

# Adverse Cardiovascular Events after a Venomous Snakebite in Korea

Oh Hyun Kim, Joon Woo Lee, Hyung Il Kim, KyoungChul Cha, Hyun Kim, Kang Hyun Lee, Sung Oh Hwang, and Yong Sung Cha

Department of Emergency Medicine, Wonju College of Medicine, Yonsei University, Wonju, Korea.

**Purpose:** Although cardiac involvement is an infrequently recognized manifestation of venomous snakebites, little is known of the adverse cardiovascular events (ACVEs) arising as a result of snakebite in Korea. Accordingly, we studied the prevalence of ACVEs associated with venomous snakebites in Korea and compared the clinical features of patients with and without ACVEs.

**Materials and Methods:** A retrospective review was conducted on 65 consecutive venomous snakebite cases diagnosed and treated at the emergency department of Wonju Severance Christian Hospital between May 2011 and October 2014. ACVEs were defined as the occurrence of at least one of the following: 1) myocardial injury, 2) shock, 3) ventricular dysrhythmia, or 4) cardiac arrest.

**Results:** Nine (13.8%) of the 65 patients had ACVEs; myocardial injury (9 patients, 13.8%) included high sensitivity troponin I (hs-TnI) elevation (7 patients, 10.8%) or electrocardiogram (ECG) determined ischemic change (2 patients, 3.1%), and shock (2 patient, 3.1%). Neither ventricular dysrhythmia nor cardiac arrest was observed. The median of elevated hs-TnI levels observed in the present study were 0.063 ng/mL (maximum: 3.000 ng/mL) and there was no mortality in the ACVEs group. Underlying cardiac diseases were more common in the ACVEs group than in the non-ACVEs group ( $p=0.017$ ). Regarding complications during hospitalization, 3 patients (5.4%) in the non-ACVEs group and 3 patients (33.3%) in the ACVEs group developed bleeding ( $p=0.031$ ).

**Conclusion:** Significant proportion of the patients with venomous snakebite is associated with occurrence of ACVEs. Patients with ACVEs had more underlying cardiac disease and bleeding complication.

**Key Words:** Snakebite, heart injury, troponin I, shock

## INTRODUCTION

An estimated 1.8 to 2.5 million venomous snakebites occur worldwide each year and result in at least 100000 to 125000 deaths.<sup>1,2</sup> As in other parts of the world, snakebites are common in Korea. Generally, in the treatment of venomous snakebite, focus of treatment is coagulation abnormalities, neuromuscular paralysis and respiratory failure in the elapid bites.<sup>3</sup> However, of the various possible complications, cardiac involve-

ment is also an infrequently recognized manifestation of venomous snakebites, and is seen mainly associated with viperine bites.<sup>4</sup>

However, little is known of the adverse cardiovascular events (ACVEs) arising as a result of snakebites in Korea, except one case report on the rare development of acute myocardial infarction after snakebite.<sup>5</sup> In particular, there has been no report on myocardial injury in Korea as determined using serum high sensitivity troponin I (hs-TnI) resulting from venomous snakebites.

Accordingly, we studied the prevalence of ACVEs associated with venomous snakebites in Korea and compared the clinical features of patients with and without ACVEs.

## MATERIALS AND METHODS

### Study design and data

This retrospective, observational study was conducted on con-

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**Corresponding author:** Dr. Yong Sung Cha, Department of Emergency Medicine, Wonju College of Medicine, Yonsei University, 20 Ilsan-ro, Wonju 26426, Korea. Tel: +82-33-741-1615, Fax: +82-33-742-3030, E-mail: zza96@hanmail.net

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secutive patients who presented with a venomous snakebite at the emergency department (ED) of Wonju Severance Christian Hospital, Wonju College of Medicine, Yonsei University, between May 2011 and October 2014. The study exclusion criteria applied were; an age of <18 years, end-stage renal disease, no admittance for treatment at our hospital, ED arrival >48 hrs after being bitten, and the absence of a measurable serum TnI level within 48 hrs of arrival at the ED.

Diagnostic criteria of venomous snakebite included the presence of one or more of the following: 1) a confirmed two fang wound; 2) a triangular head; 3) a venomous snake confirmed by patient's experience; and 4) abnormal physical and laboratory findings such as shock, tachypnea, bleeding, thrombocytopenia, disseminated intravascular coagulation (DIC), or diplopia despite insufficient other findings.<sup>6</sup> When patients had systemic signs and symptoms or severe local symptoms associated with snakebite, antivenin was administered and, if symptoms persisted, antivenin was repeated.

The following information was obtained from medical records: age, gender, site of the bite, ED arrival times, underlying diseases, severity at ED & admission, initial systolic blood pressure, and initial symptoms and signs. A traditional snakebite severity grading scale was used (Table 1).<sup>7</sup> Complications including hematologic (anemia,<sup>8</sup> thrombocytopenia, prothrombin time/partial thromboplastin time prolongation, DIC,<sup>9</sup> and bleeding) and neurologic complications (blurred vision or diplopia) occurring during hospitalization, and mortality were investigated.

Cardiac biochemical markers including hs-TnI were investigated in the ED. A hs-TnI (Siemens Healthcare Diagnostics Inc., Newark, DE, USA) was used to determine blood TnI levels (reference range: <0.046 ng/mL) and myocardial injury was defined as an elevation of hs-TnI within 48 hrs of arrival at the ED.

ACVEs were defined as the occurrence of at least one of the followings: 1) myocardial injury [based on hs-TnI elevation within 48 hrs of presentation or electrocardiogram (ECG) evidence of ischemic change, such as ST elevation, ST depression, or T wave inversion]; 2) shock (defined as hypotension requiring vasopressors); 3) ventricular dysrhythmia (ventricular tachycardia, ventricular fibrillation, torsades des pointes); and 4) cardiac arrest. We investigated ACVEs that developed within 48 hrs of treatment commencement because we wanted to minimize the possibility of ACVEs secondary to malfunctions

of other organs or systems, such as, multiple organ failure.

This study was approved by the Institutional Review Board of Wonju College of Medicine, Yonsei University.

### Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as mean and standard deviation or median and interquartile range after assessments for normality using the Shapiro-Wilk test. The chi-square test or Fisher's exact test was used to compare nominal variables, and the two-sample t-test or the Mann-Whitney U test was used to compare continuous variables. *p* values of <0.05 were considered statistically significant. The analysis was performed using IBM SPSS 20 Ver. (IBM, Armonk, NY, USA).

## RESULTS

### General and laboratory characteristics of patients with venomous snakebite

A total of 65 consecutive patients were found eligible for this study while 33 patients were excluded from the study due to the following exclusion criteria: age less than 18 years (7 patients), end-stage renal disease (1 patient), patients had not been admitted for treatment in our hospital or transfer out (4 patients), ED arrival more than 48 hrs after snakebite (4 patients), and the absence of serum hs-TnI level within 48 hrs of arrival at the ED (15 patients), and insufficient data (2 patients).

General characteristics are shown in Table 2. Forty six of the patients were male (70.8%) and the ages of the 65 study subjects ranged from 20 to 90 years with a median of 57 years. All patients were bitten in upper and lower extremities. There were 5 patients (7.7%) with cardiac diseases including coronary artery disease (unstable angina 1 patient and myocardial infarction 1 patient), valvular heart disease (aortic regurgitation 1 patient), hypertensive heart disease (hypertensive heart failure 1 patient), and arrhythmia (atrial fibrillation 1 patient). Most common grading of severity was grade II. The common symptoms and signs at initial presentation were pain (65 patients, 100%), edema (53 patients, 81.5%), discoloration (18 patients, 27.7%), and dizziness (9 patients, 13.8%). The most common hematologic complication during hospitalization was anemia (39 patients, 60%), and bleeding developed in 6 patients

**Table 1.** Traditional Snakebite Severity Grading Scale

Severity scale (0–IV)	Manifestations
0—No envenomation	Local or systemic signs or symptom absent
I—Minimal	Local swelling, absence of systemic sign, normal laboratory findings
II—Moderate	Swelling extending past bite site (6–12 inch), ≥1 systemic sign or symptom, abnormal laboratory findings
III—Severe	Marked swelling (>12 inch), tissue loss, multiple or severe systemic symptoms, immediate systemic signs, rapid progression of symptoms
IV—Very severe	Rapid development of local reaction, ecchymosis, necrosis, blebs, blisters, swelling severe enough to obstruct venous or arterial flow, swelling may involve ipsilateral trunk

**Table 2.** General Characteristics of Venomous Snakebite Victims

Characteristics	Total (n=65)	Non-ACVEs group (n=56; 86.2%)	ACVEs group (n=9; 13.8%)	p value
Age (yrs)	57.0 (50.5–67.5)*	56.0 (47.8–66.0)*	64.0 (52.5–71.5)*	0.258
Male gender	46 (70.8%)	40 (71.4%)	6 (66.7%)	0.714
Sites of bite				0.339
Hand	50 (78.1%)	41 (74.5%)	9 (100%)	
Foot	11 (17.2%)	11 (20.0%)	0 (0%)	
Leg	3 (4.7%)	3 (5.4%)	0 (0%)	
ED arrival times (hrs)	3.0 (1.0–10.8)*	4.0 (1.0–15.0)*	3.0 (1.5–3.5)*	0.560
Underlying disease				
DM	6 (9.2%)	5 (8.9%)	1 (11.1%)	>0.999
HTN	17 (26.2%)	14 (25.0%)	3 (33.3%)	0.687
Cardiac disease	5 (7.7%)	2 (3.6%)	3 (33.3%)	0.017
SBP (mm Hg)	141±27 <sup>†</sup>	143±25 <sup>†</sup>	133±40 <sup>†</sup>	0.308
Severity (ED/admission)				0.170/0.640
I	26/13 (40.0%/20.0%)	22/11 (40.7%/20.8%)	4/2 (44.4%/22.2%)	
II	31/44 (47.7%/67.7%)	28/38 (51.9%/71.7%)	3/6 (33.3%/66.7%)	
III	4/3 (6.2%/4.6%)	2/2 (3.7%/3.8%)	2/1 (22.2%/11.1%)	
IV	2/2 (3.1%/3.1%)	2/2 (3.7%/3.8%)	0/0 (0%/0%)	
Antivenin				0.501
None	17 (26.2%)	13 (23.2%)	4 (44.4%)	
Single	39 (60%)	34 (60.7%)	5 (55.5%)	
Multidose	9 (13.8%)	9 (16.1%)	0 (0%)	
Symptoms & signs				
Local effect				
Pain	65 (100%)	55 (100%)	9 (100%)	
Blister	7 (10.8%)	7 (26.9%)	0 (0%)	>0.999
Edema	53 (81.5%)	46 (88.5%)	7 (87.5%)	>0.999
Discoloration	18 (27.7%)	17 (48.6%)	1 (50.0%)	>0.999
Systemic effect				
Nausea	3 (4.6%)	2 (3.6%)	1 (11.1%)	0.365
Dizziness	9 (13.8%)	6 (10.7%)	3 (33.3%)	0.339
Headache	4 (6.2%)	3 (5.4%)	1 (11.1%)	0.458
Decreased mental	1 (1.5%)	1 (1.8%)	0 (0%)	>0.999
Dyspnea	5 (7.7%)	4 (7.1%)	1 (11.1%)	0.538
Complications				
Hematologic				
Anemia	39 (60%)	31 (55.4%)	8 (88.9%)	0.074
Thrombocytopenia	26 (40%)	22 (39.3%)	4 (44.4%)	>0.999
PT/PTT prolongation	22 (33.8%)	18 (32.1%)	4 (44.4%)	0.706
DIC	30 (46.2%)	25 (44.6%)	5 (55.6%)	0.722
Bleeding	6 (9.2%)	3 (5.4%)	3 (33.3%)	0.031
Neurologic				
Blurred vision/diplopia	2 (3.0%)	2 (3.6%)	0 (0%)	>0.999
Rhabdomyolysis	13 (20%)	12 (21.8%)	1 (11.1%)	0.672
TnI levels within 48 hrs (ng/mL)	0.015 (0.015–0.016)*	0.015 (0.015–0.015)*	0.063 (0.033–0.111)*	0.001

ED, emergency department; DM, diabetes mellitus; HTN, hypertension; SBP, systolic blood pressure; PT, prothrombin time; PTT, partial thromboplastin time; DIC, disseminated intravascular coagulation; TnI, troponin I; ACVEs, adverse cardiovascular events.

\*Median (interquartile range), <sup>†</sup>Mean±standard deviation.

Table 3. Clinical Characteristics and Laboratory Results in Patients of Venomous Snakebite with ACVEs

Patients	Age (yrs)	Gender	Cardiovascular risk factors	Severity (ED/admission)	ECG	Hs-TnI within 48 hrs	Shock	Other complications	Total hospital admission days	Survival
1	77	M	No	I/II	T wave inversion	0.013	No	Anemia, PT/PTT prolongation	9	Alive
2	71	F	HTN	II/II	QT prolongation	0.070	No	Anemia	5	Alive
3	64	M	No	I/I	T wave inversion	0.004	No	Anemia	5	Alive
4	54	F	Bradycardia	II/II	Normal	0.052	No	Anemia, PT/PTT prolongation, DIC	6	Alive
5	43	M	No	II/II	Normal	3.000	No	Anemia, thrombocytopenia, DIC, bleeding	7	Alive
6	51	M	No	I/II	Normal	0.063	No	Anemia, thrombocytopenia, PT/PTT prolongation, DIC, bleeding	32	Alive
7	72	M	DM, CAD	III/II	QT prolongation	0.105	Yes	Anemia, thrombocytopenia, DIC	13	Alive
8	68	F	HTN	I/I	QT prolongation	0.061	No	No	1	Alive
9	60	M	HTN	III/III	QT prolongation	0.116	Yes	Anemia, thrombocytopenia, PT/PTT prolongation, DIC, bleeding, rhabdomyolysis, AKI	14	Alive

ED, emergency department; ECG, electrocardiogram; Hs-TnI, high sensitivity troponin I; HTN, hypertension; DM, diabetes mellitus; DIC, disseminated intravascular coagulopathy; AKI, acute kidney injury; PT/PTT, prothrombin time/partial thromboplastin time.

at puncture site (2 patients), gastrointestinal tract (3 patients), and brain (1 patient). DIC developed in 46.2% of patients. Out of neurologic complications, blurred vision was developed in 3.0%. Other complication was a rhabdomyolysis (13 patients, 20%) and there was no mortality (Table 2).

ACVEs occurred in 9 patients (13.8%); myocardial injury (9 patients, 13.8%) included hs-TnI elevation (7 patients, 10.8%) or ECG determined ischemic change (2 patients, 3.1%), and shock (2 patient, 3.1%). Neither ventricular dysrhythmia nor cardiac arrest was observed. Cardiac biochemical markers analysis revealed median initial levels of hs-TnI of 0.015 ng/mL. ECG showed a T wave inversion in 4 patients (6.2%). QT prolongation was observed in 25 patients (38.5%) (Table 2 and 3).

### General characteristics and laboratory findings according to the presence of ACVEs

Underlying cardiac diseases were more common in the ACVEs group than in the non-myocardial injury group ( $p=0.017$ ). However, age, severity, and initial symptoms & signs were not significantly different between the two groups (Table 2).

Regarding complications during hospitalization, 3 patients (5.4%) in the non-ACVEs group and 3 patients (33.3%) in the ACVEs group developed bleeding ( $p=0.031$ ). Blurred vision or diplopia developed in 2 patients in non-ACVEs group (Table 2).

## DISCUSSION

Cardiac involvement is known mainly to be associated with viperine bites.<sup>4</sup> There are four types of venomous snakes in Korea. Three belong to the family Viperidae; that is, *Agkistrodon brevicaudus*, *Agkistrodon ussuriensis*, and *Agkistrodon saxatilis*. The other *Rhabdophis tigrinus* belongs to the family Cloubriidae.<sup>10</sup> In this study, the incidence of ACVEs development within 48 hrs following treatment commencement in a venomous snakebite cases was greater than expected (13.8%). To the best of our knowledge, this is the first report to address ACVEs after a venomous snakebite in Korea. In this study, there was no mortality, irrespective of ACVEs. In the present study, therefore, we cannot predict the prognosis of patients with ACVEs. Nevertheless, previous studies showed that the most severe complications and fatalities are unrelated to cardiac abnormalities.<sup>11,12</sup>

Serum TnI is used to detect myocardial injury, because it is expressed as a cardio-specific isoforms.<sup>13</sup> For this reason therefore, the occurrence of myocardial injury was checked in the present study by hs-TnI assay and ECG. In fact, all 9 patients who experienced ACVEs exhibited myocardial injury. Furthermore, 7 patients showed TnI elevation, but none showed TnI elevation with ECG determined ischemic change. The elevated hs-TnI levels observed in the present study (median: 0.063 ng/mL, maximum: 3.000 ng/mL) were lower than those of other myocardial injuries reported, such as myocardial infarction and myocarditis.<sup>14</sup>

In a study conducted in northeastern Nigeria involving 108 patients with a viperine snakebite, including carpet viper (93%), burrowing asp, and puff adder (4.6%) bites, more than 60% of patients were shown to have electrocardiographic abnormalities, but cardiac troponin T was elevated in only 2% of patients.<sup>11</sup> The only other systematic study, conducted in Papua New Guinea, using ECG and cardiac troponin T levels, also concluded that myocardial damage is uncommon following elapid snakebites.<sup>15</sup>

In the ACVEs group, two patients had shock requiring vasopressors. We thought that shock might be caused by anaphylaxis because all two patients had skin rash and subsequently recovered after treatment of intravenous epinephrine.

Although the mechanism of myocardial damage from snakebite remains unclear,<sup>16-22</sup> four possible mechanisms have been proposed for the development of acute myocardial infarction after a snakebite: 1) hypovolemic shock due to increased vascular permeability; 2) coronary thrombosis resulting from hypercoagulability; 3) direct cardio-toxicity; and 4) vasospasm caused by snake venom. In this study, shock occurred only in 2 patients and bleeding tendency was rather higher than hypercoagulability tendency in the ACVEs group. A well designed prospective study is needed to determine the pathogenesis of myocardial injury.

Coagulopathy is a feature of viperin snakebites.<sup>3</sup> In Korea, the prevalence of coagulopathy varies from 2.1–82.4% in snakebite victims.<sup>23-26</sup> In the present study, the prevalence of DIC was high (46.2%) in total 65 patients. Although no significant intergroup difference was observed, except for bleeding, hematologic complications were more severe in the ACVEs group. ACVEs group had more cardiac disease history, which resulted in higher chance of taking antiplatelet or anticoagulant such as aspirin or warfarin. Therefore, it is likely that ACVEs group had more bleeding complication.

This study has some limitations that bear consideration. First, the study was conducted using a retrospective design at one hospital, and thus, some relevant parameters were not included. Second, we could not conclude for cardiac function in patients with ACVEs because we performed echocardiography on only 2 out of 9 patients with ACVEs. Two patients had normal heart function. Third, our study is limited by lack of serial ECG and serum hs-TnI testing, which would have confirmed any reversal of abnormalities. Fourth, a bias might be caused by exclusions. Therefore, we propose that further prospective studies are needed to investigate serial echocardiography and prognosis of cardiac injury in patients with venomous snakebite.

In conclusion, significant proportion of the patients with venomous snakebite is associated with occurrence of ACVEs. Patients with ACVEs have more underlying cardiac disease and bleeding complication.

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