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Case Report:

Successful treatment of patients with paraquat intoxication: three case reports and review of the literature

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Abstract: Objective: To report on three patients with paraquat (PQ) intoxication surviving after combined therapy with hemoperfusion (HP), cyclophosphamide (CTX), and glucocorticoid. Methods: Three patients suffered acute renal failure in a few days after ingesting a lethal amount of PQ. Chest computed tomography (CT) scans revealed obvious pulmonary inflammation, pleural effusion, and fibrous lesions several days after ingestion. HP was performed immediately, followed by large doses of glucocorticoid (methylprednisolone, 500 g/d) and CTX (approximately 4 g). Results: After 50 d of treatments, all three patients were discharged in healthy condition, with chest CT showing small fibrous lesions, exudation, and both lungs clear of auscultation. Conclusions: The protective effect of the lungs may have been due to timely treatment at adequate doses.

Key words: Paraquat poisoning, Hemoperfusion, Glucocorticoid, Cyclophosphamide
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1 Introduction

Paraquat (PQ, 1,1′-dimethyl-4,4′-bipyridinium dichloride), which was synthesized as a redox indicator in 1882, has been widely used as a herbicide since 1962. In humans, ingestion of PQ is frequently fatal and is associated with a high mortality rate (Sabzghabaee *et al*., 2010). In general, an amount over 20 mg of PQ ion per kg body weight results in death, as a result of respiratory failure, pulmonary inflammation, and fibrosis (Vale *et al*., 1987; Xu *et al*., 2011). Shortly after ingesting large amounts of PQ, rapid development of multiple organ failure and cardiogenic shock occur, which usually result in death (Wilks *et al*., 2008). When smaller amounts are ingested, PQ accumulates in the lungs and produces large amounts of oxygen-free radicals, which lead to oxidative damage in the lungs, and may lead to death (Bismuth *et al*., 1996). To date, there is a lack of evidence for therapeutic measures including preventing absorption, increasing excretion, and the use of immunosuppressive therapies and antioxidant treatments. Early hemoperfusion (HP) is considered the first-line of treatment in patients with acute PQ intoxication (Kang *et al*., 2009). Lin J.L. *et al*. (2011) reported that repeated pulses of methylprednisolone and cyclophosphamide (CTX) may result in a lower mortality rate in patients with severe PQ poisoning. However, Gawarammana and Buckley (2011) reported that the case fatality is very high in all centers despite large variations in treatments containing HP, immunosuppression therapy, and antioxidants.

Here, we report on three individuals who ingested large amounts of PQ and survived after combined therapy with HP, CTX, and glucocorticoid.

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2 Case reports

2.1 Case 1

A 28-year-old man was present at a nearby hospital 1 h after ingesting about 40 ml PQ (20% solution) and alcohol. There, he received gastric lavage and symptomatic treatments. One day after the ingestion, he was transferred to the emergency room with complaints of short of breath, chest distress, and coughing up blood. Upon admission, physical examination revealed nothing abnormal except for pharyngeal congestion. Initial laboratory results were all within normal limits, except for slight leukocytosis (10.9×10^9 L^{-1}). The electrocardiogram was normal and chest computed tomography (CT) scans were clear (Fig. 1a). The PQ concentration in urine was detected semi-quantitatively by sodium dithionite coloring method. The result was strong positive.

HP was immediately carried out for 4 h, until the detection of urine PQ was negative. Subsequently, the patient received immuno suppressive therapy (methylprednisolone 500 g/d and CTX 0.6 g/d). Besides, antibiotics and antioxidants (vitamin C, vitamin E, ambroxol, glutathione, and *n*-acetylcysteine, etc.) were administered through venous channel.

Hemodialysis started immediately after serum creatinine (Cr) reached 321 μmol/L (reference range, 44–133 μmol/L) and blood urea nitrogen (BUN) reached 14.2 mmol/L (reference range, 2.0–7.14 mmol/L). The levels of Cr and BUN elevated gradually to 604 μmol/L and 27.9 mmol/L, respectively. HP was performed a total of six times following admission, while hemodialysis was continuously performed until serum Cr and BUN were back to normal.

On Day 3, the dose of CTX was reduced to 0.4 g/d, and the total dose used was approximately 4 g. Meanwhile, glucocorticoid was used as a long-term therapy with gradually reducing dosage. During the treatment, oxygen saturation dropped to 78%–88%, and arterial partial pressure of oxygen fluctuated between 36–43 mmHg. One week after admission, chest CT scans revealed multiple exudative changes in both lungs with bilateral pleural effusion (Fig. 1b). Two weeks after admission, chest CT showed significantly worse outcomes (Fig. 1c). The patient continuously received combined therapies of glucocorticoid, antioxidants, and antibiotics, and the exudative lesions were gradually absorbed (Fig. 1d).

After 50 d, the patient was discharged in a good condition, with chest CT scans showing small fibrous lesions and exudation (Fig. 1e), and both lungs clear to auscultation. About two months after discharge, chest CT scans showed continued improvement (Fig. 1f).

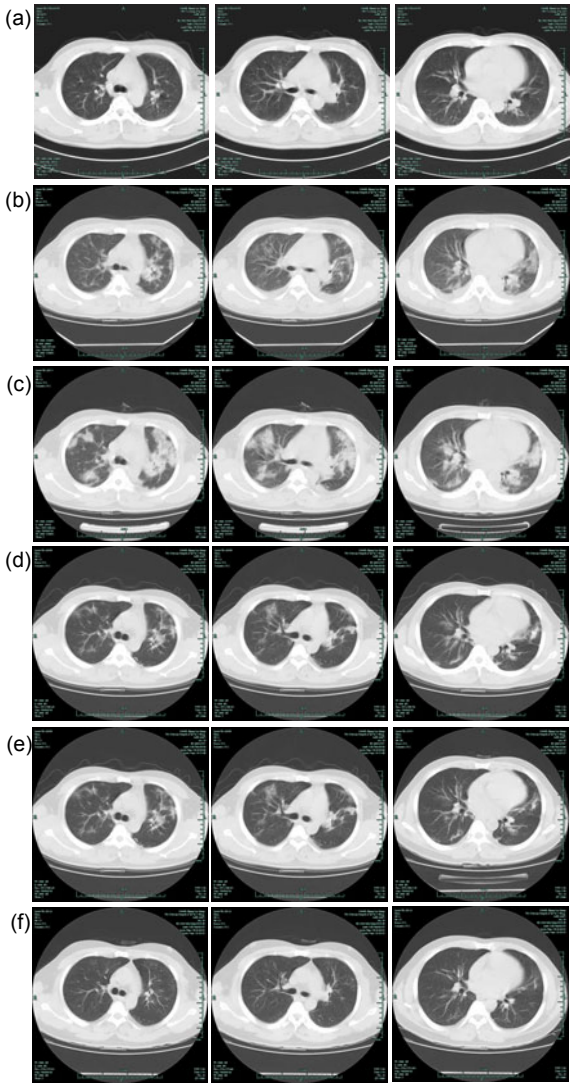

Fig. 1 Chest CT scans of Case 1

(a) Chest CT scans on admission showed nothing abnormal in the lungs. (b) Chest CT scans one week after admission. It revealed multiple irregular flakes, high-density shadows with obscure edges in the lungs, and a curved fluid region along the lateral thorax. (c) Chest CT scans about two weeks after admission. An increasing number of lesions can be observed. (d) Chest CT scans four weeks after admission. Both lungs had less multiple irregular flakes and high-density shadows after combined therapy. (e) Chest CT scans at discharge. It showed little irregular flakes and high-density shadows in the lungs. (f) Chest CT scans about two months after discharge. It showed continued improvement in the lungs

2.2 Case 2

A 44-year-old man ingested about 30 ml PQ (20% solution) as a suicide attempt and vomited a large amount of yellow-green frothy liquid. Thirty minutes later, he was treated with gastric lavage and symptomatic treatments at the local hospital. He was admitted to our emergency room 2 d later.

Upon admission, the patient reported nausea and vomiting, and denied any other symptoms. Upon physical examination, his skin was moderately stained yellow, both lungs were clear to auscultation, and no other abnormalities were found. Laboratory tests showed leukocytosis (about 19.4×10^9 L^{-1}) and a slight increase of serum Cr (227 μmol/L). The result of urine PQ detection was strongly positive. Chest CT scans revealed diffuse distribution of miliary nodules in both lungs (Fig. 2a).

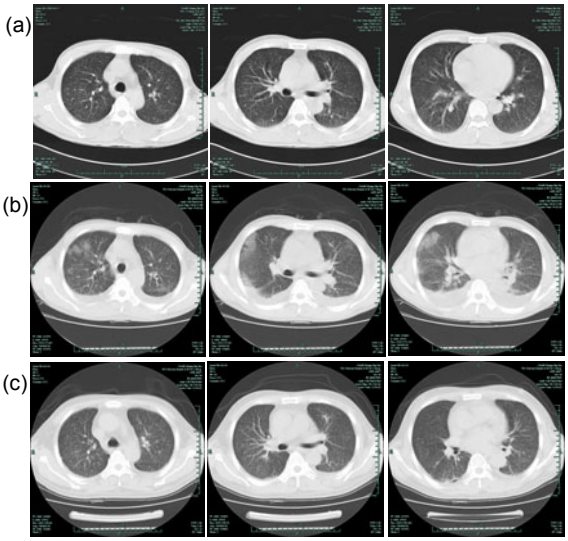

Fig. 2 Chest CT scans of Case 2

(a) Chest CT scans on admission. It revealed diffuse distribution of miliary nodules in both lungs. (b) Chest CT scans one week after admission. Both lungs showed scattered flocculent pieces and ground glass shadow with indistinct edges. The lung markings showed coarse texture, spotty, grid-like changes, and revealed an arc-like low-density fluid area together with the adjacent collapsed lung tissue. (c) Chest CT scans at discharge. It showed only slightly diffused distribution of miliary nodules and patchy high density in both lungs

After admission, the patient was given therapy similar to Case 1. During hospitalization, he experienced abdominal pain, angina, and shortness of breath, together with an oxygen saturation of about 82%–90%. Chest CT revealed interstitial inflammatory changes of both lungs and bilateral pleural effusion (Fig. 2b). Subsequently, despite an episode of pulmonary aspergillosis, he fully recovered after timely treatment with voriconazole. When he was discharged after 55 d of treatments, His serum Cr returned to normal, and chest CT scans revealed only modest radiological changes in both lungs (Fig. 2c).

2.3 Case 3

A 27-year-old woman was sent to a local hospital after ingesting 30 ml of herbicide. According to her relatives, she had ingested glyphosate, and was therefore treated with gastric lavage, atropine, and fluid administration. The patient was given oxygen before it was clear that the herbicide was PQ. During the treatment, she experienced nausea and vomiting.

The patient was sent to our emergency room 2 d after PQ poisoning. Physical examination revealed that the skin around her lips was ulcerated and her oral mucosa and tongue were festered; however, both lungs were clear to auscultation. Laboratory tests showed leukocytosis (about 17.8×10^9 L^{-1}) and a slight rise of serum Cr (177 μmol/L). The result of urine PQ detection was strongly positive. Chest CT scans showed nothing abnormal in the lungs (Fig. 3a).

Upon admission, the patient was immediately treated with HP, followed by large doses of glucocorticoid, CTX, and several kinds of antioxidants. Two days later, her serum Cr level increased to 435 μmol/L. From that day on, hemodialysis was given together with HP. About one week later, chest CT revealed patchy, cord-like, nodular density shadows in both lungs, and bilateral pleural effusion (Fig. 3b). Ten days later, she complained of shortness of breath, coughing, expectoration, and hemoptysis. Three weeks later, her oxygen saturation was 76%–80%, and her chest CT scans showed interstitial pneumonia in both lungs, small bilateral pleural effusion, and an increasing number of lesions compared with the previous scans (Fig. 3c). When she was discharged after 58 d of treatments, both lungs were clear to auscultation and a chest CT revealed only slight lesions in both lungs (Fig. 3d).

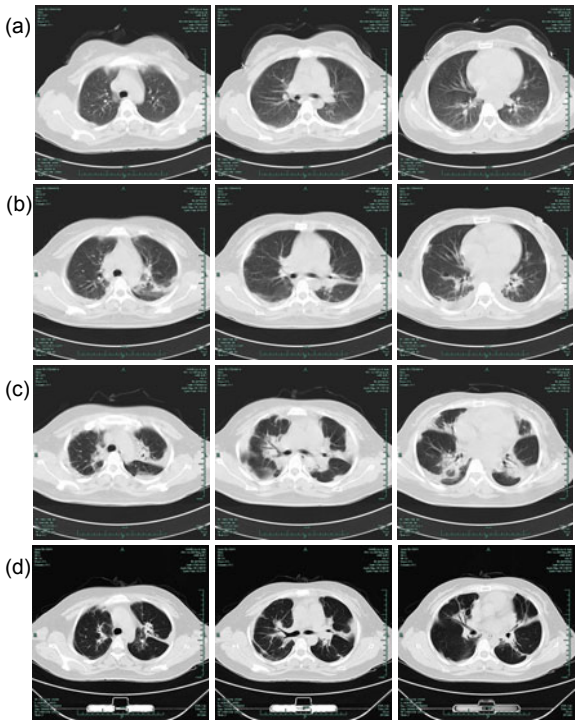

Fig. 3 Chest CT scans of Case 3

(a) Chest CT scans on admission. It showed nothing abnormal in the lungs. (b) Chest CT scans one week after admission. It revealed patchy, cord-like, nodular density shadows in both lungs and an arc-like low-density fluid area in the lateral thorax. (c) Chest CT scans three weeks after admission. Compared with (b), the exudative lesions increased. (d) Chest CT scans at discharge. It showed only slight lesions in the lungs

3 Discussion

PQ is a nonselective contact herbicide of great toxicological importance. The in-hospital fatality rate of PQ poisoning is approximately 55%, with no significant differences between survivors and non-survivors with respect to the patient characteristics (Sabzghabaee *et al*., 2010). As Vale *et al*. (1987) reported, three degrees of PQ intoxication have been differentiated: (1) mild poisoning (occurs after ingesting <20 mg of PQ ion per kg body weight), which usually results in full recovery; (2) moderate-to-severe poisoning (20–40 mg of PQ ion per kg body weight), which is fatal in the majority of cases 2–3 weeks after ingestion; and (3) acute fulminant poisoning (>40 mg of PQ ion per kg body weight), which is fatal in the majority of cases within hours to days of ingestion. In this case series all three patients ingested >20 ml of 20% PQ, and according to the classification above, they would be classified as having acute fulminant poisoning, and should have died within a few days after ingesting. However, despite serious complications, including acute renal failure, infection, pulmonary infiltration, and pleural effusion, they all survived.

After being ingested, PQ is rapidly distributed to organs and tissues, particularly the lungs (Dinis-Oliveira *et al*., 2009). The lung PQ concentration is more than 10 times higher than that in the plasma. It has been suggested that the mechanism is primarily related to oxidative damage, reactive oxygen species, immune activation, inflammatory mediators, etc. (Dinis-Oliveira *et al*., 2009; Sabzghabaee *et al*., 2010; Huang *et al*., 2011). At present, oxygen is not a part of treatment, because too much oxygen can rapidly promote pulmonary changes through oxidation. In Case 3, the patient was misdiagnosed as having glyphosate poisoning and given oxygen during the early treatment, but in the end she survived with slight lesions in both lungs.

PQ is excreted primarily by kidneys, and therefore, HP has often been indicated as an appropriate step for treatment (Suh *et al*., 2008; Kang *et al*., 2009; Lu *et al*., 2011) and is considered 4–6 times more effective than hemodialysis (Hong *et al*., 2003). Additionally, it is believed that HP should be started as early as possible after PQ poisoning, and should be continued for >10 h (Suh *et al*., 2008). It is difficult, however, to completely remove PQ through HP, since patients often swallow several times the lethal dose, and by the time HP is administered the PQ has already spread to lung tissue and other vital organs, and only a small amount of PQ is remained in the blood circulation. Blood purification can significantly decrease the levels of inflammatory cytokines and oxygen free radicals, and improve the physiological environment. Every time, HP is continued about 4 h until the result of urine PQ detection is negative.

Currently, many experts point out that therapy combining glucocorticoid and CTX should be effective to treat PQ poisoning (Lin N.C. *et al*., 2003; Afzali and Gholyaf, 2008; Li *et al*., 2010; Ghaffari *et al*., 2011). Activation of mononuclear macrophages and granular leukocytes causes acute lung injury and

pulmonary fibrosis (Yoon, 2009). By stabilizing cell membranes and fighting against lipid peroxidation and non-specific immune suppression, glucocorticoid reduces leukocytes gathering in the damaged area, decreases collagen activity and improves respiratory function (Zerin *et al*., 2012). CTX also plays an important role in the cellular and humoral immune response, and reduces the severity of inflammation (Afzali and Gholyaf, 2008). In a word, therapy combining glucocorticoid and CTX for PQ poisoning can reduce the severity of inflammation, decrease the number of leukocytes to slow the process of pulmonary fibrosis, and reduce mortality in patients with moderate-to-severe PQ poisoning (Addo *et al*., 1984; Lin J.L. *et al*., 1996; Agarwal *et al*., 2007). However, limited evidence exists regarding the appropriate therapeutic dose and duration of treatment. We believe that early large-dose glucocorticoid therapy can produce its best effect, and a combination with a total dose of 4 g CTX may be more effective in treating patients with severe PQ poisoning. Additionally, in order to ensure the immunosuppressive effect, we suggest increasing the dose and administering these drugs after HP.

Moreover, it has been reported that antioxidants can prevent the progress of pulmonary fibrosis (Suntres, 2002; Jo *et al*., 2008). The commonly used drugs include vitamin C, vitamin E, ambroxol, glutathione, and *n*-acetylcysteine (Moon and Chun, 2011). In spite of numerous studies attempting to reduce the oxygen free radical injury induced by the antioxidants, these therapies have shown few survival benefits and are unable to reduce mortality rate (Suntres, 2002; Lee *et al*., 2008; Yang *et al*., 2009).

In most cases, since patients were sent to our hospital over 6 h after PQ ingestion, the PQ had already spread to various tissues and organs, resulting in a very low concentration of PQ in the blood. In these cases, the degree of PQ poisoning is identified via the assessment of dosage ingested and clinical features presented. In our study, all three cases developed acute renal failure within a few days, and their chest CTs showed similar changes (pulmonary infiltration, pleural effusion, and pulmonary fibrosis). They were all treated by similar compound methods and survived. Our treatment strategies included performing HP six times, together with hemodialysis to cure acute renal failure; early large-dose glucocorticoid therapy, combining with an adequate dose of CTX (about 4 g of total dose); givening several kinds of antioxidants and symptomatic treatments.

So far, we have treated 23 cases using the same treatment regimen (HP as early as possible, large doses of CTX and glucocorticoid), and 14 cases survived. Due to the small number of cases, our study lacked large-scale validation and had some limitations. Randomized controlled trials with large sample sizes are still required in order to determine the true efficacy of the proposed treatments for PQ poisoning.

References

Addo, E., Ramdial, S., Poon-King, T., 1984. High dosage cyclophosphamide and dexamethasone treatment of paraquat poisoning with 75% survival. *West Indian Med. J.*, **33**(4):220-226.

Afzali, S., Gholyaf, M., 2008. The effectiveness of combined treatment with methylprednisolone and cyclophosphamide in oral paraquat poisoning. *Arch. Iran Med.*, **11**(4):387-391.

Agarwal, R., Srinivas, R., Aggarwal, A.N., Gupta, D., 2007. Immunosuppressive therapy in lung injury due to paraquat poisoning: a meta-analysis. *Singapore Med. J.*, **48**(11):1000-1005.

Bismuth, C., Hall, A.H., Baud, F.J., Borron, S., 1996. Pulmonary dysfunction in survivors of acute paraquat poisoning. *Vet. Hum. Toxicol.*, **38**(3):220-222.

Dinis-Oliveira, R.J., de Pinho, P.G., Santos, L., Teixeira, H., Magalhaes, T., Santos, A., de Lourdes Bastos, M., Remiao, F., Duarte, J.A., Carvalho, F., 2009. Postmortem analyses unveil the poor efficacy of decontamination, anti-inflammatory and immunosuppressive therapies in paraquat human intoxications. *PloS One*, **4**(9):e7149. [doi:10.1371/journal.pone.0007149]

Gawarammana, I.B., Buckley, N.A., 2011. Medical management of paraquat ingestion. *Br. J. Clin. Pharmacol.*, **72**(5):745-757. [doi:10.1111/j.1365-2125.2011.04026.x]

Ghaffari, A.R., Noshad, H., Ostadi, A., Hasanzadeh, N., 2011. Effect of pulse therapy with glucocorticoid and cyclophosphamide in lung fibrosis due to paraquat poisoning in rats. *Saudi Med. J.*, **32**(3):249-253.

Hong, S.Y., Yang, J.O., Lee, E.Y., Kim, S.H., 2003. Effect of haemoperfusion on plasma paraquat concentration in vitro and in vivo. *Toxicol. Ind. Health*, **19**(1):17-23. [doi:10.1191/0748233703th171oa]

Huang, W.D., Wang, J.Z., Lu, Y.Q., DI, Y.M., Jiang, J.K., Zhang, Q., 2011. Lysine acetylsalicylate ameliorates lung injury in rats acutely exposed to paraquat. *Chin. Med. J.*, **124**(16):2496-2501. [doi:10.3760/cma.j.issn.0366-6999.2011.16.018]

Jo, Y.H., Kwon, W.Y., Lee, J.H., Kim, K., Shin, S.D., Kang, Y.J., Suh, G.J., 2008. The effect of ethyl pyruvate on

dapsone-induced methemoglobinemia in rats. *Clin. Toxicol.*, **46**(9):811-814. [doi:10.1080/15563650802304419]

Kang, M.S., Gil, H.W., Yang, J.O., Lee, E.Y., Hong, S.Y., 2009. Comparison between kidney and hemoperfusion for paraquat elimination. *J. Korean Med. Sci.*, **24**(Suppl.): S156-S160. [doi:10.3346/jkms.2009.24.S1.S156]

Lee, J., Kwon, W., Jo, Y., Suh, G., Youn, Y., 2008. Protective effects of ethyl pyruvate treatment on paraquat-intoxicated rats. *Hum. Exp. Toxicol.*, **27**(1):49-54. [doi:10.1177/0960327108088976]

Li, L.R., Sydenham, E., Chaudhary, B., You, C., 2010. Glucocorticoid with cyclophosphamide for paraquat-induced lung fibrosis. *Cochrane Database Syst. Rev.*, (4): CD008084. [doi:10.1002/14651858.CD008084]

Lin, J.L., Wei, M.C., Liu, Y.C., 1996. Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. *Thorax*, **51**(7):661-663. [doi:10.1136/thx.51.7.661]

Lin, J.L., Lin-Tan, D.T., Chen, K.H., Huang, W.H., Hsu, C.W., Hsu, H.H., Yen, T.H., 2011. Improved survival in severe paraquat poisoning with repeated pulse therapy of cyclophosphamide and steroids. *Intensive Care Med.*, **37**(6):1006-1013. [doi:10.1007/s00134-010-2127-7]

Lin, N.C., Lin, J.L., Lin-Tan, D.T., Yu, C.C., 2003. Combined initial cyclophosphamide with repeated methylprednisolone pulse therapy for severe paraquat poisoning from dermal exposure. *J. Toxicol. Clin. Toxicol.*, **41**(6): 877-881. [doi:10.1081/CLT-120025356]

Lu, Y.Q., Jiang, J.K., Huang, W.D., 2011. Clinical features and treatment in patients with acute 2,4-dinitrophenol poisoning. *J. Zhejiang Univ.-Sci. B (Biomed. & Biotechnol.)*, **12**(3):189-192. [doi:10.1631/jzus.B1000265]

Moon, J.M., Chun, B.J., 2011. The efficacy of high doses of vitamin C in patients with paraquat poisoning. *Hum. Exp. Toxicol.*, **30**(8):844-850. [doi:10.1177/0960327110385633]

Sabzghabaee, A.M., Eizadi-Mood, N., Montazeri, K., Yaraghi, A., Golabi, M., 2010. Fatality in paraquat poisoning. *Singapore Med. J.*, **51**(6):496-500.

Suh, G.J., Lee, C.C., Jo, I.J., Shin, S.D., Lee, J.C., Min, B.G., Singer, A.J., 2008. Hemoperfusion using dual pulsatile pump in paraquat poisoning. *Am. J. Emerg. Med.*, **26**(6): 641-648. [doi:10.1016/j.ajem.2007.09.022]

Suntres, Z.E., 2002. Role of antioxidants in paraquat toxicity. *Toxicology*, **180**(1):65-77. [doi:10.1016/S0300-483X(02)00382-7]

Vale, J.A., Meredith, T.J., Buckley, B.M., 1987. Paraquat poisoning: clinical features and immediate general management. *Hum. Exp. Toxicol.*, **6**(1):41-47. [doi:10.1177/096032718700600107]

Wilks, M.F., Fernando, R., Ariyananda, P.L., Eddleston, M., Berry, D.J., Tomenson, J.A., Buckley, N.A., Jayamanne, S., Gunnell, D., Dawson, A., 2008. Improvement in survival after paraquat ingestion following introduction of a new formulation in Sri Lanka. *PloS Med.*, **5**(2):e49. [doi:10.1371/journal.pmed.0050049]

Xu, X.L., Wang, W., Song, Z.J., Ding, H., Duan, X.H., Meng, H.C., Chong, J., 2011. Imaging in detecting sites of pulmonary fibrosis induced by paraquat. *World J. Emerg. Med.*, **2**(1):45-49. [doi:10.5847/wjem.j.1920-8642.2011.01.008]

Yang, J.O., Gil, H.W., Kang, M.S., Lee, E.Y., Hong, S.Y., 2009. Serum total antioxidant statuses of survivors and nonsurvivors after acute paraquat poisoning. *Clin. Toxicol.*, **47**(3):226-229. [doi:10.1080/15563650802269901]

Yoon, S.C., 2009. Clinical outcome of paraquat poisoning. *Korean J. Intern. Med.*, **24**(2):93-94. [doi:10.3904/kjim.2009.24.2.93]

Zerin, T., Kim, Y.S., Hong, S.Y., Song, H.Y., 2012. Protective effect of methylprednisolone on paraquat-induced A549 cell cytotoxicity via induction of efflux transporter, P-glycoprotein expression. *Toxicol. Lett.*, **208**(2):101-107. [doi:10.1016/j.toxlet.2011.10.019]