

ORIGINAL ARTICLE

Development of *Latrodectus* Envenomation Severity Score (LESS); a Severity Index for Widow Spider Bite: Initial Step

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Abstract

Background: In order to describe the patients and evaluate the effectiveness of treatments for widow spider envenomation, investigators require a reliable assessment tool. In this paper, the development of a clinical index for measuring the widow spider bite severity, *Latrodectus* Envenomation Severity Score (LESS), is described.

Methods: According to the valid methods for index development, a Delphi group process was applied. A panel of 13 experienced medical toxicologists and physician experts in treatment of black widow spider bites was assembled in December 2013. The participants were asked to score clinical manifestations of *Latrodectus* envenomation based on their importance on the severity and patients' prognosis. Hence, an initial draft of the severity index was developed and in the second phase of study, the draft was discussed in a focus group of experts to finally comment on each variable and vote about the final scores.

Results: The proposed version of LESS comprises of 34 clinical items categorized in 8 organ systems. The index includes definition of each clinical variable to help users of the index how to ascertain or rule out the clinical finding. The maximum theoretical score according to LESS is 87. Acute renal failure, myocarditis, pulmonary edema and ileus received the highest scores in this index.

Conclusion: The LESS is a new assessment tool that is designed to more objectively evaluate the severity and progression of envenomation in victims of widow spider bite. The prognostic-ability, reliability and sensitivity to change of the index should be investigated in future studies.

Keywords: Black Widow Spider; Health Status Indicators; Severity of Illness Index; Spider Bites

How to cite this article: Monzavi SM, Afshari R. Development of *Latrodectus* Envenomation Severity Score (LESS); a Severity Index for Widow Spider Bite: Initial Step. *Asia Pac J Med Toxicol* 2014;3:18-22.

INTRODUCTION

Venomous bites of *Latrodectus* genus or the widow spiders can produce several morbidities due to severe neurotoxicity caused by their venom. A widow spider bite induces effects ranging from puncture marks without apparent clinical signs to systemic envenomation syndrome known as "latrodectism" that classically includes generalized muscle pain, diaphoresis, cramps, vomiting and chills (1-3). Moreover, in serious cases, metabolic acidosis, electrolyte disturbances, hypertension, dysrhythmia, renal failure and ileus may occur (2-5).

Systemic *Latrodectus* envenomation develops in approximately a third of victims (2). In addition, all possible consequences may not occur in a victim due to individual's characteristics, the amount of venom injected into blood circulation, variability in widow spider species and the impact of climate and season on the quality of venom (6). Clinical picture of systemic envenomation exhibits in a dynamic trend that initiates with limited localized pain progressing to system organ involvements (1,2). In this regard, severe venom effects may not become evident in the first 24 hours (7). On the other hand, the envenomation

syndrome may start with critical signs in some patients, but fail to deteriorate in later stages. Hence, repeated assessment of the patient has been recommended for the efficient management. Furthermore, the protean nature of the disease complicates any evaluation and comparison of envenomation severity in similar studies. Although, there have been some efforts for grading the severity of *Latrodectus* envenomation (8), those scales are unable to quantitatively describe the exact condition and compare two patients with each other. In order to assess the effectiveness of treatments for widow spider envenomation, investigators have used various outcome measures including pain (using visual analogue scale) and sweating (using hyperhidrosis disease severity scale) (9-11). However, these features represent only a part of envenomation syndrome and do not reveal the clear overall condition.

In order to standardize the evaluation of severity of widow spider bites, a major concern has been raised in Mashhad Medical Toxicology Centre for development of a comprehensive instrument. In this paper, the development of a clinical index for the measurement of widow spider bite severity, *Latrodectus* Envenomation Severity Score (LESS), is described.

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Received 16 December 2013; Accepted 17 February 2014

METHODS

According to the valid methods for index development (12), a Delphi group process was applied that provides an environment for a group of experts to express their opinions anonymously (12,13). A panel of 13 experienced medical toxicologists and physician experts in treatment of black widow spider bites in Khorasan region was assembled in December 2013. The purpose of the panel was to define and standardize a clinical index for assessment of widow spider bite severity. A questionnaire was given to participants that contained a comprehensive list of clinical features (symptoms, signs and laboratory findings) of widow spider bite reported in the literature and medical toxicology textbooks (1-9,14-16), amended with discussion with experts in the management of the disease.

In order to score each clinical variable a general question was asked from the participants: Which of the following clinical presentations has the higher importance for giving the patient more serious or intensive care or rule out the discharge of the patient? The participants were asked to score each variable on a scale of 0 (no importance) to 5 (most important) to indicate the weight of each variable for measuring disease severity. The scores of each item were analyzed using Microsoft Excel software (Microsoft Corp., Redmond, WA, USA) and the results were showed with mean and standard deviation (SD), median and interquartile range (IQR), and mode.

Consequently, an initial draft of the severity index was developed. In the second phase of study, the draft was discussed in a focus group of experts to finally comment on each variable and vote about the final scores. Definition of each clinical variable was also provided to help users of the index how to ascertain or rule out the clinical finding.

RESULTS

Development of the severity index

The results of the scores for clinical features of widow spider bite allocated by the panel members (in the Delphi process) are illustrated in the table 1. Based on these scores, the initial draft of the LESS was proposed and presented to the focus group. For most variables, the mean of allocated scores was considered to determine the score on the LESS. Nevertheless, for variables that the decimal of their means were close to 5 (e.g. flushing, leukocytosis), modes and medians were also taken into account. However, for hypokalemia with mean score of 2.5, the final score proposed by the focus group was 2, though the mode and median was 3 based on opinions of panel members (in Delphi process). This decision was mainly made due to the fact that generally hypokalemia can be better tolerated by the patients and easier to treat compared to hyperkalemia (17). Transient hyperglycemia and puncture marks did not receive any importance on describing the severity of envenomation and thus were not included in the initial draft. On the other hand, the feeling of pain in the entire affected limb was added to the initial draft (followed by the recommendation of focus group), though it was not present in the questionnaire. Some experts in the focus group believed that between localized pain and generalized body pain, another descriptor should exist to distinguish the pain at the bite site, the pain that spreads over the bitten limb and pain

that extends to the body of victim. For this variable, the proposed score was 2 (between 1 for localized pain and 3 for generalized pain). After these modifications and also categorization of the clinical effects in system organs and adding definitions for ascertainment of the clinical effects, the final draft of LESS was developed (Figure 1).

Table 1. Scores allocated by the panel members (in the Delphi process) to the clinical features of widow spider bites based on their importance in envenomation severity

Clinical feature	Mean (SD)	Median (IQR)	Mode
Acute renal failure	4.8 (0.4)	5.0 (4.5-5.0)	5.0
Myocarditis	4.7 (0.9)	5.0 (4.0-5.0)	5.0
Pulmonary edema	4.6 (0.7)	5.0 (4.0-5.0)	5.0
Ileus	4.1 (1.2)	5.0 (3.0-5.0)	5.0
Dysrhythmia	3.8 (1.7)	5.0 (3.0-5.0)	5.0
Metabolic acidosis	3.5 (1.2)	4.0 (2.3-4.0)	4.0
Dehydration	3.2 (1.1)	3.0 (2.0-4.0)	4.0
Generalized muscle pain	3.2 (1.1)	3.0 (2.0-4.0)	2.0
Hyperkalemia	3.1 (1.4)	3.0 (2.0-4.0)	3.0
Chills / Muscle cramping	3.1 (1.3)	3.0 (2.5-4.0)	3.0
Abdominal rigidity	3.0 (1.6)	3.0 (1.0-2.0)	4.0
Diaphoresis	3.0 (1.4)	3.0 (2.0-4.0)	3.0
Bradycardia	3.0 (0.9)	3.0 (2.5-3.5)	3.0
Hypertension	2.8 (1.0)	3.0 (2.0-4.0)	3.0
Dyspnea	2.7 (1.2)	3.0 (1.5-4.0)	3.0
Dermal necrosis	2.7 (1.4)	3.0 (2.0-4.0)	2.0
Vomiting	2.7 (1.2)	3.0 (2.0-3.0)	2.0
Restlessness	2.6 (0.5)	3.0 (2.0-3.0)	3.0
Hypokalemia	2.5 (1.6)	3.0 (1.0-4.0)	3.0
Sinus tachycardia	2.4 (1.1)	2.0 (1.5-3.0)	2.0
Abdominal pain	2.3 (1.0)	2.0 (1.5-3.0)	2.0
Confusion / Hallucination	2.1 (1.1)	2.0 (1.5-3.0)	2.0
Mydriasis	1.8 (1.0)	1.5 (1.0-2.8)	1.0
Localized pain	1.4 (0.5)	1.0 (1.0-2.0)	1.0
Headache	1.4 (0.8)	1.0 (2.0-4.0)	1.0
Leukocytosis	1.4 (1.2)	1.0 (1.0-2.0)	1.0
Flushing	1.4 (0.9)	1.0 (1.0-2.0)	1.0
Increased CPK	1.4 (0.9)	1.0 (1.0-2.0)	1.0
Oliguria	1.3 (0.9)	1.0 (1.0-2.0)	1.0
Periorbital edema	1.2 (0.6)	1.0 (1.0-1.8)	1.0
Fever	1.2 (0.5)	1.0 (1.0-1.8)	1.0
Nausea	1.1 (0.4)	1.0 (1.0-2.0)	1.0
Regional lymphadenopathy	0.7 (0.5)	1.0 (0.0-1.0)	1.0
Transient hyperglycemia	0.4 (0.6)	0.0 (0.0-1.0)	0.0
Puncture marks	0.3 (0.5)	0.0 (0.0-1.0)	0.0

Case no.: Name of patient: Name of physician: Time of Visit: .../.../... Hour: ... : ...		
Clinical Features	Definition	Score
General condition		
Dehydration	Moderate to severe dehydration, increased skin turgor (> 2 seconds)	3
Headache	Severe persistent headache	2
Fever	Body temperature (axillary measurement) > 38°C, exclude infectious etiologies	1
Cardiovascular system		
Myocarditis	Stabbing chest pain, dysrhythmia, elevated cardiac enzymes (troponin, CPK-MB), congestive heart failure (edema, dyspnea and hepatic congestion), fever	5
Dysrhythmia	ST-T changes in precordial leads, QT prolongation, bundle branch block, arterial fibrillation	4
Bradycardia	Heart rate < 60 beats/min	3
Hypertension	140 mmHg < SBP or 90 mmHg < DBP	3
Sinus tachycardia	Heart rate > 100 beats/min, sinus rhythm	2
Neurologic system		
Increased body secretions	Diaphoresis, sialorrhea (increased salivation), lacrimation (excessive secretion of tears), bronchorrhea, involuntary ejaculation	3
Chills / Muscle cramping	Subjective feeling of coldness associated with shivering or shaking, involuntary contraction and spasm of muscles	3
Restlessness	Inability to remain at rest, feeling of aggravation	3
Generalized pain	Subjective feeling of pain in the body especially in the trunk (chest or back pain)	3
Whole limb pain	Pain in the entire affected limb	2
Confusion / Hallucination	Impaired orientation and consciousness / A profound distorted perception of reality typically accompanied by powerful sensory impulses	2
Mydriasis	Abnormally dilated pupils	2
Localized pain	Subjective pain at the wound site	1
Respiratory system		
Pulmonary edema	Shortness of breath, restlessness, pale skin, sweating, leg edema, air hunger, grunting, blunting of costophrenic angles and pleural effusions in chest X-ray	5
Dyspnea	20 < breaths per min, chest tightness	3
Renal system		
Acute renal failure	Rise of serum creatinine, oliguria	5
Oliguria	Urine output < 400-500 mL/24 h in adults, < 0.5 mL/Kg/h in children	1
Gastrointestinal system		
Ileus	Abdominal distension, absence of bowel sounds, no gas passing, constipation	5
Abdominal tenderness / rigidity	Pain that is felt after applying pressure on the abdomen. Guarding of abdominal muscles	3
Vomiting	Involuntary, forceful expulsion of the stomach contents	3
Abdominal Pain	Subjective pain in the abdominal region	2
Nausea	Feeling of uneasiness and discomfort in the upper stomach with an involuntary urge to vomit	1
Cutaneous		
Dermal necrosis	Swelling, discoloration and severe damage of skin and subcutaneous tissue	3
Periorbital edema	Marked swelling in the tissues around the eye	1
Flushing	Marked redness of skin especially in the face	1
Regional lymphadenopathy	Pain, tenderness, and swelling of regional lymph nodes in vicinity of the bite site	1
Laboratory findings		
Metabolic acidosis	pH < 7.35, HCO ₃ ⁻ < 24 mmol/L	4
Hyperkalemia	5.5 mEq/L < K	3
Hypokalemia	K < 3.5 mEq/L	2
Leukocytosis	> 11000 white blood cells/dL	1
Increased serum CPK	190 IU/L in men, 165 IU/L in women < CPK	1
Total score		

Figure 1. *Latrodectus* Envenomation Severity Score

CPK: creatine phosphokinase, SBP: systolic blood pressure, DBP: diastolic blood pressure
Upper limit of CPK in various commercial kits may be different.

Application of the index in practice and research

The proposed version of LESS includes 34 clinical items categorized in 7 organ systems. Although the LESS has a theoretically possible range of 0 to 87; in practice and according to our experience, the presence of all clinical effects is an impossible event. Furthermore, some clinical items can occur independently or in the complex of a complicated feature. In this situation, both items can be scored. For example, increased creatine phosphokinase (CPK) can be present isolatedly or in the set of myocarditis. Hence, both features should be scored in a time unit if the other characteristics of myocarditis (i.e. dysrhythmia, chest pain, heart failure) are present. For sequential measurements of severity during hospitalization, only active features should be scored in a time unit (and not resolved ones or the ones that were present prior to admission and currently undetectable). For example, myocarditis is not scored after resolving dysrhythmia, chest pain and heart failure, though the CPK is still high. In this situation, the item of Increased CPK should still be scored. The severity of envenomation in a time unit is the sum of scores of the existing clinical items. A higher score indicates a more severe case.

DISCUSSION

Latrodectism is a condition with intense clinical presentation that is mostly resolvable with proper treatments while very rarely results in death (2,3). Northeast part of Iran (Khorasan) is an endemic environment for Mediterranean black widow spider or *Latrodectus tredecimguttatus* (2,3,16,18). Its venom that mostly contains neurotoxins can induce neurotransmitter release from nerve endings and consequently facilitate calcium influx into the presynaptic neuron that leads to massive release of acetylcholine at the neuromuscular junction (1,19). This induces direct neurologic effects and reactive inflammatory responses. The severity of reactions and the envenomation syndrome in general will be lessened throughout the time. Nevertheless, an effective treatment can shorten this duration (8,9). However, whether the current recommended treatments such as analgesics and antivenom are meaningfully efficient on improving the patients and reducing the hospital stay or not have been subjects of controversy (10). In previous research done for evaluating the effectiveness of treatments for latrodectism, only scales for measuring the severity of an isolated clinical effect were used (9-11). This approach can be misleading, because the whole picture of the envenomation syndrome is neglected and not assessed. In the present study, a severity index for assessment of possible clinical manifestations of widow spider bite (in human subjects) has been developed for the first time. The scores have been allocated based on clinicians' global judgment on prognosis of widow spider victims. The Delphi process utilized in this evaluation assures that the resulting index represents the consensus of a group of experts in treating and research on widow spider bite envenomation (12,13).

In this measure, acute renal failure, myocarditis, pulmonary edema and ileus received the highest scores, though they are rare consequences of widow spider bite

(4,5,20-23). However, they are potentially life-threatening for the victims. One of the deaths due to *Latrodectus* envenomation reported in Mashhad had developed ileus (3). Despite acute renal failure and myocarditis in latrodectism have been shown to be reversible, they entail more aggressive treatments and longer duration of hospitalization (4,5,22,23). Moreover, myocarditis due to widow spider bite caused one death in Madagascar; however, it was mainly due to limited facility (24). On the other hand, increased CPK that is a more common phenomenon in *Latrodectus* envenomation was among the items receiving the lowest score. The reason was that the rise of CPK in widow spider bite even in very high levels is simply resolvable and is unlikely to be clinically important or contribute to the rhabdomyolysis or acute renal injury (3,8).

In the clinical practice, the management of *Latrodectus* envenomed patients is not dependent on the availability of the index for describing the severity of envenomation. However, the index can help junior physicians not to forget examining all the possible features of latrodectism. Hence, it can assist as a useful teaching tool for less experienced clinicians. In addition, the index can better describe and classify the profile of a series of patients and can serve as a reliable tool for comparing series of patients at different centers and in different published studies. Moreover, the LESS can be applied as a monitoring tool for assessment of worsening or improvement of the patient during admission. A scoring system that reliably monitors the clinical course would be able to provide purposive comparisons among different treatment approaches (25).

LIMITATIONS

The proposed version of the LESS index presented in this article has been mainly based on clinicians' judgment. This represents only the initial step of validation. This necessitates evaluation of the score validity by application of the index on widow spider victims in prospective studies. Moreover, the scores of some clinical items might be overestimated or underestimated by the panel members and thus calculating value of the score of each clinical item based on patients' prognosis in further studies is necessary. In this study, opinions and recommendations of experts in treating black widow spider bite, endemic in Khorasan region, were applied to develop the index. Participation of experts in *Latrodectus* envenomation from other parts of the world would probably gave more comprehensive results.

CONCLUSION

The LESS is a new assessment tool that is designed to more objectively evaluate the severity and progression of envenomation in victims of widow spider bite. The prognostic-ability, reliability and sensitivity to change of the index should be investigated in future studies.

ACKNOWLEDGMENT

The authors would like to thank Dr. G. A. Zare, Dr. H. Khosrojerdi, Dr. O. Mehrpour, Dr. A. Ghassemi Toussi, Dr. B. Dadpour, Dr. Z. Oghabian, Dr. M. Maleki, Dr. K. Ghasempouri, Dr. A. Gharaie, Dr. M. Vahabzadeh and

Dr. M. Khadem-Rezaiyan for their kind cooperation and recommendations.

Conflict of interest: None to be declared

Funding and support: None

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