

Chlorine exposure accidents characteristics and recent progress in treatment

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Abstract

Introduction: As a choking agent, chlorine (Cl_2) exposure accidents occur frequently, which brings great threat to safety of people's lives and property.

Objective: In this work, the study systematically reviewed the Cl_2 exposure accidents from 1967 to 2022, and would like to find valuable new insights and paths in treatment of Cl_2 poisoning.

Methods: Eight databases (Wanfang, VIP, CNKI, CBM, Pubmed, Embase, PsycINFO and Cochrane) were searched from the date of establishment to January 2022.

Results: A total of 159 articles involving 14,197 people with acute Cl_2 exposure were included. 125 articles reported on accident types. The most frequent type of accident was industry (71.2%), followed by swimming pools (17.6%). Common symptoms were mainly manifested in the eyes, oropharynx, skin, upper and lower respiratory tract, etc. Laboratory tested mainly include physical examination, blood, and X-ray examination to provide reliable basis for treatment. Conventional treated options include glucocorticoids, nebulized inhalation, oxygen inhalation, anti-inflammatory, etc. Extracorporeal Membrane oxygenation (ECMO) was used in critically ill patients.

Conclusions: Timely and effective treatment is extremely important for the life safety of patients exposed to Cl_2 . This study provides the latest first-hand information for Cl_2 exposure accidents characteristics and management strategies, which are mainly related to treatment, and can provide reference and ideas for drug screen and new treatment plans in the future.

Keywords

Chlorine; Chlorine exposure accidents; Chlorine poisoning; Lung injury; Accident statistics.

Abbreviations

Cl₂: Chlorine; ECMO: Extracorporeal Membrane Oxygenation; HOCl: Hypochlorous Acid; HCl: Hydrochloric Acid; ARDS: Acute Respiratory Syndrome; ATP: Adenosine Triphosphate; FDP: Fructose-1,6-Bisphosphate; PTX: Pentoxifylline.

Introduction

Chlorine (Cl₂) is a kind of yellow-green toxic gas. Up to now, Cl₂ is still the most common of all the inhaled toxicants. It is widely used in household disinfection and industrial production. Accidental Cl₂ exposure may occur during the production, transportation and use of Cl₂. So far, many Cl₂ exposure accidents have been reported all over the world. For example, the largest Cl₂ leak to date occurred in South Carolina in 2005 [1], and the most recent was a Cl₂ leak at the Aquatics Centre in London, England, on March 23, 2022 [2]. In fact, Cl₂ leaks are not limited to accidental leaks, but have also been used as a chemical weapon for large-scale deliberate releases in wars and terrorist activities [3], have caused a large number of casualties.

Cl₂ poisoning has a rapid onset and is inhaled through the respiratory tract. Various Cl₂ injury case reports and studies have shown that exposure to 3 ppm Cl₂ can cause mild irritation symptoms such as photophobia, lacrimation, and throat discomfort; 5-15 ppm cause moderate irritation symptoms such as expectoration and chest tightness; >15 ppm causes severe lung irritation, causing symptoms such as dyspnea, retrosternal pain; but exposure to ≥430 ppm for 30 mins or less results in death [4]. When Cl₂ is inhaled, it reacts with the solution on the mucosa and alveolar to produce hypochlorous acid (HOCl) and hydrochloric acid (HCl). The toxicity of Cl₂ is mainly due to its oxidation potential. The released ions can pass through the cell wall and produce oxygen free radicals [5]. The injury can lead to bronchospasm, edema, epithelial cell erosion, shedding, etc. In addition to causing epithelial cell damage, the presence of HOCl and hypochlorite in the airway can also cause inflammatory reactions. Inflammatory cells and free radicals destroy cell membrane and protein, resulting in the destruction of alveolar cells and endothelial cells of adjacent capillaries, increasing the permeability of pulmonary vascular endothelial cells, and ultimately leading to pulmonary edema and acute respiratory syndrome (ARDS) [6]. Various treatment modalities exist for acute Cl₂ exposure. At present, the conventional treatment is mainly symptomatic treatment such as oxygen inhalation, glucocorticoid, bronchodilator, and anti-inflammatory, but there is no effective treatment drug.

On the basis of the previous literature [7], this study collected Cl₂ poisoning accidents in a longer time range through an open source database, especially from 2017 to 2022. The study observed the events characteristics and clinical management systematically in order to find out some trails for the treatment and public health management after Cl₂ exposure accident in the future.

Methods

Search strategies

From November 2021, this study systematically searched 8 databases (Wanfang, VIP, CNKI, CBM, Pubmed, Ebmase, PsycINFO and Cochrane) for eligible articles on Cl₂ exposure accidents in Chinese and English. Medical Subject Headings (MeSH) and free-text terms related to Cl₂ spill accidents. MeSH terms used include "Chlorine", "Gas Poisoning", "Chemically-Induced Disorders", etc. An example of a search strategy for the database PubMed is given in the appendix.

Inclusion criteria

The study excluded duplicate reports of the same accident. Review articles were excluded unless the article also contained a case report or case series. Chronic Cl₂ poisoning (occupational disease) and exposure to mixture poisoning are excluded.

Literature screening and data extraction

Two researchers first independently screened literature based on study titles and abstracts. Then, after reading the full text, a decision was made whether to include the literature in this study. Two reviewers extracted data based on predesigned data and cross-checked them. Differences in data extraction and literature screening, if any, were explored with a third investigator until agreement was reached. The extracted data included the first author of the article, the age and gender of the participants, the time and place of the accident, the number of casualties, clinical symptoms, interventions, physical examination results, and more.

Data analysis: Statistics were made using descriptive statistical methods.

Results

Search results

A total of 7483 potentially eligible literatures were identified through systematic retrieval of 8 databases. After reviewing the title and summary, 3285 records were excluded. Read the remaining 4198 articles for further screening, excluding 3970 articles not related to this study. 69 articles were excluded because they were unable to obtain the full text. Finally, 159 articles were included in this analysis (Figure 1) [8-165].

A total of 14,197 people were identified as exposed to Cl₂, of which 159 articles reported the area of occurrence and 125 articles reported the type of accident. There were 4641 males and 3478 females. The age of contact ranged from 3 months to 90 years. Over 99% of cases survived to hospital discharge; 57 died (0.004%). Complications included chronic pharyngitis, pulmonary tuberculosis, pneumonia, bronchitis,

bronchial asthma, myocarditis, and so on.

Characteristics of time distribution of Cl₂ exposure accidents

This paper made statistics on Cl₂ exposure accidents in the world from 1967 to 2020. The statistical results are shown in Figure 2. It can be seen that the high incidence of Cl₂ exposure accidents can be mainly distributed in three stages: (1) The first stage is from 2000 to 2002. The Cl₂ exposure accidents occurred in 7 cases (4.3%), 9 cases (5.5%) and 5 cases (3.1%). (2) The second stage is from 2004 to 2006. Compared with the first stage, Cl₂ exposure accidents had increased, with 9 cases (5.5%), 6 cases (3.7%) and 10 cases (6.1%), respectively. (3) The third stage is from 2011 to 2014. Since 2015, the frequency of accident has been no peak, and stabilized about 1.2%.

Categories of Cl₂ exposure accidents

Among the Cl₂ exposure accidents, 89 cases (71.2%) were industrially exposed to Cl₂; 22 cases (17.6%) were related to swimming pool; 6 cases (4.8%) were related to Cl₂ produced by hypochlorite reaction, and 2 cases (1.6%) were related to traffic accidents, military, laboratory, and swimming pool plus industrial exposure (Figure 3).

Clinical features of Cl₂ poisoning

Some clinical signs and symptoms were collected that may be related to Cl₂ exposure (Table 1). Eye symptoms mainly include: photophobia, lacrimation, ophthalmalgia, blurred vision; oropharyngeal symptoms include: Pharyngeal congestion and swelling, burning sensation; skin symptoms such as sweating, paleness, and cyanosis. The upper respiratory tract was mainly characterized by vocal cord edema, hoarseness, swollen tonsils, sore throat, dry throat, laryngospasm, sneezing and other symptoms; the lower respiratory tract was mainly characterized by cough, expectoration, dyspnea, shortness of breath, chest tightness, chest pain, pulmonary atelectasis, acute pulmonary edema, respiratory failure. Some patients experienced limb symptoms such as difficulty walking, limb numbness, and gait deformity. There even had central nervous system-related symptoms such as: unconsciousness, sleepiness, coma, headache, dysphoria, slurred speech, and tetany. Gastrointestinal tract symptoms such as nausea, vomiting, epigastric pain, and upper gastrointestinal bleeding were also present. Cardiogenic shock, sinus bradycardia, palpitations, arrhythmia, flustered, elevated blood pressure, atrial premature beats, heart arrest appeared in the cardiovascular system. A small number of patients had symptoms of gatism and hypopourocrinia in excretion.

Examination results of Cl₂ poisoning

At the same time, this study also summarized and classified the laboratory test results (Table 2). Physical examination showed moist rales and/or wheezing in the lungs, rough breathing sounds in bilateral lungs, and triple concave sign (+). Blood tests showed increased white blood cells, elevated erythrocyte sedimentation rate, slightly elevated serum sodium⁺, Cl⁻, hypokalemia, hypoxemia, and hypercapnia. Elevated white blood cell counts and blood sedimentation suggested that an inflammatory response may have occurred in the patients' body. Renal function examination showed that some patients had increased

urea nitrogen, serum creatinine and urinary protein (+). A series of indicators of liver function, such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and serum γ -glutamyl transpeptidase were all elevated. A small number of patients showed abnormal manifestations such as ST segment depression, T wave inversion or low level, I-degree atrioventricular block, and left ventricular hypertension in ECG examination. Almost all patients underwent X-ray. The examination results showed that the hilar shadow increased and blurred, the lung texture was enhanced and disordered, the transparency of the lung field was reduced, and scattered dotted, a low density patch in the middle and upper fields of the two lungs and other pulmonary infection and disease states.

Clinical treatment of Cl₂ poisoning

In this study, the treatment methods obtained in 163 literatures were classified and summarized (Table 3). Dexamethasone was the mainstay of glucocorticoid treatment, and methylprednisolone were used in severe cases [29,30,35,36,37,40,43,44,46,67,78,84,88,90,95,97]. The main treatment options for atomization inhalation are: alternate aerosol inhalation of 2-5% sodium bicarbonate solution with dexamethasone, gentamicin, aminophylline, α -chymotrypsin, distilled water [102,122,134,145] 0.25-0.5% isoproterenol or 0.2% salbutamol or dexamethasone aerosol, each inhalation for half a minute to a few minutes [82,83,85,86, 88] Isoproterenol and dexamethasone mixture and sodium bicarbonate are used in the treatment of throat spray.

Severe cough could be given codeine tablets oral or intravenous with promethazine or wintermin. Intravenous aminophylline was given to patients with dyspnea. Morphine and propofol combined with midazolam are used for analgesic and sedative effects, respectively [106, 109, 110, 123, 126]. Chloral hydrate could be given when patients are agitated. When nasal bleeding occurred, the nasal vestibular was pressed in time and the mucosal blood vessels are contracted by instilling 1-2% ephedrine [139, 140, 144, 156]. Patients with vomiting were given intramuscular injection of vitamin B6. Mucosal irritation symptoms: local administration of 2-3% sodium bicarbonate could be used to repeatedly flush the hyperemia site, after flushing, hydrocortisone eye drops or antibiotic eye drops could be applied to the conjunctiva [134, 148]; 1-2% ephedrine could be dropped into the nasal cavity liquid; pharynx could use Huasu tablets or Golden Throat Lozenges [73-89]. Patients with pulmonary edema were given intermittent use of 1% dimethicone aerosol to eliminate air bubbles in the respiratory tract.

Patients whose eyes were irritated by Cl₂ should be flushed with water or normal saline; 5% cortisone eye drops, chloramphenicol eye drops; erythromycin eye ointment should be applied to the eyes at night. Most patients who inhale Cl₂ would have an inflammatory reaction in their body, and they need to be given 2nd and 3rd generation cephalosporins or quinolones for anti-infective treatment. Adenosine Triphosphate (ATP), coenzyme A, inosine, Fructose-1,6-Bisphosphate (FDP) were usually used for myocardial protection. Some critically ill patients used Extracorporeal membrane oxygenation (ECMO) and ventilator for life support [95-112].

We also found a use of integrated traditional Chinese and Western medicine drug "Chaihuangshenquduguben" (the main components include: bupleurum, scutellaria, rhubarb, rhizoma

coptidis, red peony root, radix scrophulariae, salvia miltiorrhiza, ginseng, radix rehmanniae, honeysuckle, forsythia, fructus aurantii, gardenia, licorice) used in clinical Cl₂ poisoning treatment [147]. This treatment plan has a significant effect on improving pulmonary edema. It is a typical case of clinical treatment of Cl₂ poisoning. However, the basic research on the mechanism of action and the principle of effect still needs to be further improved and deepened.

Experimental research progress

With the development of laboratory research in recent years, some promising treatments for Cl₂ poisoning have been proposed, but most are still based on antioxidant and anti-inflammatory. At present, N-acetyl-L-cysteine, iron chelating agent and a low molecular antioxidant, AEOL10150 [4,5,7,166] and so on, are the rugs reported in the laboratory about antioxidant damage. Anti-inflammatory drugs include triptolide, nitrite, mometasone [3,10,15].

Pentoxifline (PTX) is widely used in various vascular injury diseases, as a phosphodiesterase inhibitor. Our group has discovered that compared with Cl₂ group, PTX intervention could down-regulate levels of MDA, GSSG, TOM 20 protein expression and activities of Na⁺, K⁺-ATPase and Ca²⁺, Mg²⁺-ATPase, and upregulate GSH level, GSH/GSSG ratio and CAT protein expression level in rat lung tissues [167,172]. Additionally, the results also showed that PTX exerted an inhibition effect on protein expressions of HIF-1 α , VEGF and occludin, and increased the level of E-cadherin in rat lung tissues [168,172,174]. In order to further explore the mechanism of PTX against oxidative damage and mitochondrial protection, we conducted a series of in vitro experiments [169]. The results show that compared with the control group, the green fluorescence intensity of Mito Tracker Green and Rho 123 decreased, while the red fluorescence intensity of Mito SOX increased after t-BHP (tert-butyl hydroperoxide) treatment. Compared with t-BHP group, PTX increased cell viability, decreased the levels of LDH, MDA and GSSG in cell culture supernatant, SOD activity and Nrf-2 protein expression in HUVECs (human umbilical vein endothelial cells), and increased levels of GSH, GSH/GSSG ratio, SOD1 protein expression, ATP, and the activities of Na⁺, K⁺-ATPase and Ca²⁺, Mg²⁺-ATPase [169]. As an original drug, the biggest advantage of PTX is that the new use of old drug can not be used for clinical application safety evaluation.

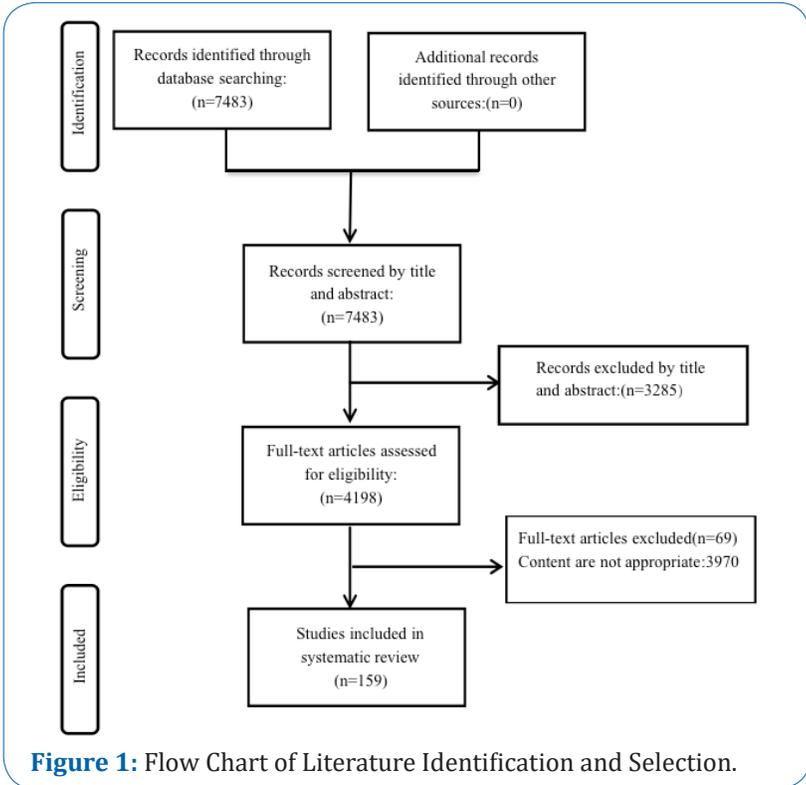


Figure 1: Flow Chart of Literature Identification and Selection.

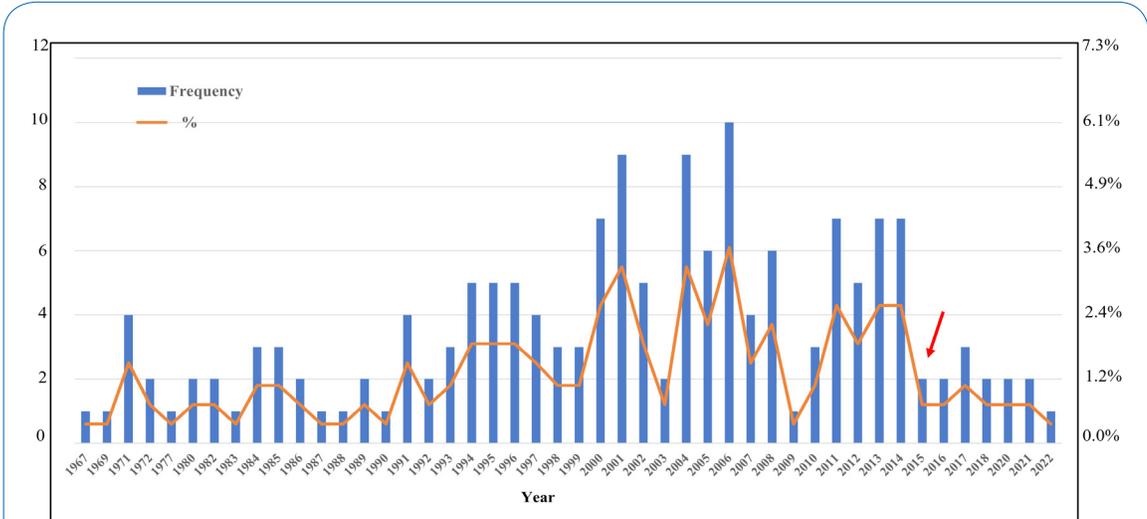


Figure 2: Statistics of the Frequency and Rate of Cl₂ Exposure Accidents from 1967-2022. Red Arrow: Events Drop Point.

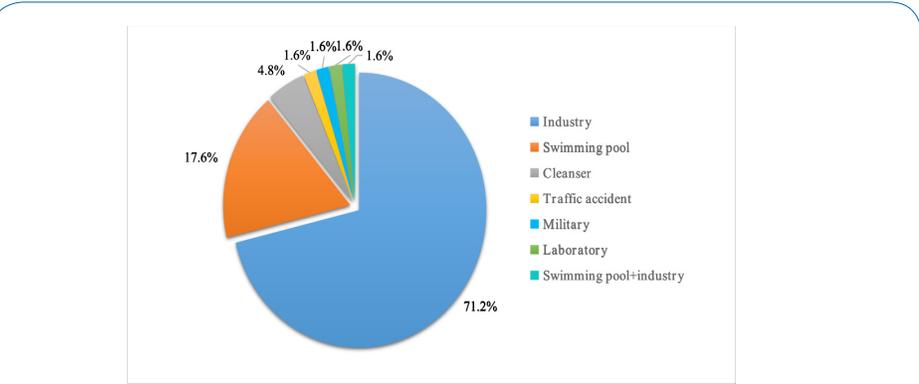


Figure 3: Statistics of the Types of Cl₂ Exposure Accidents from 1967 to 2022.

Table 1: Classification of Clinical Features after Cl₂ Poisoning.

Body Region	Symptoms
Ophthalmic	Photophobia, lacrimation, ophthalmalgia, blurred vision
Oropharynx	Pharyngeal congestion and swelling, burning sensation
Skin	Sweat, pale complexion, cyanosis
Upper respiratory tract	Vocal cord edema, hoarseness, tonsil swelling, Sore throat, dry throat, laryngospasm, sneeze
Lower respiratory tract	Cough, expectoration, dyspnea, shortness of breath, chest distress, chest pain, pulmonary atelectasis, acute lung edema, respiratory failure
Limbs	Difficult to walk, limb numbness, gait deformity
Central nervous system	Unconsciousness, sleepiness, coma, headache, dysphoria, slurred speech, tetany
Gastrointestinal tract	Nausea, vomit, epigastric pain, upper gastrointestinal bleeding
Cardiovascular system	Cardiogenic shock, sinus bradycardia, palpitation, arrhythmia, flustered, elevated blood pressure, atrial premature beats, heart arrest
Defecate and urinate	Gatism, hypourocrinia

Table 2: Laboratory Examination after Cl₂ Poisoning.

Laboratory examination	Results
Physical examination	Pulmonary moist rales and/or wheezes, rough breathing sounds in both lungs, bubbling sound, three depressions sign (+)
Blood examination	Leukocyte increase, blood sedimentation increase, blood Na +, Cl slightly elevated, hypokalemia, hyoxemia, hypercapnia
Renal function tests	Increased urea nitrogen, elevated serum creatinine, urine protein (+)
Liver function test	Aspartic acid aminotransferase, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and serum Y-glutamyl transpeptidase increased
ECG	ST segment depression, T wave inversion or low level, I-degree atrioventricular block, left ventricular high voltage
X-ray	The hilar shadow is enlarged and blurred, lung texture enhanced and disorder, lung field transparency decreases, scattered, a low density patch in the middle and upper fields of the two lungs

Table 3: Laboratory Examination after Cl₂ Poisoning.

Therapy	Scheme
Glucocorticoid	Dexamethasone, severe administration to methylprednisolone
Atomization inhalation	Alternate aerosol inhalation of 2-5% sodium bicarbonate solution with dexamethasone, gentamicin, aminophylline, a-chymotrypsin, distilled water, 0.25%-0.5% isoproterenol or 0.2% salbutamol or dexamethasone aerosol, each inhalation for half a minute to a few minutes
Laryngeal spraying	Isoproterenol and dexamethasone mixture, sodium bicarbonate
Severe cough	Codeine tablets (PO); promethazine or wintermin (IV)
Dyspnea	Aminophylline (IV)
Analgesia	Morphine
Sedation	Propofol combined with midazolam
Restlessness	Chloral hydrate
Nasal bleeding	Compress the nasal vestibule and instill 1%-2% ephedrine to constrict the mucosal blood vessels to stop bleeding
Vomiting	Vitamin B6 (IM)
Mucosal irritation	Locally given 2%-3% sodium bicarbonate repeatedly washing the congestion site, after washing the conjunctiva can drop hydrocortisone eye drops or antibiotic eye drops; cydiodine buccal tablets or Golden Throat Lozenges available in throat
Pulmonary edema	1% dimethicone aerosol
Ocular region	Rinse with water or normal saline; 5% cortisone eye drops, chloramphenicol eye drops; erythromycin eye ointment at night
Anti-infection	2nd and 3rd generation cephalosporins or quinolones
Myocardial protection Equipment	ATP, coenzyme A, inosine, FDP ECMO, ventilator

Discussion

Through the statistical analysis of the types of Cl₂ exposure accidents, this study found that most exposure accidents were related to civil industrial use, which accounted for as high as 71.2%. There have been two military-related accidents, the most recent of which was the Syrian armed conflict in 2014, in which 15 people were injured. The main symptoms were related to respiratory tract injury. At present, symptomatic treatment is still the mainstay. Interestingly, this study found that the frequency of Cl₂ exposure events was in a high-low cycle before 2015, but the accident rate has kept a lower level after 2015. This change could be related to the increasing emphasis on emergency management investment by countries around the world.

After a sudden Cl₂ expose, saving lives is of paramount importance. How to deliver treatment in a timely and effective manner is an ongoing concern in many countries, while still presenting challenges for medical staff.

It is known that the main symptoms of Cl₂ injury are manifested in the respiratory system. In this study, it was found that the main symptoms of the patients were mainly the upper and lower respiratory tract, such as dyspnea, acute pulmonary edema, respiratory failure and so on. During the study, a massive Cl₂ spill occurred on 23 March 2022 at the Aquatics Centre in London, UK, injuring 29 people, most of whom were taken to hospital for breathing difficulties. However, the mechanism of injury to the respiratory system remains unclear. This study need to continue to pay attention to the relevant literature at the forefront.

The majority of the Cl₂ exposure animal studies show that a series of inflammatory reactions occur in the body after Cl₂ inhalation. Blood tests results showed increased white blood cell count and erythrocyte sedimentation rate. X-ray showed reduced transparency of the lung fields and scattered patchy shadows in both lungs. The results of these tests showed that there was inflammatory response in the body. It has been reported that inflammatory factor storm may be the main pathological cause of pulmonary lesions such as pulmonary edema and respiratory distress after Cl₂ exposure. However, its specific molecular mechanism still needs to be further explored.

New solutions for Cl₂ poisoning treatment are constantly being sought, among which Yue et al. proposed a new scheme of combined treatment of traditional Chinese medicine and western medicine in the process of clinical treatment of 1539 cases of sudden mass Cl₂ poisoning [147]. On the basis of comprehensive treatment, the use of Fengnuo's combination with vitamin B6, short-course anisodamine combined with dexamethasone pulse therapy and the traditional Chinese medicine "Chaihuangshenquduguben" has good effects on severe patients with Cl₂ poisoning, but the mechanism remains unclear.

The research group had been conducting research on the mechanism and treatment of choking agent poisoning [175-167]. The team discovered PTX, a drug that improves microvascular circulation, which could reverse the Cl₂ induced ALI in rats through its anti-inflammatory and antioxidant effects [172]. In the early stage, our research group found that the oxidation damage reaction induced by Cl₂ was impro-

ved after PTX intervention through in vivo and in vitro experiments. For example, raise GSH, GSH/GSSG and CAT, and reduce MDA and GSSG. It shows that the mitochondrial function of Cl₂ damage could be repaired after PTX intervention. And the same effect had been verified in another choking agent phosgene induced lung injury.¹⁷⁵ Recently, PTX was also used for ALI caused by COVID-19 [176-177], and it was found to have a good therapeutic effect in some clinical observation. All of these once again verified the improvement effect of PTX on ALI. PTX may be a potential drug candidate for Cl₂ injury treatment.

Limitation

For literature inclusion, a scientific and comprehensive search and screening was carried out in this study. However, except for only a few randomized controlled trials, most of the literatures are case reports, and there may be some reporting bias.

Conclusion

In conclusion, this work systematically reviewed the Cl₂ poisoning accidents that occurred worldwide in the past 55 years, analyzed and summarized the events characteristics and current status of diagnosis and treatment, and reported valuable research results. The treatment of traditional Chinese medicine and PTX, a methylxanthine derivative, in the treatment of Cl₂ poisoning should be given more attention. It is hoped that the clinical application and laboratory research of drugs can provide help and reference for future research on Cl₂ poisoning treatment strategies.

Declarations

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Author contributions: CQZ and QF designed/performed most of the investigation, data analysis and wrote the manuscript. MML contributed to interpretation of the data and analyses. CXH and XDZ was responsible for review design and manuscript revision.

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