment for the pulmonary injury caused by chlorine gas exposure, the fundamental approach is symptomatic treatment with moistened oxygen and bronchodilators.[5,10] In this study, we have investigated whether nebulized sodium bicarbonate treatment prevents pulmonary injury caused by chlorine gas.

In our country, in emergency practice, the etiology behind chlorine exposure cases is mixing the bleach water and hydrochloric acid used in the household cleaning. The number of patients presenting to the emergency units for this reason is not

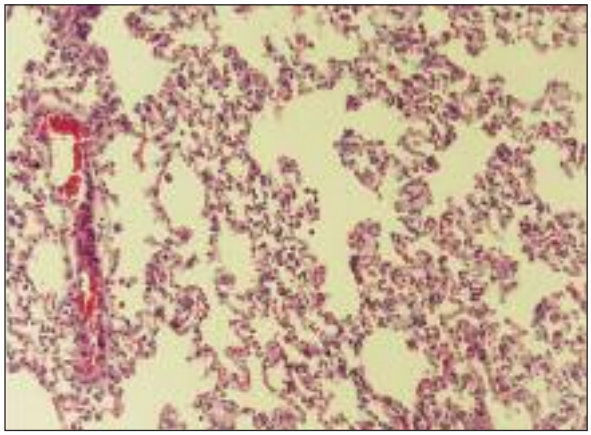

FIGURE 1: Normal rat lung (Group 1) (HE, x200).

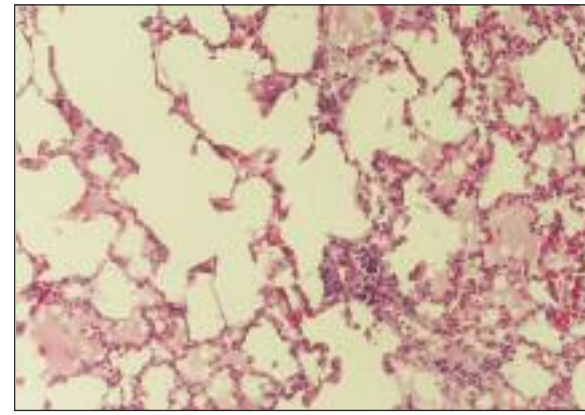

FIGURE 2: Grade 1 alveolar and interstitial edema (Group 2) (HE, x200).

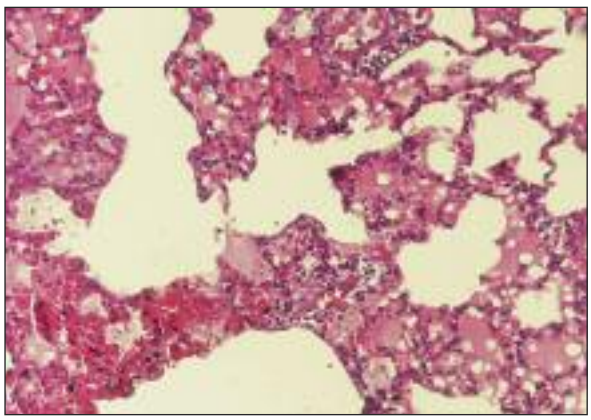

FIGURE 3: Grade 2 alveolar and interstitial edema and hemorrhage in the interstitial area (Group 3) (HE, x200).

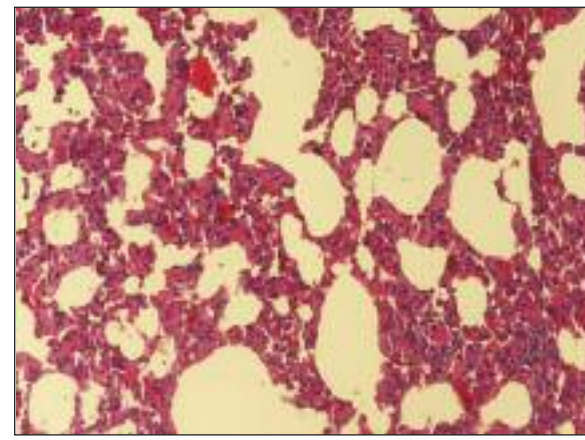

FIGURE 4: Grade 2 interstitial fibrosis (Group 4) (HE, x200).

so few. However, due to the fact that university faculty hospitals are not the primary healthcare centers to which these patients generally present to, we believe that most of these patients go unregistered, as regular statistical data only come from faculties, and scientific researches are only carried out in these faculties. Nevertheless, there are numerous case series in our country reported by the medical faculties.[3,9,12]

There have been previous studies carried out with various doses and duration on chlorine gas in rats, sheep, porcine and dormice.[4,13-15] We selected rats as the experiment animals in our study, since they met our conditions the best. Most of the recently reported chlorine gas exposures include exposures caused by the inhalation of toxic vapor arising from mixing of hypochlorite-containing household cleaning products with acid products.[1,8,12,16] Therefore, we obtained the chlorine gas by mixing bleach water and hydrochloric acid sold in the market. Pulmonary injury caused by chlorine gas inhalation depends on the dose and duration of inhalation. We observed accelerated respiration in all rats by the third minute, and immobility by the fifth minute. In addition, we found that this immobility continued until the end of the experiment in the rats in Groups 2 and 3, and the motor activities of rats in Groups 4 and 5 began to recover slowly by the first hour. No deaths were observed in the experimental groups throughout the experiment.

In the histopathological examination of the pulmonary tissues of the rats in Group 2, we found mild congestion, interstitial and alveolar edema, and a mild injury associated with interstitial neu-

trophil infiltration, and alveolar neutrophil and erythrocyte infiltration. The difference between Group 1 and Group 2 was statistically significant.

In the study of Yildirim et al. in which 1330 ppm of Cl_2 gas was administered for 15 minutes, it was reported that vascular congestion, diffuse intra-alveolar edema, and acute alterations associated with interstitial and alveolar hemorrhages were found in the pulmonary tissues of rats sacrificed immediately after the inhalation.[5] We found similar alterations in Group 2 and Group 3. However, the findings in our experiment were milder, as we gave chlorine gas at a lower dose and for a shorter period.

Batchinsky et al. carried out a study giving Cl_2 gas of 120, 240-350 and 400-500 ppm concentrations for 30 minutes to sheep under anesthesia and followed up the subjects in the mechanical ventilator for 96 hours post- chlorine gas inhalation.[15] During the follow-up, no deaths were seen in the

TABLE 2: Results of histopathological examination of lungs of rats in groups.

Groups	Grades				Total, N, %
	0	1	2	3	
Group 1					
N	8	0	0	0	8
%	100	0	0	0	100
Group 2					
N	0	8	0	0	8
%	0	100	0	0	100
Group 3					
N	0	4	4	0	8
%	0	50	50	0	100
Group 4					
N	5	4	3	0	12
%	41.7	33.3	25	0	100
Group 5					
N	6	5	1	0	12
%	50	41.7	8.3	0	100
Total					
N	19	21	8	0	48
%	39.6	43.7	16.7	0	100

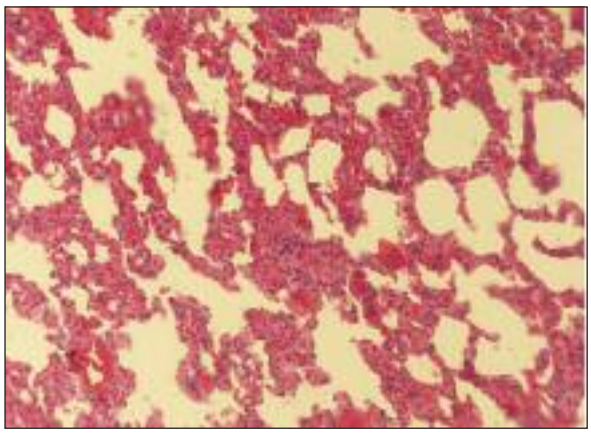

FIGURE 5: Grade 1 interstitial fibrosis (Group 5) (HE, x200).

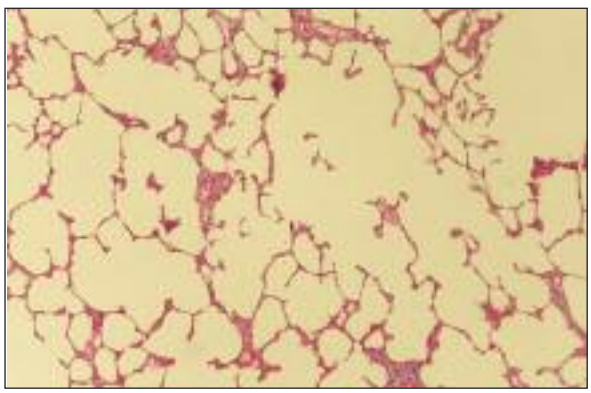

FIGURE 6: Grade 1 emphysema (Group 5) (HE, x100)

Group treated with 120 ppm chlorine gas, while five out of 11 sheep had died in the group treated with 240-350 ppm, and 10 out of 12 sheep died in the group treated with 400-500 ppm chlorine gas. In the microscopic examination of the pulmonary tissues of the group treated with 120 ppm chlorine gas, they found localized regional necrosis associated with capillary congestion, edema, fibrin deposits and acute inflammation in the bronchial epithelium. They showed that higher doses caused necrosis, fibrin accumulation and spread of inflammation to all adjoining alveoli and that the lesions invaded the entire lung. They also determined that there was an increase in edema and necrosis in line with the increase in the dose of chlorine gas. No deaths were observed in our study throughout the study in the rats given 155 ppm chlorine gas. Our findings were consistent with the histopathology of sheep given 120 ppm chlorine gas.

Martin et al. found bronchial epithelium erosion, patch injury in the alveoli, proteinous exudates and inflammatory cells in the wall of the alveoli in the histopathological examination of mice pulmonary tissues 24 hours after the exposure

to 800 ppm chlorine gas.[17] They found macrophages, granulocytes, epithelial cells and an increase in the nitrate/nitrite levels in the alveolar lavage liquid. They reported that chlorine gas caused functional and pathological alterations in the bronchioles in relation with oxidative stress.

Demnati et al. exposed Sprague-Dawley rats to 1500 ppm chlorine gas for 5 minutes.[8] They observed epithelial necrosis and detachment, increase in the smooth muscle volume, mucous cellular hyperplasia and epithelial regeneration, and reported that most of these alterations recovered within 90 days. They reported a significant correlation between histopathological and functional alterations.

Gunnarsson et al. administered 140 ppm of chlorine gas for 10 minutes to pigs under anesthesia, connected them to the mechanic ventilator, and observed them for six hours.[6] Then, the animals were sacrificed for histopathological examination. They reported that severe pulmonary dysfunction developed during this interval, in addition to dilatation in the small and intermediate bronchioles, enlargement in the alveolar space, edema in the alveolar septum, and desquamation in the epithelial cilia at the mucosal surface and inflammatory cells in the desquamated cells.

In the histopathological examination of pulmonary tissue samples of the rats in Group 3, we found mild injury in four rats, and moderate congestion and moderate injury associated with interstitial and alveolar edema in four rats. The difference between Group 3 and Group 1 was statistically significant. The injury was more severe in the rats in Group 3 when compared to Group 2. These results showed that nebulized sodium bicarbonate increased the severity of pulmonary tissue injury in the short-term.

There are a limited number of reports on the use of nebulized sodium bicarbonate following chlorine gas inhalation. Most of these reports are case series, reporting that nebulized sodium bicarbonate has reduced the symptoms of the patients. These reports include no recovery of the patients with serious symptoms following the nebulized sodium bicarbonate treatment, but only mention recovery in patients with mild symptoms. We found only one study about nebulized sodium bicarbonate use following experimental chlorine gas treatment, in the form of a congress presentation. In this study on sheep, one group was given 4% nebulized sodium bicarbonate following chlorine gas inhalation and another group was given nebulized physiological serum. This study reports that the PO_2 values were higher and the PCO_2 values were lower in the treatment group, and that the mortality rate was similar in the two groups after the 24-hour observation period, and no difference was found between the two groups in the histopathological examination of lungs of the animals sacrificed after 24 hours.[18] We did not carry out blood gas analysis and respiratory function tests in our current study. The injury in the nebulized sodium bicarbonate group was higher in the pulmonary histopathology, compared to the results of our study.

Aslan et al. administered short acting β_2 agonist and intravenous corticosteroid to all of the 44 patients that developed RADS following exposure to chlorine gas, arising from the combination of NaOCl and HCl in inappropriate conditions.[9] Additionally, half of the patients were given 4.2% nebulized sodium bicarbonate. They tested the pulmonary functions of all patients before and after the treatment. They found that pre-treatment FEV_1 scores were similar in all patients; post-treatment FEV_1 scores were evidently higher, compared to other patients in patients who were given nebulized sodium bicarbonate in addition to standard treatment. They reported that the use of nebulized sodium bicarbonate was advantageous. Vinsel reported that the symptoms of three patients with cough, dyspnea and chest pain following chlorine gas inhalation at the swimming pool recovered following the administration of 3.75% nebulized sodium bicarbonate.[10] Bosse reported that 86 patients with cough, dyspnea, wheezing, without pulmonary edema and with respiratory insufficiency not requiring mechanical ventilation following chlorine gas inhalation were given 5% nebulized sodium bicarbonate and that no deterioration in the clinical status of the patients developed following nebulized sodium bicarbonate treatment.[1]

Bosse reported that the use of nebulized sodium bicarbonate following Cl_2 gas inhalation was safe and advantageous. In America, 22 soldiers out of 72, suffering from exposure caused by chloramine gas arising from mixing of hypochlorite with ammonia during barracks cleaning, were given nebulized sodium bicarbonate of 3.75% concentration. No significant difference was reported in the comparison of the results with the soldiers not treated with nebulized sodium bicarbonate.[19] Ahmed et al. administered nebulized sodium bicarbonate to five patients with acute asthma attack in order to investigate whether the alkalinization of the sticky acidic mucus in asthma patients would cause an improvement of symptoms.[20] They reported that PEFR scores of patients showed a rapid increase following the nebulized sodium bicarbonate administration and no deterioration in their symptoms was observed. They also stated that the recovery was due to the recovery of bronchospasm, rather than alkalinization of the mucus.

In the histopathological examinations, we found complete recovery in the lungs of some of the rats in Group 4 and Group 5, and alveolar emphysematous alterations associated with mild and moderate interstitial fibrosis in some of the rats. The comparison of these two groups showed no statistically significant difference.

Yildirim et al. gave 1330 ppm chlorine gas for 15 minutes to the rats, observed them for 45 days after the inhalation, and found thickening in the alveoler septa of the lungs in all rats due to interstitial fibrosis and basal membrane thickening.[5] Exposing rats to high doses of chlorine, Demnati et al found that the acute findings recovered in the histopathological investigation of pulmonary tissues of rats after 90 days, however bronchial resistance continued in six rats out of eight.[8] Deschamps et al. reported a case, which presented with the complaints of cough and wheezing two days after inhalation of the gas arising from the mixture of sodium hypochlorite and hydrochloric acid.[21] The patient had mild bronchial obstruction and hyperactivity in the respiratory function test. The symptoms were alleviated by bronchodilators, but the patient suffered from asthma attacks two months later. Although inhalational steroid was begun, they reported that the asthma attacks of the patient still continued after two years. They found epithelial destruction, a mild inflammatory response, and sub-epithelial connective tissue thickening in the bronchial biopsy performed before the steroid treatment. In our study, we found emphysematous alterations and interstitial fibrosis in some of the rats at the end of 45 days. In 1975, Schwartz et al. found obstruction in the flow of air and a ventilation trap from the respiratory function tests in 20 healthy individuals exposed to high doses of chlorine gas.[22] During approximately 12 years of observation of these people, they found that the ventilation trap had recovered, but the ventilation obstruction persisted, and that there was a reduction in the residual volume. They reported that exposure to high dose chlorine gas can result in chronic pulmonary complications characterized with low residual volume. Moore and Sherman have reported a case with chronic asthma following exposure to chlorine gas.[23] Lemiere et al. reported a case with RADS development following inhalation of chlorine gas whose symptoms persisted for 5 months.[24] In our study, we observed that there was still interstitial fibrosis and emphysematous alterations after 45 days in some of the rats.

Considering the results of these studies and our study, chlorine gas inhalation can cause severe problems and death due to severe pulmonary injury. The tissue injury can occur over prolonged periods and can lead to chronic pulmonary diseases. The observation period of the patients suffering from exposure to chlorine gas inhalations should be kept long. After the treatment in the emergency unit, these patients should be monitored for the development of chronic pulmonary diseases.

In conclusion, we suggest that nebulized sodium bicarbonate treatment following chlorine gas inhalation increases the pulmonary injury in the short term, and does not reduce the pulmonary injury in the long-term. Therefore, we suggest that the use of nebulized sodium carbonate is not appropriate following chlorine gas inhalation.

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