J Surg Med. 2019;3(9):676-680.
DOI: 10.28982/josam.621050

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of changes in perfusion index in patients with cytotoxic tissue damage after snake bite: A prospective cohort study

Yılan ısırması sonrası sitotoksik doku hasarı olan hastalarda perfüzyon indeks değerindeki değişimlerin değerlendirilmesi: Prospektif kohort çalışma

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Ethics Committee Approval: Ethics committee of Harran University approved the study (Approval No.: 13.07.2017, meeting number 07 and decision number 24).
Etik Kurul Onayı: Harran Üniversitesi Etik Kurulu çalışmayı onayladı (Onay No: 13.07.2017, toplantı sayısı 07 ve karar numarası 24).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/21/2019
Yayın Tarihi: 21.09.2019

Abstract

Aim: Pain, edema, and heat loss that develop and gradually increase in the extremities following a snake bite reduce microcirculation. The perfusion index indicates the intensity of the pulsatile signal relative to the nonpulsatile signal. The aim of this study was to measure the changes in perfusion index (PI) in the extremities of patients suffering from a snake bite who are treated in an intensive care unit, to detect early ischemia or necrosis in the affected organ, and to investigate the effectiveness of the administered antivenom.

Methods: Twenty patients admitted to our hospital with cytotoxic swelling of the upper or lower extremities after a snake bite were included in this prospective cohort study. Initial treatment was provided to the patients based on the snake bite treatment protocol. PI values of the affected extremity of each patient were measured for 24 hours using a finger probe and compared with the unaffected extremity in the same region. Patient age, gender, bites, antivenom administration times, and complications were also recorded and compared.

Results: Of all patients, 13 (65%) were male and 7 (35%) were female. The mean age of the patients was 37.5 (14.15) years. Eight patients (40%) were bitten in the lower extremity, and 12 patients (60%) were bitten in the upper extremity. PI values measured at the 19th, 23rd, and 24th hours were significantly higher in the affected extremity than in the unaffected extremity (P=0.043, P=0.049 and P=0.018, respectively). PI values measured at the 20th, 21st, and 22nd hours were insignificantly higher in the affected extremity than in the unaffected extremity (P=0.088, P=0.096 and P=0.085, respectively). An increase in the ratio between the PI of the unaffected extremity and that of the affected extremity was associated with a decrease in complications. One patient who had a snake bite in the right upper extremity developed necrosis and another patient developed compartment syndrome.

Conclusion: PI is a rapid, painless, and continuous measurement that provides clinicians with valuable information on both the effectiveness of the antivenom and perfusion of the extremity. Patients with local reactions such as swelling and bruising should be monitored for at least 24 hours, and clinicians should pay attention to the development of compartment syndrome or tissue necrosis in the following hours.

Keywords: Snakebite, Antivenom, Perfusion index, Venom

Öz

Amaç: Yılanın ısırması sonrası ekstremitede başlayan ve giderek artan ağrı, ödem ve ısı azalması mikrosirkülasyonu azaltmaktadır. Perfüzyon indeks pulsatil sinyalin pulsatil olmayana göre nabız şiddetini belirtir. Bu çalışmada Yoğun bakım ünitesinde takip edilen yılan ısırmasına maruz kalan hastaların ekstremitesinde perfüzyon indeksi (PI) değerindeki değişimlerin ölçülmesini; etkilenen organdaki erken dönem iskemi veya nekrozu tespit etmeyi ayrıca verilen antivenomun etkinliğini araştırmayı amaçladık.

Yöntemler: Hastanemize üst veya alt ekstremitelerinin yılan ısırığından sitotoksik şişmesi ile başvuran 20 hasta bu prospektif kohort çalışmasına dahil edildi. Hastalar yılan ısırması tedavi protokolü ile ilk tedavileri yapıldı. Her hastanın etkilenmiş ekstremitesi, parmak probu yardımıyla 24 saat boyunca PI ölçümleri yapıldı ve aynı bölgedeki etkilenmemiş ekstremite ile karşılaştırıldı. Hastaların yaşları, cinsiyetleri, ısırıkları, antivenin alma zamanları ve komplikasyonları kaydedildi ve karşılaştırıldı.

Bulgular: Hastaların 13'ü (%65) erkek, 7'si (%35) kadındı. Hastaların ortalama yaşları 37,5 (14,15) idi. 8 hasta (%40) alt ekstremiteden, 12 hasta (%60) ise üst ekstremiteden ısırığa maruz kalmıştı. 24 saat boyunca yapılan PI ölçümlerinde ve her iki ekstremite bölge ölçüm oranlarında sağlam ekstremite lehine olmak üzere 19., 23. ile 24. saatlerde istatiksel olarak anlamlı (Sırasıyla P=0,043, P=0,049 ve P=0,018); 20., 21. ve 22. saatte ise sınırda anlamlı sonuç bulunmuştur (Sırasıyla P=0,088 ve P=0,096, P=0,085). Etkilenmemiş ekstremitenin PI ile etkilenen ekstremitenin PI arasındaki orandaki bir artış, komplikasyonlardaki bir azalmayla ilişkilendirildi. Sağ üst ekstremite yılan ısırığına maruz kalan bir hastada nekroz, bir hastada da kompartman sendromu gelişti.

Sonuç: Klinisyene hem antivenomun etkinliği hem de ekstemite perfüzyonu konusunda değerli bilgiler sağlayan PI, hızlı, ağrısız ve sürekli ölçüm sağlayan bir ölçümdür. Şişlik ve morarma gibi lokal reaksiyonu olan hastalar en az 24 saat boyunca izlenmeli ilerleyen saatlerde kompartman sendromu veya doku nekrozu oluşmasına dikkat etmelidir.

Anahtar kelimeler: Yılan ısırması, Antivenom, Perfüzyon indeksi, Zehir

How to cite / Atıf için: Karahan MA, Büyükfırat E. Evaluation of changes in perfusion index in patients with cytotoxic tissue damage after snake bite: A prospective cohort study. J Surg Med. 2019;3(9):676-680.

Introduction

Bites of poisonous animals are a major cause of mortality and morbidity worldwide. Every year, more than five million people are bitten by snakes, resulting in approximately 20,000–25,000 deaths [1]. Because snake venom is a combination of many toxic proteins and enzymes, it is the most complex of all poisons. Snake venom contains low-molecular-weight peptides and numerous other components such as neurotoxins; cytotoxins; hemotoxins; glycoproteins; proteolytic, hydrolytic, and hyaluronidase enzymes; and metallic ions [2]. The enzymes present in the snake venom, which enter the human body after a snake bite, lead to the clinical picture associated with snake bite [3]. This clinical picture varies depending on individual factors and on whether the poison enters systemic circulation; and snake bite poisoning may be asymptomatic or may even result in mortality [4]. The main treatment modality for snake bite poisoning is systemic antivenom treatment. However, there are different opinions about the time of initiating the antivenom treatment and the dose to be administered. Although there is a consensus that the effectiveness of antivenom is sufficient against the systemic effects of the venom, its effectiveness against local effects is controversial [5].

Enzymes in snake venom cause edema and vasoconstriction. Ischemic damage starts in the bite area within the first 2 h due to the direct contact of the toxin with the tissues, leading to local tissue edema. Enzymes such as metalloproteinases cause capillary endothelial damage and cell apoptosis. Increased microvascular permeability, early leukocytosis, and increase in interleukin and tumor necrosis factor levels occur as part of the inflammatory response to this envenomation, all of which increase the painful swelling. Tissue necrosis may develop in approximately 10% of cases [6]. Myonecrosis may result from the toxic effects of snake venom proteins that directly cause necrosis without increasing compartment pressure. However, it may progress to compartment syndrome, which is a rare but fatal complication with symptoms such as severe pain, paresthesia, delayed capillary filling, pain in passive stretching, no pulse, and coldness [2].

Perfusion index (PI) is a continuous and non-invasive measurement of peripheral perfusion obtained using a pulse oximeter. PI indicates the percentage of the pulsatile signal relative to the nonpulsatile signal (pulse intensity). In other words, it enables the evaluation of the patient in terms of microcirculation by showing early real-time changes in blood flow [7].

The aim of this study was to measure the changes in PI in the extremities of patients suffering from a snake bite and being treated in an intensive care unit (ICU), to detect early ischemia or necrosis in the affected organ, and to investigate the effectiveness of the administered antivenom.

Materials and methods

The present study is a single-center, prospective, observational cohort study. The study was approved by the Harran University Faculty of Medicine Ethics Committee (13.07.2017, meeting number 07 and decision number 24) and conducted in the medical ICU of the Harran University Medical Faculty Hospital.

Patient selection

The study included 20 patients with upper or lower extremity swelling who were followed up in our ICU after a snake bite between August 2017 and August 2019. Written informed consents were obtained from all patients. Flow diagram of the study is shown in Figure 1.

Patients who refused to participate in the study, pregnant women, patients with minimal or no swelling in the affected extremity, patients who were bitten in anatomical sites other than extremities or had predominantly hemotoxic or neurotoxic envenomation, patients who were hospitalized for <1 day, patients with known peripheral vascular disease or hepatic cirrhosis, and patients aged <18 years were excluded from the study.

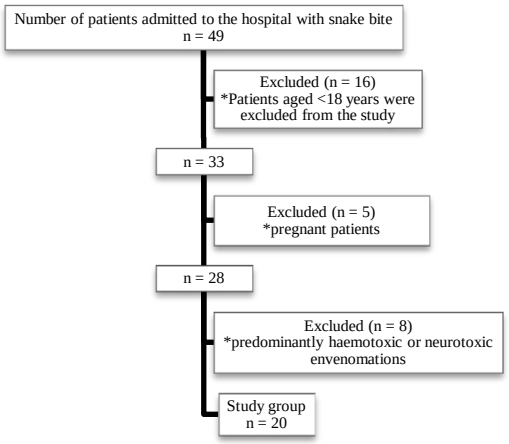

Figure 1: Flow diagram of the study

Measurement method

Twenty patients who were exposed to snake venom and followed up in the ICU were followed with 3-lead electrocardiography, peripheral O_2 saturation, and non-invasive blood pressure monitoring as part of standard evaluation.

All patients underwent routine blood tests and basic standard treatment such as the administration of analgesia, intravenous fluids, and tetanus toxoid. Bite wounds were washed with soap and water and the extremities immobilized. During this period, 10 mL Polysera snake anti-serum (Vetal Serum Manufacturing Limited, Adıyaman, Turkey) in 150 mL of saline, along with steroids and antihistamines, was administered intravenously on the basis of algorithms to ensure that one or two vials would last for 45 min [8].

After the initial treatment, finger probes were placed on the patients and the non-invasive Masimo Radical-7 Pulse co-oximeter (Masimo Corporation, Irvine, USA) measuring device was used to measure PI values both at the area bitten by the snake and at the corresponding unaffected area of the opposite extremity. Measurements were performed when the blood pressure cuff was not inflated. The ICU was air-conditioned, and room temperature was maintained at about 25°C. Patients were not provided additional oxygen therapy, and it was assumed that the fraction of inspired oxygen was 21%. Whenever the device issued a “low perfusion” alarm, the measurements were repeated on another finger for confirmation purposes. Measurements were recorded at 1-h intervals for a period of 24 h.

The study was initiated after recording the basal PI values of patients. In addition to the demographic data of the patients, we recorded the time elapsed between snake bite and antivenom administration, the extremity area that was bitten, the observed complications, and the ratio between hourly measurements of the PI of the unaffected extremity and that of the affected extremity.

Statistical analysis

Statistical analysis was performed using the IBM SPSS software (Armonk, NY, USA). Consistent factors were presented as mean (standard deviation) (SD) or median (interquartile range) and analyzed with Mann–Whitney U test. All factors were presented as frequency (percentage), and chi-square test or Fisher's exact test were used when necessary. Multiple logistic regression analysis was used to determine the independent predictors of achievement, and logistic regression was used to model independent predictors. All statistical tests were two-sided, and $P<0.05$ was considered as statistically significant.

Results

Patient characteristics

The present study comprised 20 patients [13 (65%) men and 7 (35%) women; mean age, 37.5 (14.15) years]. The mean age of female patients was 36.14 (15.35) years and that of male patients was 40.53 (13.99) years. Of all, 85% patients were farmers, whereas the rest belonged to different occupational groups. Eight patients (40%) were bitten in the lower extremity and 12 (60%) in the upper extremity. Three of the lower extremity bites were on the left side (37.5%), whereas five were on the right side (62.5%). Seven of the upper extremity bites were on the right side (58.3%), whereas five were on the left side (41.7%). One patient with snake bite in the right upper extremity developed necrosis and another patient developed compartment syndrome. Patients were brought to the emergency department in an average time of 1.5 (0.5–2.5) h. The mean time between snake bite and antivenom administration was 2 h.

Perfusion index values

PI values measured at the 19th, 23rd, and 24th hours were significantly higher in the affected extremity than in the unaffected extremity ($P=0.043$, $P=0.049$ and $P=0.018$, respectively). PI values measured at the 20th, 21st, and 22nd hours were insignificantly higher in the affected extremity than in the unaffected extremity ($P=0.088$, $P=0.096$ and $P=0.085$, respectively) (Table 1, Figure 2). On examining PI measurements at each time point, it was found that the PI value of 4.33 at the 1st hour in the unaffected extremity decreased to 3.98 at the 6th hour ($P=0.009$) and to 3.29 at the 24th hour ($P=0.05$). Furthermore, PI value significantly decreased from 5.12 at the 12th hour to 3.29 at the 24th hour ($P=0.02$). In the affected extremity, the PI value decreased from 5.84 at the 1st hour to 1.76 in 5 hours ($P=0.05$). The decrease in PI value from 4.39 at the 12th hour to 1.76 at the 24th hour was also significant ($P=0.012$) (Table 2).

Multiple logistic regression

In the regression analysis performed to investigate whether complications developed in the patients included in this study, complications were considered as a dependent variable. The results of the regression analysis are shown in Table 3.

Based on the regression analysis results, the likelihood of complications was found lower in males. There was a negative correlation between the affected extremity and complications. The likelihood of complications increased significantly when the upper right extremity was affected, and decreased when the upper left, lower left, and lower right extremities were affected. There was a positive correlation between the unaffected extremity/affected extremity (UE/AE) PI ratio and complications. As the ratio increased, the occurrence of complications decreased. We also investigated the effect of the time of antivenom administration on the likelihood of developing complications. As the time elapsed between snake bite and antivenom administration increased, the likelihood of complications increased.

Table 1: PI changes in the extremities within 24 hours after snake bite

Hour	Affected extremity		Unaffected extremity		Ratio	*P*-value
	Mean	SD	Mean	SD	Mean	0.204
1	5.84	3.64	4.33	2.62	2.04	0.204
2	5.34	3.27	3.92	3.06	1.90	0.326
3	3.39	2.87	3.80	2.25	1.66	0.453
4	4.73	2.52	4.52	4.09	1.94	0.326
5	5.67	2.38	3.80	2.51	1.86	0.057
6	4.19	2.79	3.98	2.67	1.20	0.885
7	3.52	2.71	3.13	1.26	1.16	0.602
8	4.19	2.73	5.34	3.8	1.52	0.326
9	4.41	2.3	4.58	2.51	2.21	0.954
10	4.18	2.75	4.46	2.48	1.14	0.470
11	3.16	2.58	4.12	2.56	0.98	0.729
12	4.39	3.23	5.12	4.01	1.03	0.603
13	4.02	2.14	4.31	2.59	1.30	0.954
14	3.27	1.62	5.04	2.4	0.86	0.094
15	4.40	2.22	4.63	2.61	1.11	0.908
16	2.95	0.88	3.13	1.27	1.39	0.795
17	3.24	0.71	3.37	2.01	1.64	0.312
18	2.74	0.69	3.62	1.82	1.09	0.224
19	2.51	0.35	2.92	1.19	1.42	0.043
20	3.03	1.44	3.26	1.28	1.15	0.088
21	2.74	1.01	2.99	1.36	1.13	0.096
22	2.48	1.00	2.89	1.21	1.08	0.085
23	1.99	0.87	3.21	1.46	0.73	0.049
24	1.76	0.81	3.29	1.67	0.75	0.018
P-value	0.002		0.012		0.02	

SD: Standard deviation

Table 2: PI changes in the extremities between two time points

	Unaffected extremity *P*-value	Affected extremity *P*-value
6th h PI−1st h PI	0.009	0.875
12th h PI−1st h PI	0.059	0.366
24th h PI−1st h PI	0.002	0.050
12th h PI−6th h PI	0.937	0.070
24th h PI−12th h PI	0.020	0.012

h: hour, PI: Perfusion Index

Table 3: Multiple Logistic Regression Results

Variable	Coefficient	SD	t-Statistic	*P*-value
Complication	0.9846	0.1235	7.9718	<0.001
Gender	−0.7062	0.0063	−11.1682	0.0002
Affected Extremity	−0.0405	0.0219	−1.8478	0.0662
Patient	0.0313	0.0153	2.0520	0.0416
UE/AE	0.0290	0.0157	1.8502	0.0659
Antivenom Time	0.4160	0.0526	7.9023	0.0004
Age	0.0186	0.0043	4.2885	0.0003
Complication Time	0.0010	0.0029	0.3363	0.7370
R-squared	0.6099			
Adjusted R-squared	0.5951			
F-statistic	41.1036			
P-value	<0.001			

SD: Standard deviation, UE/AE; Unaffected extremity/Affected extremity

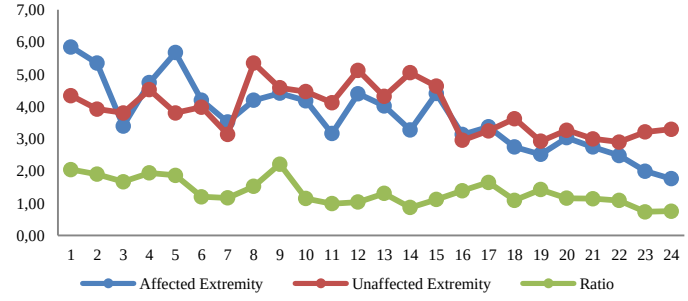

Figure 2: Changes in PI over time (affected extremity, unaffected extremity, ratio*)

Discussion

This is a single-center, prospective, observational cohort study that is the first to evaluate the changes in PI, the presence of early ischemia and necrosis in the affected organ, and the effectiveness of the administered antivenom among patients with increasingly painful swellings in the upper and lower extremities following snake bites, for which antivenom treatment was administered. Our results indicate that PI measurements can be used to evaluate the severity of snake bite in the extremities. PI values in the bitten extremity decreased, especially after 19 hours, compared with those in the contralateral extremity.

Snake bites in Turkey are mostly encountered in the Southern and Southeastern Anatolia regions of the country and represent an important cause of morbidity and mortality [4]. The venom of the snakes belonging to the Viperidae family, most commonly implicated in snake bites in Turkey, is known to be both cardiotoxic and myotoxic and contains hyaluronidase, phospholipase A, and various proteases that lead to tissue disruption [9]. When a snake of the Viperidae family bites, hyaluronidase in the venom accelerates the spread of the venom in the tissues. Myonecrosis is mainly caused by the effect of myotoxic phospholipase A2. Phospholipase A2 induces hemolysis by converting lecithin to lysolecithin, and hemorrhagin causes rapid hemorrhagic edema by destroying the inner endothelium that covers the blood vessels in the bite area. In addition to myonecrosis, blood vessel integrity is affected. Metalloproteinases cause basal hydrolysis of the basal membrane of capillaries, particularly of type IV collagen, and weaken the mechanical stability of microvessels [3,10].

Systemic antivenom treatment is the main treatment modality for patients with snake bite envenomation. There are different opinions regarding the time of initiation of antivenom treatment and the dose to be administered. In a series in which Viperidae bite cases were treated, it was reported that the complication rates and severity increased when antivenom treatment was inadequate [11-13]. Although complication rate is lower when the appropriate antivenom treatment is applied, it should be kept in mind that various complications can be encountered in envenomation cases associated with snake bites. The most common complication is necrosis, with a reported rate of 10% [3]. On the other hand, as the venom activity increases, the mediators of vasodilatation increase as well, and the increase in vasodilatation and vascular permeability increase the pressure inside and outside the compartment. Consequently, even if the necrotic period is not triggered due to insufficient circulation alone, the lysis and degradation caused by the venom increase and may trigger compartment syndrome. Therefore, strict follow-up is necessary for compartment syndrome that may occur in patients with snake bites on the extremities, and fasciotomy should be performed to achieve full functional recovery when compartment syndrome is clinically suspected [2].

To date, no rapid, painless, and objective methods have been developed that can help keep track of the complex clinical picture observed in the extremities following a snake bite and that can provide valuable information to the clinician about the extent of soft tissue damage. The only current method that has been proposed for these purposes is ultrasound evaluation [14,15]. In relevant studies, the exposed extremity of patients was evaluated at the point of maximum swelling, and the thickness of the tissue structures was compared between the affected (subcutaneous tissue or muscle compartment) and unaffected extremities. Imaging was focused on identifying the depth and location of tissue edema, the presence of fluid accumulation, the evidence of muscle fasciculation, and fascia and tendon lesions. However, ultrasound evaluation was performed only once, after admission, for the patients included in these studies. Repeat ultrasound measurements were not performed. As the findings depend on personal interpretations, it is possible to overlook or misinterpret fine sonographic findings. Considering all these findings and the circulatory mechanisms mentioned above and taking into account the needs of the clinicians, PI measurement may be a preferable method for evaluating snake bite cases because it is a relatively new predictor of blood pulsatility in the extremities that is calculated using the infrared spectrum within the scope of the plethysmography waveform procedure. It is a simple, cost-effective, and non-invasive method for evaluating peripheral perfusion determined using the percentage of pulsatile-to-nonpulsatile blood flow in the extremities. PI reflects the state of microcirculation, which is intensely stimulated by sympathetic nerves, and is thus influenced by factors that cause vasodilatation or vasoconstriction of the microvascular system [16]. There are reports showing that PI measurement in ICU is effective in evaluating different patient groups of different ages [17-19].

In this study, we performed 24 hour-PI monitoring of the affected area of the extremity that was exposed to the snake bite and the corresponding unaffected area of the opposite extremity. In our follow-up results, we observed a significant decrease in PI values at the end of 24 hours compared with those at the 1st hour in both areas. Although PI measurements showed variability in the first 12 hours, we found a significant decrease in PI values in both extremities. PI was insignificantly higher in the unaffected extremity between the 12th and 19th hours. On the other hand, PI was significantly higher in the unaffected extremity in the next three measurements, and a limited significant change was observed in the last three measurements. Although there is no definitive information in the literature regarding the duration of antivenom activity, there is information indicating that the local effectiveness of antivenom, such as in the extremities, is minimal [5]. We attributed the decrease and increase in PI values within the first 12 hours to the positive effective of the administered antivenom. We believe that the changes observed after 12 hours are due to decreased effectiveness of the antivenom.

UE/AE PI ratio decreased significantly at the end of the 24th hour, compared with that at the 1st hour. The decrease was especially prominent after the 19th hour. There is a positive correlation between the UE/AE PI ratio and complications. As this ratio increases, the complications decrease. One patient developed necrosis on the second day of hospitalization, and another patient developed compartment syndrome on the third day.

Limitations

One of the limitations of the present study is that PI measurements were obtained only in the first 24 hours, despite

the time of occurrence and duration of the complications. Another limitation is that the PI values obtained in the present study are valid only for the venom of the snakes observed in Turkey. We could not determine how PI measurements would change in response to the venom of other snake species.

Conclusion

We propose that PI measurements be used to monitor the extremities with snake bite and the resulting swelling. It is a rapid, painless, and continuous measurement that provides the clinician with valuable information on both the effectiveness of the antivenom and perfusion of the extremity. Patients with local reactions such as swelling and bruising should be monitored for at least 24 h, and clinicians should be careful against the occurrence of compartment syndrome or tissue necrosis.

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Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine