



Review

Wasp venom and acute kidney injury: The mechanisms and therapeutic role of renal replacement therapy



Jianhua Gong¹, Hai Yuan¹, Zhao Gao, Fengqi Hu*

Department of Nephrology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, 441000, Hubei, China

ARTICLE INFO

Keywords:

Wasp stings

Venom

Acute kidney injury

Renal replacement therapy

ABSTRACT

Stinging accidents involving wasp venom are a notable cause of acute kidney injury (AKI) in Asia. However, very little attention has been paid to the understanding of the mechanisms involved in this type of AKI. The aims of this review are to explore the evidence for the mechanisms and the therapeutic role of renal replacement therapy of wasp venom and AKI. A systematic literature search was conducted using PubMed for the association among wasp venom and AKI. Wasp venom is a complex mixture of biologically active components, including enzymes, amines, and peptides. Wasp venom may induce local anaphylaxis reactions as well as systemic reactions such as AKI. AKI may develop as a result of direct nephrotoxic effects of the venom or secondary intravascular hemolysis and/or rhabdomyolysis. Histopathological features of renal biopsies predominantly include acute tubular necrosis and acute interstitial nephritis. Renal replacement therapy, which includes intermittent hemodialysis, hemoperfusion, plasmapheresis, continuous renal replacement therapy, and peritoneal dialysis, has been used to treat severe AKI cases induced by wasp stings. Continuous renal replacement therapy appears to provide more benefit than intermittent hemodialysis in the treatment of wasp sting-induced AKI. In this review, we summarize the existing evidence of the mechanisms and treatment for venom-induced AKI, with a particular emphasis on the role of renal replacement therapy in the management of severe AKI following massive wasp stings.

1. Introduction

Insect stings and bites are known to cause a variety of allergic reactions and direct toxic effects. Stinging insects are classified into orders, including Hymenoptera, Diptera, Coleoptera, Lepidoptera (Walker et al., 2018). The order Hymenoptera includes Apoidea (bees), Vespoidea (wasps, yellow jackets & hornets), Formicoidea (ants) and sawflies (Casale and Burks, 2014; Walker et al., 2018). Venom from Vespoidea and Apoidea have different characteristics. For instance, previous studies have reported that melittin and apamin were only found in venom from Apoidea (Moreno and Giral, 2015; Silva et al., 2017; Zhang et al., 2013). However, in a recent study, melittin was identified as a member of a highly diverse superfamily of peptides that are found ubiquitously in hymenopteran venoms (Robinson et al., 2018).

Acute kidney injury (AKI) is one of the unusual complications that is associated with Hymenoptera stings (Dongol et al., 2013; Li et al., 2015). However, stinging accidents with wasp venom are a notable cause of AKI in Asia, especially in regions of Southern China, South Asia, and Southeast Asia (India, Vietnam, Thailand, Malaysia, and

Nepal) (Vikrant and Parashar, 2017c; Yang, 2016). A few successive stings normally only cause a local allergic reaction. However, in some reports, even a single wasp sting has been reported to cause AKI and multiple organ dysfunction syndrome (MODS) (Kumar et al., 2013; Sharmila et al., 2007). Massive wasp stings may cause severe systemic symptoms, affecting multiple organs, with a high mortality rate. In 1972, Sitprija et al. first reported the occurrence of AKI following wasp stings (Sitprija and Boonpucknavig, 1972). Since this seminal study, wasp sting-induced AKI and MODS have occasionally been reported. The study with the largest sample size was performed in China, in which AKI was observed in 21% of 1091 hospitalized wasp sting patients (Xie et al., 2013). Xie et al. further reported that the overall incidence of AKI was higher in patients with multiple stings than in those with fewer stings (Xie et al., 2013). The incidence of AKI after wasp stings was found to be approximately 20%–50%, depending on the number of wasp stings and other factors, such as age (Xie et al., 2013).

The diagnosis of wasp stings is determined according to the clinical history as well as findings based on physical examinations. AKI may develop as a result of direct nephrotoxic effects of the venom or

* Corresponding author.

E-mail address: hufengqi1@gmail.com (F. Hu).

¹ These authors contributed equally to this work.

secondary hemolysis and/or rhabdomyolysis. Thus, typical histological manifestations include acute tubular necrosis (ATN) and/or acute interstitial nephritis (AIN), with symptoms of oliguria (Nandi and Sarkar, 2012; Xie et al., 2013; Yuan et al., 2016; Zhang et al., 2013). The majority of patients with AKI induced by wasp stings require renal replacement therapy (RRT). Early diagnosis and management, including the removal of the stingers, antianaphylactic treatment, proper hydration, and intensive RRT in the case of rapidly progressive renal failure and anuria, can reduce morbidity and mortality in these cases (Yang, 2016; Zhang et al., 2013). Recovery of kidney function can be achieved in a considerable proportion of patients following sufficient treatment (Zhang et al., 2013). However, the mortality rates remain high, ranging from 5.6 to 50.0% (Vikrant and Parashar, 2017a). The common causes of death in these cases are acute pulmonary edema, anaphylactic or non-anaphylactic shock, MODS, and massive bleeding (Si et al., 2015; Vikrant and Parashar, 2017a). In addition to AKI, wasp stings have also been reported to cause nephrotic syndrome (Tauk et al., 1999). In two separate studies, researchers found that wasp stings could cause type 1 renal tubular acidosis (Agarwal et al., 2005; D'Cruz et al., 2008). Since a renal biopsy was not performed in either of these cases, the exact pathogenesis was difficult to define and the mechanism was not clear. Given that both cases of type 1 renal tubular acidosis were observed in the same geographical area (Indian), it is possible that wasp venoms in this region may contain special toxins that precipitate renal tubular acidosis. It has been postulated that these special toxins might inhibit sodium-hydrogen ion exchange (NHE3) in the proximal tubule or inhibit NaHCO_3 cotransport.

The majority of reports on AKI associated with wasp stings have been presented as case reports or relatively small retrospective case series, with the majority of patients coming from rural areas. Wasp sting-induced injuries, especially AKI, have occurred more frequently in recent years, and have become an increasingly serious public health problem that has received little attention (Vikrant and Parashar, 2017c; Xie et al., 2013). This review will provide a comprehensive overview of the current understanding on the mechanisms of wasp venom-induced AKI, as well as RRT for such patients.

2. Wasp venom components

Wasp venom is a complex mixture of biologically active components, including enzymes, such as phospholipase A (PLA) and hyaluronidase, amines, such as histamine, serotonin and catecholamines, peptides, such as mastoparans and wasp kinin, and other components, such as acetylcholine and antigen 5 (Dhanapriya et al., 2016; Dongol et al., 2013; Habermann, 1972; Silva et al., 2017; Sookrung et al., 2014; Thiruvethiran et al., 1999). Recently, the molecular composition and structural characteristics of wasp venoms have been elucidated in detail (Dos Santos-Pinto et al., 2018). In this review, more insights into molecular composition and functions of wasp venoms are revealed.

2.1. Venom-induced anaphylaxis reactions

The major allergens in venom are PLA, hyaluronidase, and antigen 5. These allergens are commonly able to trigger IgE-mediated type I hypersensitivity reactions. The toxic effect of a sting manifests as an area of redness, swelling, and hotness, and is often accompanied by skin pain. A mild response is generally observed as a reaction of less than 10 cm in diameter and shows marked improvement within 24 h of the sting. A severe reaction, however, can exceed 10 cm in diameter on the skin, and may persist for several days or progress to mild systemic symptoms (Przybilla and Rueff, 2012). Fatal stings usually occur in the head or neck, with the main causes of death being airway obstruction, laryngeal edema, and anaphylactic shock due to anaphylaxis (Przybilla and Rueff, 2012; Zhang et al., 2013).

2.2. Venom-induced systemic reactions

Large wasp stings usually cause severe toxic reactions, rather than simple anaphylaxis reactions. The systemic and toxic effects of wasp venom are attributed to certain enzymes that have hemolytic, myotoxic, neurotoxic, vasodilatory, nephrotoxic, and/or hepatotoxic actions. These components are detrimental to the body, and induce systemic disorders including shock, rhabdomyolysis, intravascular hemolysis, coagulopathy, respiratory distress, disseminated intravascular coagulation, cardiovascular abnormalities, hepatic damage, and AKI (Vikrant and Parashar, 2017c). The mechanisms that underlie venom-induced disorders include the direct nephrotoxicity of the venom and/or the immune and inflammatory response to the venom. The active components of wasp venom are found to induce the release of inflammatory mediators, such as tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8 (Xie et al., 2013; Yuan et al., 2016). Although severe or even fatal cases are commonly seen in patients with multiple stings, some reports have also reported worse outcomes following a single or low number of wasp stings (Kumar et al., 2013; Sharmila et al., 2007). Further studies have found that the severity of wasp sting-induced symptoms appears to be associated with the number of stings, and patients with massive stings are more likely to develop AKI, hepatic damage and coagulation disorders (Xie et al., 2013).

The functions of the different wasp venom components are described in detail below.

2.2.1. PLA

PLAs (PLA1 or PLA2) are 10–34 kDa proteins that are regarded to be the allergens primarily responsible for IgE-mediated allergic reactions. PLA1 is believed to be able to disrupt the phospholipids of biological membranes, causing the formation of membrane pores that leads to cell lysis and hemolysis (Moreno and Giral, 2015; Rungsa et al., 2018). PLA2 is a calcium-dependent enzyme, which can disrupt the cell membrane by attacking structural phospholipids. PLA2 in wasp venom exerts toxic actions on skeletal muscle and red blood cell membranes, resulting in hemolysis and rhabdomyolysis (Dongol et al., 2013; Moreno and Giral, 2015).

2.2.2. Histamine and serotonin

Histamine and serotonin in wasp venom are known to increase vascular permeability and enhance cytolytic activity. These components are primarily responsible for pain and edema (Mortari et al., 2012).

2.2.3. Wasp kinin

In addition to being structurally and chemically similar to bradykinin, wasp kinin also functions similarly to bradykinin to produce pain and increase vascular permeability. It also causes weak mast cell degranulation and the formation of edema (Konno et al., 2016).

2.2.4. Hyaluronidase

Hyaluronidase is a 45 kDa glycosylated enzyme that hydrolyses hyaluronic acid, which is one of the primary components ubiquitously distributed in the extracellular matrix of vertebrates. Hyaluronidase acts as a “spreading factor” by breaking the viscous polymer hyaluronic acid into non-viscous fragments. Hyaluronidase may facilitate the diffusion of venom toxins via the degradation of the extracellular matrix (Rungsa et al., 2018).

2.2.5. Antigen 5

Antigen 5 from wasp venom is a non-glycosylated protein with a molecular weight of approximately 23 kDa. It has been identified as an allergen that strongly induces an acute hypersensitivity response after stinging events (Bazon et al., 2017; Henriksen et al., 2001).

2.2.6. Mastoparan

Mastoparan is a membrane-active amphipathic peptide that contains 14 amino acid residues. The biological actions of mastoparan include insertion into the membrane bilayer causing membrane destabilization and consequent lysis, or direct interaction with G proteins on the cytoplasmic face, thus perturbing transmembrane signaling, stimulation of phospholipases, mobilization of Ca^{2+} from mitochondria and the sarcoplasmic reticulum, and cell death by necrosis and/or apoptosis (Moreno and Giralt, 2015). Mastoparan also has effects on ion channels and ion transport. Previous studies have found that mastoparan can stimulate insulin secretion in pancreatic cells via the inhibition of ATP dependent K^{+} channels and the enhancement of the Ca^{2+} concentration (Daniel et al., 2002; Eddlestone et al., 1995). In Madin-Darby canine kidney epithelial cells, mastoparan activates apical membrane chloride and potassium conductances, decreases cell volume and increases the permeability of kidney epithelial cell monolayers (Winter et al., 1992).

3. Pathophysiology of AKI induced by wasp stings (Fig. 1)

Only a small number of patients with wasp sting-induced AKI undergo renal biopsy. The histopathological features of the renal biopsy predominantly include acute tubular necrosis (ATN), as well as occasional acute interstitial nephritis (AIN) or acute cortical necrosis (ACN) (Table 1). It has also been shown, through biopsy findings, that wasp sting-induced ATN typically manifests as tubular necrosis and acute tubular injury, with or without pigment casts. AIN following a wasp sting is characterized by normal glomeruli, peritubular eosinophilic and mononuclear cell infiltration, with hyaline and pigmented granular casts in the tubules (Sharma et al., 2006).

Currently, the pathophysiological mechanisms underlying wasp

sting-induced kidney injury remain unclear. AKI may develop following a wasp sting as a result of the direct nephrotoxic effects of the venom, secondary to intravascular hemolysis/rhabdomyolysis, or through a hypersensitivity reaction to the venom.

3.1. Direct nephrotoxic effects of the venom

Recent studies have shown that the tubular cell membrane is a primary site of damage in AKI (Agarwal et al., 2016). PLA1, PLA2 and mastoparan can disrupt the integrity of renal tubular cell membrane, resulting in the extrusion of intracellular components. In the cells undergoing apoptosis, there is translocation of phospholipids from the inner to the outer membrane leaflet, followed by membrane blebbing (Agarwal et al., 2016).

3.2. Secondary to intravascular hemolysis and/or rhabdomyolysis

Studies have shown that wasp venom has hemolytic activities and myotoxic activities, which may induce hemolysis and/or rhabdomyolysis (de Castro e Silva et al., 2016). For example, wasp mastoparan impairs the phosphorylation of dystrophin, and disturbs Ca^{2+} mobilization with obvious implications on sarcoplasmic reticulum and mitochondrial functioning (Rocha et al., 2007). Further studies have found that wasp mastoparan can cause myonecrosis as well as apoptosis involving caspases signaling, corroborated by mitochondrial damage and cytokines activation. In addition, both wasp PLA1 and PLA2 exhibit direct hemolytic action against red blood cells (Santos et al., 2007). Moreover, PLA1 and PLA2 are also potential causes of rhabdomyolysis due to their action on membrane destruction.

Previous studies have shown that wasp sting-induced AKI is usually secondary to intravascular hemolysis and/or rhabdomyolysis, which

Table 1
Summary of previous studies on wasp sting-induced AKI.

Authors	Year	No. of cases with AKI	Hemolysis	Rhabdomyolysis	Renal biopsy	RRT	Outcomes
Sitprijafrs et al. (Sitprija and Boonpucknavig, 1972)	1972	1	No	Yes	ATN	PD	Recovered
Vachvanichsanong et al. (Vachvanichsanong et al., 1997)	1997	2	Yes	No	AIN	PD (2 children)	Recovered
Thiruvethiran et al. (Thiruvethiran et al., 1999)	1999	1	Yes	No	ATN	NO	Recovered
Zhang et al. (Zhang et al., 2001)	2001	1	Yes	Yes	AIN	IHD	Recovered
Chao et al. (Chao et al., 2004)	2004	1	Yes	Yes	ATN + AIN	NO	Recovered
Vikrant et al. (Vikrant et al., 2005)	2005	3	Yes	Yes	NI	IHD(2), PD (1 child)	2 recovered 1 dead (PD)
Sharmila et al. (Sharmila et al., 2007)	2007	1	Yes	No	NI	IHD	Dead
Vachvanichsanong et al. (Vachvanichsanong and Dissaneewate, 2009)	2009	7	Yes	Yes	NI	PD (6 children)	6 recovered 1 dead
Zhang et al. (Zhang et al., 2010)	2010	2	NI	NI	NI	CVVH + PE	Recovered
Nandi et al. (Nandi and Sarkar, 2012)	2012	1	No	No	AIN	IHD	Recovered
Zhang et al. (Zhang et al., 2013)	2013	87	Yes	Yes	NI	IHD (40), CVVH (27), CVVH + PE (14), PD (6)	9 Dead (4 IHD, 2 CVVH, 1 CVVH + PE, 2 PD) 5 ESRD (2 IHD, 3PD)
Kumar et al. (Kumar et al., 2013)	2013	1	No	No	ACN	IHD	Recovered
Xie et al. (Xie et al., 2013)	2013	183	Yes	Yes	NI	NI	NI
Radhakrishnan et al. (Radhakrishnan, 2014)	2014	1	No	Yes	NI	IHD	Recovered
Si et al. (Si et al., 2015)	2015	36	Yes	NI	NI	21 (CVVH + HP), 15 (IHD + HP)	6 dead (3 CVVH + HP, 3 HD + HP)
Yuan et al. (Yuan et al., 2016)	2016	23	Yes	Yes	NI	CVVHDF + HP, CVVHDF + PE	NI
Natarajan et al. (Natarajan et al., 2016)	2016	1	Yes	Yes	ATN	IHD	Recovered
Dhanapriya et al. (Dhanapriya et al., 2016)	2016	11	Yes	Yes	ATN (2), AIN (1), ATN + AIN (1)	IHD	1 dead
Vikrant et al. (Vikrant and Parashar, 2017a)	2017	29	Yes	Yes	ATN (4), AIN (3), ATN + AIN (6)	IHD	NI
Vikrant et al. (Vikrant and Parashar, 2017b)	2017	2	Yes	Yes	NI	IHD	Recovered

AKI, acute kidney injury; ATN, acute tubular necrosis; AIN, acute interstitial nephritis; ACN, acute cortical necrosis; RRT, renal replacement therapy; PD, peritoneal dialysis; IHD, intermittent hemodialysis; HP, hemoperfusion; PE, plasmapheresis; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; ESRD, end stage renal disease; NI, not investigated.

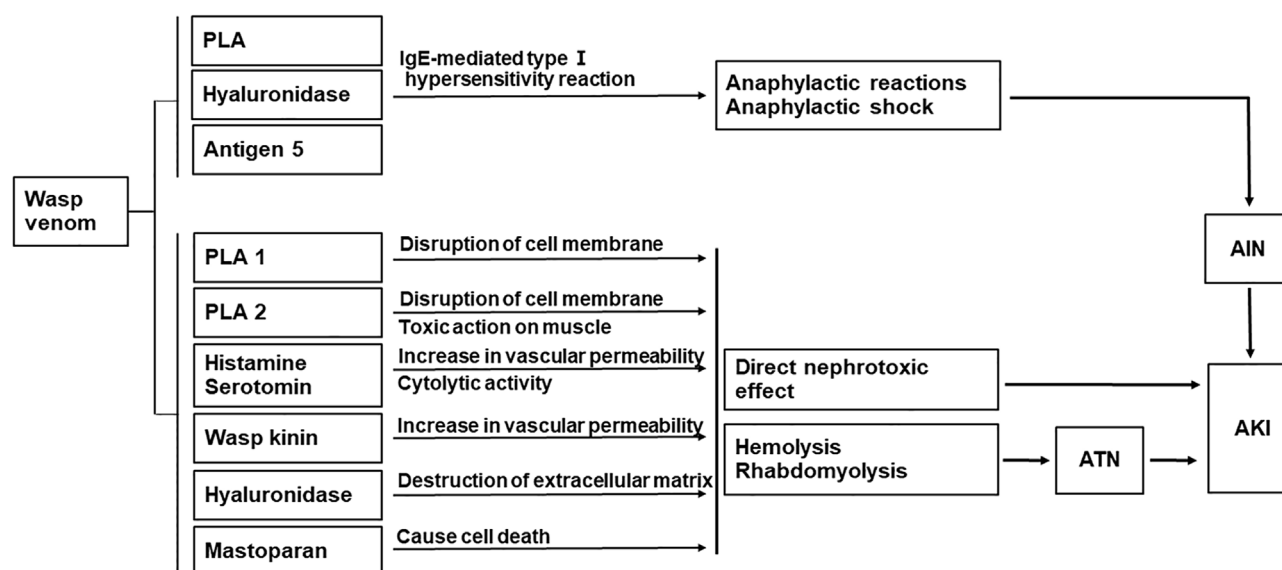


Fig. 1. The mechanisms of wasp venom-induced anaphylactic reactions and AKI. PLA, phospholipase A; ATN, acute tubular necrosis; AIN, acute interstitial nephritis; AKI, acute kidney injury.

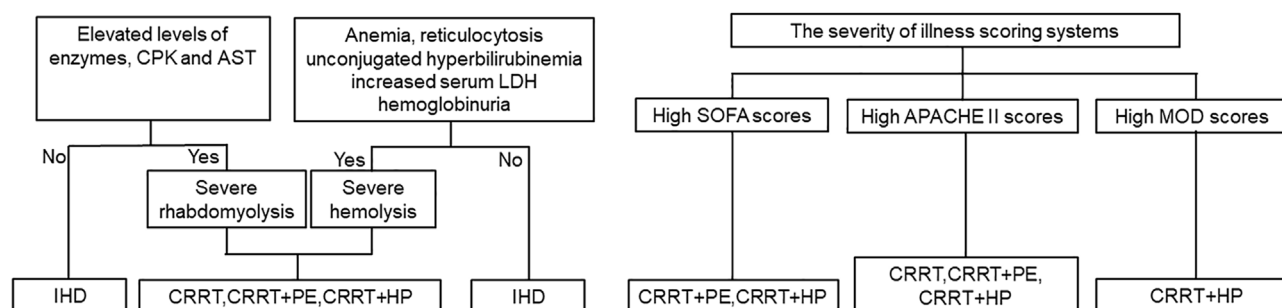


Fig. 2. The algorithm for selection of RRT modes after wasp stings-induced AKI. CPK, creatine phosphokinase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; MOD, multiple organ dysfunction; AKI, acute kidney injury; RRT, renal replacement therapy; CRRT, continuous renal replacement therapy; PE, plasmapheresis; HP, hemoperfusion.

specifically occurs in patients with multiple wasp stings (Vikrant et al., 2005; Xuan et al., 2010; Zhang et al., 2001). Xie et al. also found that, among patients with wasp stings, those who experienced rhabdomyolysis and/or hemolysis were more susceptible to the development of AKI (Xie et al., 2013). Positive immunohistochemical staining of myoglobin and/or hemoglobin can be found in renal tubular granular casts. This is in agreement with the indication that kidney damage results from hemolysis and/or rhabdomyolysis after a wasp sting (Dhanapriya et al., 2016; Zhang et al., 2013). With regards to laboratory findings, rhabdomyolysis is indicated through elevated levels of enzymes, creatine phosphokinase, and aspartate aminotransferase, while hemolysis can be inferred by anemia, unconjugated hyperbilirubinemia, reticulocytosis, increased serum lactate dehydrogenase, and hemoglobinuria (Vikrant et al., 2005).

The associations between hemolysis/rhabdomyolysis and AKI are well known and have been described in the literature (Petejova and Martinek, 2014; Zager, 1996). However, the precise molecular mechanisms of wasp sting-induced AKI are still unclear, which may be explained by direct toxicity of myoglobin/hemoglobin on renal tubule epithelial cells, through the formation of intratubular obstructive casts and renal vasoconstriction (Petejova and Martinek, 2014; Zager, 1996).

3.2.1. Direct cytotoxicity

Myoglobin is an oxygen and iron binding protein with a molecular weight of 17.5 kDa. Myoglobin is catabolized within proximal tubule cells and is easily filtered through the glomerular basement membrane.

The direct cytotoxicity of myoglobin to the renal tubule epithelial cell occurs through the hemoglobin, which induces the production of free radicals, causing lipid peroxidation and cell damage. In addition, in peripheral vascular beds, hemoglobin can scavenge nitric oxide (an important endogenous vasodilator), and induce vasoconstriction.

3.2.2. Intratubular obstruction

In the renal tubular lumen, myoglobin binds to Tamm-Horsfall protein, forming tubular casts, especially in the presence of a low urine pH. This process is promoted by the decrease in renal blood flow due to volume depletion.

3.2.3. Renal vasoconstriction

Muscle necrosis causes dramatic fluid third spacing, leading to intravascular volume depletion and hypovolemia. Severe muscle injury also activates the endotoxin cytokine cascade. Renal vasoconstriction is caused by reduced renal blood flow due to excessive leakage of extracellular fluid into the damaged muscle cells and by secondary activation of the renin-angiotensin-aldosterone system (RAAS). The activation of the RAAS is induced by volume depletion secondary to fluid sequestration within damaged muscle.

All these factors reduce glomerular and peritubular blood flow, leading to the development of ATN and worsening of kidney injury.

3.3. Hypersensitivity reaction to the venom

A hypersensitivity reaction to wasp venom leading to AIN has been reported as a cause of AKI alone or in combination with pigment tubulopathy (Nandi and Sarkar, 2012; Zhang et al., 2001), indicating that wasp venom components as allergens can mediate the AIN and induce AKI.

4. Treatment

Although there is no specific treatment for wasp stings, and no anti-venom is available for severe cases, the short-term management of wasp stings depends on the clinical manifestations. Most patients are treated with oral or intravenous glucocorticoids, potent topical glucocorticoid creams and ointments, or antihistamines, such as a H1-receptor blocker. Severe, local reactions in the head and neck require additional observation and emergency treatment in cases of airway obstruction to achieve prompt relief of symptoms (Przybilla and Rueff, 2012). Patients should be diagnosed and treated as quickly as possible; delayed diagnosis and treatment increases the rate of morbidity and can be fatal in some cases (Yang, 2016).

Therapeutic approaches for wasp sting-induced AKI include: (1) correction of hypovolemia and improvement of renal ischemia; (2) enhancement of toxic substance clearance from circulation; and (3) prevention or alleviation of direct adverse consequences caused by venom toxins, electrolyte imbalance, and hemoproteins (Zager, 1996). Early pharmacological intervention consists of adequate volume replacement and alkaline diuresis, with the aim to eliminate the factors that aggravate AKI. For instance, dehydration and renal hypoperfusion, formation of intratubular casts and tubular obstruction, aciduria, and free radical release. In the case that overt kidney injury is established, the timing of the initiation of RRT is important for the removal of venom toxins and inflammatory factors, as well as the liberation of the myoglobin and hemoglobin that is generated during rhabdomyolysis and/or hemolysis. RRT is particularly suitable for patient with AKI who have oliguria or are compromised by hyperkalemia, metabolic acidosis, or acute pulmonary edema (Zhang et al., 2013). RRT has been proven to be successful in the treatment of severe wasp sting-induced AKI. With appropriate treatment, the majority of patients with wasp sting-induced AKI achieve favorable renal recovery.

It is well known that RRT is not only effective in the removal of toxic substances and inflammatory mediators, but also for the maintenance of hemodynamic stability (Yuan et al., 2016). Available RRT modalities for the treatment of severe wasp sting-induced AKI were introduced in our previous work as well as in other studies (see Table 1). These modalities include intermittent hemodialysis (IHD), hemoperfusion (HP), plasmapheresis (PE), continuous renal replacement therapy (CRRT), and peritoneal dialysis (PD). CRRT can be performed using convective clearance (continuous veno-venous hemofiltration [CVVH]), diffusive clearance (continuous veno-venous hemodialysis [CVVHD]), or a combination of both for solute clearance (continuous veno-venous hemodiafiltration [CVVHDF]). Patients with wasp sting-induced AKI can be treated with CVVH or CVVHDF. The RRT treatment may require a maximum duration of 2–4 weeks, with renal function returning to normal within 1–3 months in most patients (Vikrant et al., 2005) (Table 1).

4.1. IHD and CRRT

Conventional 4-h, standard-flux IHD offers the most rapid solute clearance of all available therapies and is the initial preferred option in the treatment of life-threatening hyperkalemia and drug-related poisoning. Based on previous reports (Table 1), IHD remains the main treatment option for wasp sting-induced AKI. However, IHD involves the removal of large volumes of fluid during a short period of time, which can potentially result in unstable hemodynamics. CRRT is

commonly used for the treatment of critically ill patients with AKI who are unable to tolerate traditional IHD due to the hemodynamic instability or for whom IHD is incapable of managing the volume or metabolic derangements. Compared with the effect of IHD, CRRT is thought to provide better hemodynamic tolerance, ensuring a more stable internal environment and smoother fluid balance control. Thus, patients receiving CRRT are more likely to regain kidney function and have a decreased mortality rate than patients that receive IHD (Heung and Yessayan, 2017; Zhang et al., 2010).

IHD can only clear small substances from the blood using passive diffusion. Compared with IHD, the CRRT modality, such as CVVH or CVVHDF, may provide more effective clearance of certain toxins with higher molecular weights (Zhang et al., 2013). Wasp venom is composed of mid-to high-molecular-weight proteins, which makes CVVH/CVVHDF more suitable means of clearance, as it can remove these high-molecular-weight toxins more effectively than IHD. Moreover, hemolysis and rhabdomyolysis play a pivotal role in multiple wasp sting-induced AKI. Myoglobin (17 kDa), the “secondary toxin” generated from rhabdomyolysis following wasp stings, can be more efficiently cleared by CVVH/CVVHDF than IHD. Conversely, CVVH/CVVHDF can also remove mid-molecular-weight solutes (5–60 kDa), including plasma cytokines, through the displacement of a high-concentration hemofiltration solution. Thus, this therapy is more effective at reducing the plasma concentrations of various inflammatory cytokines (Jacka et al., 2005).

Given that convection is more effective at removing larger-molecular-weight solutes than diffusion, CVVH/CVVHDF may be more efficient at reducing the concentration of these solutes. In the study reported by Zhang et al., although the patients who began RRT with CVVH were more frequently complicated with MODS, they experienced a better and more rapid recovery of kidney function than those who began with IHD (Zhang et al., 2013). In another study performed by Si et al., patients receiving CVVH had a faster recovery time than those receiving IHD alone, as evidenced by an improvement in multiple organ dysfunction (MOD) scores and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. In addition, CVVH was more effective in decreasing the plasma levels of myoglobin, creatine phosphokinase, lactate dehydrogenase, bilirubin, and creatinine, thereby reducing the incidence of oliguria and vasopressor use as well as shortening the duration of hospitalization (Si et al., 2015). These findings suggest that CVVH may be superior to IHD for the treatment of wasp sting-induced AKI.

4.2. HP

The HP approach is effective for the removal of mid-to large-sized molecules and toxins bound to proteins, which is why HP is widely used to manage cases of drug overdose and intoxications. Moreover, HP has a therapeutic role in systemic inflammatory response syndrome, acute respiratory distress syndrome, sepsis, and acute necrotic pancreatitis. Two studies (Table 1) have investigated the functions of HP in wasp venom-induced AKI (Si et al., 2015; Yuan et al., 2016). Our recent results revealed that CVVHDF+HP was relatively effective in the management of patients with wasp sting-induced AKI via the removal of the venom components and inflammatory cytokines, while maintaining hemodynamic stability and improving the general outcome of patients (Yuan et al., 2016).

4.3. PE

PE is a modality that is capable of removing antibodies, immune complexes, and toxins as well as replenishing coagulation factors and other bioactive substances by exchanging fresh frozen plasma. PE may be considered necessary for patients with severe hemolysis and rhabdomyolysis (Zhang et al., 2013). This method has been found useful for the treatment of wasp sting-induced AKI as it enables the reduction of a

large amount of circulating venom or the removal of the circulating inflammatory mediators that are induced by the venom (Vikrant et al., 2005). However, PE alone cannot provide efficient removal of small- or medium-sized toxin particles. Zhang et al. found that initiation with CVVH in combination with PE may help to achieve a better and more rapid recovery of kidney function than IHD (Zhang et al., 2013). In addition, the results of our previous study showed that, similar to CVVHDF + HP, CVVHDF + PE was capable of improving venom-induced MODS. In particular, the combination of CVVHDF + PE was more effective at reducing the levels of inflammatory mediators as well as the Sequential Organ Failure Assessment (SOFA) score than CVVHDF + HP (Yuan et al., 2016). Based on the observations from our study and those of others, the combination of CRRT and PE appears to be a therapeutic option for severe hemolysis and/or rhabdomyolysis caused by wasp stings.

The main complications that are associated with blood purification are arrhythmia, hypotension, bleeding, and hemodynamic instability during therapy. IHD has been found to be related to a higher incidence of hypotension than CVVH and CVVH + PE (Zhang et al., 2013). Patients receiving CVVH are more likely to have hypophosphatemia, but usually improve without the use of additional interventions after the cessation of CVVH (Zhang et al., 2013). Si et al. also found a lower incidence of cardiac dysfunction (e.g. palpitations, chest tightness, and arrhythmia) in patients receiving CVVH than in those receiving IHD. This suggests that CVVH performs similarly to IHD in maintaining hemodynamic stability (Si et al., 2015).

4.4. PD

There is currently not enough evidence to determine whether there are significant differences in the mortality rates between patients with AKI that are treated with PD or hemodialysis (Liu et al., 2017). In general, the efficacy of PD in treating wasp sting-induced AKI remains controversial. This is partially because a very limited number of patients have been treated with PD for wasp sting-induced AKI; so far, the total number of cases that have been reported is less than 20 (Sitprija and Boonpucknavig, 1972; Vikrant et al., 2005; Zhang et al., 2013). Furthermore, the selection of patients and the experience of clinical centers may have significantly influenced the outcomes of these cases. Therefore, the role of PD in patients with multiple wasp stings will require further investigation. Zhang et al. reported that, among six adult patients with wasp stings that received PD treatment, three patients developed end-stage renal disease and two died (Zhang et al., 2013). However, in some cases, PD appears to be a useful approach for the treatment of children with wasp-induced AKI, as they may recover completely after appropriate management with PD (Vachvanichsanong et al., 1997) (Vachvanichsanong and Dissaneewate, 2009).

At present, evidence-based therapy of wasp sting-induced AKI is generally lacking. The selection of RRT modes for wasp sting-induced AKI should be dependent on the individual patient. Compared to IHD, CRRT offers better hemodynamic tolerance and control of volume, which is more applicable for severe patients who have higher SOFA scores, MOD scores, APACHE II scores, severe rhabdomyolysis and/or hemolysis. Based on the clinical index, a proposed algorithm for the selection of RRT modes after wasp sting-induced AKI is shown in Fig. 2. Patients who were administered with CRRT therapy with or without HP/PE appeared to have a better and more rapid kidney recovery than patients who received IHD. However, the majority of cases of wasp stings have occurred in rural areas in developing countries where the patients are more likely to have a low income and poor financial status. Thus, the cost of RRT therapy should also be considered. IHD offers the advantage of flexible timing of treatment and relatively low cost. Therefore, it may be reasonable to replace CRRT with IHD when the condition of a patient becomes stable. PD appears to not to be applicable for adult patients because of the high mortality according to the limited evidence.

5. Conclusions

AKI is a serious complication following multiple wasp stings that has a high mortality rate. Currently, the treatment of such cases remains supportive, with no available specific anti-venom. To prevent secondary hemolysis and rhabdomyolysis, patients with severe wasp stings should be hospitalized early and should receive sufficient treatment, including aggressive hydration and urine alkalization (Vikrant and Parashar, 2017c). The available reports on wasp sting-induced AKI are typically retrospective and observational in nature, with a very limited number of patients, especially when considering those who have undergone a renal biopsy or have received PD therapy. For patients with delayed recovery of renal function after wasp stings, renal biopsy should strongly be considered, which may guide the early use of steroids if histological changes of AIN are present, to prevent the development of interstitial fibrosis and facilitate the restoration of renal function (Vikrant et al., 2005). Multicentric randomized controlled trials are required to evaluate the efficacy and safety of various RRT modalities in patients with wasp sting-induced AKI.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.toxicol.2019.03.008>.

Funding

This work was funded by grants from the National Natural Science Foundation of China (81300617) and Hubei Province Health and Family Planning Scientific Research Project (WJ2015Q038).

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