

## Perspective in future pharmacological approach to sulfur mustard lung injuries

Sir,

Treatment of sulfur mustard (SM) injured patient with pulmonary involvement remains as a challenging issue and almost all of used medications, such as corticosteroid, are conservative treatments. Also, we would like to recommend some medications which it theoretically can be effective on patients with SM lung injuries.

At the beginning, we should know what do we expect from medications to do in patients with SM lung injury? The most common findings in these patients were dyspnea and chronic cough with thick sputum, which is concordant with a disorder in small airway such as bronchiolitis obliterans (BO).<sup>[1]</sup> BO is significantly associated with two pathogenesis; oxidant-antioxidant imbalance and chronic inflammation, although other pathogenesis such as protease dysfunction was weekly recommended for these patients.<sup>[2]</sup> Also, it seems that chronic inflammation in these patients relief when the antioxidants supply is enhanced.<sup>[3]</sup> Previously, it was approved that N-Acetyl Cysteine (NAC) increase the main anti-oxidant product of lung named glutathione (GSH) in these patients.<sup>[4]</sup> Hence, every therapeutic agent that can enhance cellular anti-oxidant supply may be effective on both of mentioned pathway.

Hypertonic saline (HTS), a hyperosmolar sodium chloride solution, which was used for bronchiolitis, especially in children septic shock and sputum induction, was introduced.<sup>[5]</sup> One of the main problems that annoy the SM induced lung injury is dense sputum which is composed of apoptotic cell, thick mucus and various cell products in small airways. Also, nebulization with HTS can dilute this sputum via regulating sodium transport in airways membrane.<sup>[6]</sup> HTS frequently were used for this propose in similar disorders such as cystic fibrosis.<sup>[7]</sup> Sodium-chloride solution, even in normal osmolarity (0.5%), has an approved effect on respiratory symptoms.<sup>[8]</sup> Inhalation of HTS improves ciliary function of epithelial cell in which can be useful in these patients.<sup>[9]</sup> In addition, the anti inflammatory effect of HTS was demonstrated.<sup>[10]</sup> This effect is consonant with the role of glycosaminoglycans and IL-8 in neutrophil chemotaxis and inflammation. In

addition, cell membrane potential imbalance due to protein misfolding was recommended as the other pathogenesis of SM injury.<sup>[2]</sup> Nebulization of HTS 5% was safely used <sup>[11]</sup> and can be superior to current therapy for early treatment of SM injured patient with bronchiolitis obliterans.

Also, the efficacy of curcumin on the apoptotic pathway (such as JNK and NF-KB) was declared. Curcumin is a derivate of turmeric (*Curcuma Longa*) a famous Indian herbal medication. It was confirmed that curcumin is effective on inflammation (such as rheumatoid arthritis), antioxidant supply and neoplastic disorders.<sup>[12,13]</sup> Likewise, it was clarified that defect in cell repair was introduced as the main cellular mechanism, which justified the SM injury pathogenesis.<sup>[2]</sup> At the same, Li *et al.* demonstrated that curcumin can affect the TGF-beta/smads signaling pathway in which seriously considered in SM injured patients.<sup>[14,15]</sup> Also, curcumin can modulate some inter-cellular signals such as MMP and VEGF, which have considerable role in these patients.<sup>[16]</sup> Fibroblasts via overproduction of collagen and impaired inter-cellular adhering molecule (such as laminin and cathepsin) <sup>[2,17]</sup> has the main role in SM pathogenesis and likely, curcumin can regulate these cells as well.<sup>[18]</sup> Recently, curcumin was effectively used for late skin lesion of SM.<sup>[19]</sup> Moreover, it seems that it can be effective on SM induced lung disease because there is some evidence that is confirmed the efficacy of curcumin on airway epithelial cell injured by toxic agents.<sup>[20]</sup>

Although, TGF-beta regulating medication such as gamma interferon was effectively used in these patients and other anti-inflammatory treatment such as anti cytokines and TNF-alpha antagonist theoretically may be effective but we need medications which impress the main pathogenesis pathway.<sup>[21]</sup>

Another therapeutic option such as vitamin E and proanthocyanidin was sporadically used on patients with SM injury but more study is needed to approve their results.<sup>[22,23]</sup> On the other hand, using other ways to administrate routine medications e.g. corticosteroids such as chest patch and inhaled spray as nano-particle or micelle (such as chitosan) can be more effective than oral prescription on clinical symptoms, in addition to lower side effects.

Finally, it is necessary to find the main etiology of the mustard lung (regarding to the role of TGF- $\beta$  increases and oxidant-antioxidant imbalances) to find the completely effective treatment for these patients.

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