

RESEARCH LETTER

Evaluation of The effects of Anti-Inflammatory Drugs on Local and Systemic manifestations of snakebite: A cross-sectional study

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Received: 15 March 2021 | Revised: 25 May 2021 | Accepted: 25 May 2021 | Published: 25 May 2021

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ABSTRACT

Although the predominant treatment for snakebite is the antivenom, other treatments are also considered. We studied the effects of single or multiple-doses of anti-inflammatory drugs on local, systemic and laboratory findings of the snakebite victims. In this cross-sectional study, 101 patients (90 male: 89.1%) with snakebite envenomation who were admitted to the Medical Toxicology Center of Khorshid Hospital, Isfahan, Iran, were investigated. One group (35 patients: 34.7%) received a single-dose of anti-inflammatory drugs containing chlorpheniramine (10mg intramuscular injection) with cimetidine (200mg intravenous injection) or ranitidine (50mg intravenous injection) plus hydrocortisone (100mg intravenous injection). The other 55 patients (54.5%) received multiple doses of the same drug combination every 8hr until the symptoms resolved. Local, systemic symptoms and laboratory findings on admission, and during 24hr and 48hr of admission, were recorded. The frequency of the localized signs of inflammation ($p=0.03$), swelling ($p<0.001$) and bruising ($p<0.001$) showed a significant difference between the two treated groups. In addition, the recovery time in the patients who received multiple doses was faster ($p<0.001$). There was no significant difference in any of the systemic signs, laboratory findings or the outcome between the patients in the various groups during hospitalization. Our data indicate that the administration of multiple doses of anti-inflammatory drugs had a greater effect on reducing local symptoms of snakebite including inflammatory manifestations.

KEYWORDS: Envenomation, Snakebite, Anti-Inflammatory Drugs, Symptoms

INTRODUCTION

Snakebite is a common problem in tropical climates with incidents occurring in almost every country in the world (Nelson et al, 2019). The specific treatment for snakebite is the use of antivenom, which itself has early and delayed side-effects. Injection of antivenom up to thirty minutes after a snakebite is very effective for preventing local edema, toxins neutralization and inactivation of inflammatory mediators. However, local tissue damage is not well prevented by this treatment,

especially since anti-venom is often prescribed with a delay of few hours after the snakebite (Nelson et al, 2019). Due to the low effect of delayed antivenom therapy in the treatment of local edema in patients bitten by snakes, other types of anti-inflammatory therapies have been considered. Concomitant administration of antivenom and anti-inflammatory drugs, such as some herbal medication, corticosteroids with different potency and duration of action has been suggested in the treatment of localized tissue reactions evoked by toxins (Olivo et al, 2007, Strauch et al, 2019).

In the case of pain induced by venom, an analgesic could be administered (Di Nicola et al, 2021). In a study by Olivo et al, indomethacin with or without antivenom was effective in inhibiting edema caused by the venom. However, the results showed that the combination of dexamethasone and the antivenom was more effective providing a longer effect on inhibiting edema than indomethacin and antivenom (Olivo et al, 2007). This effect may be due to the indirect activity of the antiphospholipase by dexamethasone, which inhibits the biosynthesis of mediators in cyclooxygenase and lipoxygenase pathways (Barnes et al, 1993). In another study conducted in Brazil on mice, the combination of antivenom and dexamethasone showed the highest inhibitory effect when injected 45 minutes after the *Bothrops jararaca* snake venom in mice. However, in this study, the antivenom or anti-inflammatory drugs alone were ineffective (Araújo et al, 2007). In addition, some studies have shown that pretreatment of animals with anti-inflammatory drugs can significantly reduce edema (De Faria et al, 2001). In a study conducted in India in 2008, it was suggested that oral antihistamines, such as chlorpheniramine, given for five days help reduce delayed effects of the antivenom treatment (Ahmed et al, 2008). Also, a recent review article, has suggested that anti-inflammatory drugs should be avoided (Di Nicola et al, 2021) in snakebites treatment; however, several specialists routinely use these treatments.

Although the above studies have been performed on the effect of antivenom association with anti-inflammatory drugs, no research has studied the effect of repeated anti-inflammatory drugs in snakebite victims. Therefore, this study was performed to compare the effects of single-dose versus multi-dose of corticosteroids and antihistamine drugs on local and systemic symptoms and laboratory parameters in victims of snakebites between 2013 and 2018 year in Iran.

METHODS

In a cross sectional study, after receiving the ethics code (IR.MUI.MED.REC.1397.145), the information related to all patients with snakebites hospitalized in the Khorshid Hospital from 2013 to 2018 were reviewed. Patients who had snakebites in the last 6hr in the upper or lower extremities who received single-dose or multiple- dose corticosteroids and antihistamines in addition to antivenom were included in the study. Patients who were treated with glucocorticoids or non-steroid anti-inflammatory drugs for any reason, had a dry bite, or had received antivenom before entrance to the emergency department were excluded. The single-dose group recipients received a single-dose of the following drugs: a 10mg intramuscular injection of Chlorpheniramine, a 100mg intravenous injection of Hydrocortisone and a 200mg intravenous injection of Cimetidine or a 50mg intravenous injection of Ranitidine. The multiple-dose group patients received the same drug combination every 8hr until the symptoms resolved.

Symptoms of snakebite, including local symptoms and systemic symptoms, were assessed and recorded.

Complicated recovery was defined as amputation and compartment syndrome following snakebites.

These variables were recorded daily in the data collection form in the first 24hr and then in 48 and 72hr after and until the last day of hospitalization, and improvement of local and systemic symptoms were recorded. After data collection, the variables were analyzed using SPSS software (version 23) and repeated measures ANOVA, Chi-square or Fisher Exact, independent t-test and Cochran statistical tests. P values less than 0.05 were considered as significant differences.

RESULTS AND DISCUSSION

A total of 101 patients were hospitalized during the study period. Snakebite events were more common in men (89.1%) than in women (10.9%). The mean age of patients was 36.35 years; the youngest patient was 4.5 years and the oldest was 73 years old. A study, which was conducted in Morocco and published the results in 2018, showed that 58.7% of all snake bites were related to men and the mean±SD age of snake bites was 25.48 ±17.25 years (Chafiq et al, 2018).

Thirty-five patients received single-dose treatment (34.7%) with a mean age of (35.76 ±12.31) years and 55 patients (54.5%) received multiple-dose treatment with a mean age of (38.94 ±14.53) years (p=0.29). In terms of gender, 31 men (34.4%) and 4 women were included in the single-dose group and 48 men (58.8%) and 7 women participated in the multiple-dose group (p=0.83). The results revealed that among the local symptoms, inflammation (p=0.03), swelling (p<0.001) and bruising (p<0.001) were significantly different between the groups. The patients who received the compound in multiple doses recovered better and swifter (p<0.001). The frequency distribution of local symptoms in the groups receiving single-dose and multiple-dose anti-inflammatory drugs is shown in Table 1. In addition, in the daily comparison, the rate of first-day improvement of symptoms such as pain and bruising was higher in the group receiving multiple-doses (p<0.001).

The frequency distribution of systemic symptoms of snakebite in the two groups during hospitalization is shown in Table 2. There was no significant difference in any of the systemic symptoms of snakebite between the recipients of single dose and multiple doses of anti-inflammatory drugs on admission time (p>0.05). Loss of consciousness, local bleeding and rhabdomyolysis showed a significant improvement in the multiple-dose treatment during the study (p<0.001). Nevertheless, in the single dose group, such symptoms as tachycardia, disseminated intravascular coagulation (DIC) and renal failure had significantly improved during the study (p<0.001).

According to extensive research by the researchers in reputable international databases, no study has been conducted to compare the effects of single-dose and multiple dose anti-inflammatory drugs on snakebite symptoms. Systemic steroids have also been used and have been shown to provide positive results in local

Table 1: Frequency distribution of local symptoms after single-dose or multiple-dose administration of anti-inflammatory drugs during the study.

variables N (%)	Type of treatment	On admission	1st day	2nd day	3rd day	4th day	5th day	6th day	P1	P2
Pain	Single-dose	23 (65.7)	16	3	1	0	0	0	0.006	0.33
	Multiple-dose	41 (74.5)	36	28	15	4	3	0	<0.001	
P3		0.96	0.03	0.10	0.16	1.00	1.00	1.00		
Inflammatory symptoms (warmth and redness other than swelling)	Single-dose	8 (22.9)	2	1	1	0	0	0	0.42	0.03
	Multiple-dose	25 (45.5)	16	11	4	1	1	1	<0.001	
P3		0.03	0.07	0.10	0.42	1.00	1.00	1.00		
Swelling	Single-dose	11(31.4)	8	4	1	1	0	0	0.006	<0.001
	Multiple-dose	4(76.4)	37	24	15	2	2	1	<0.001	
P3		>0.001	0.29	0.10	0.42	0.42	1.00	1.00		
Necrosis	Single-dose	0	0	0	0	0	0	0	-	0.13
	Multiple-dose	4 (7.3)	0	0	0	0	0	0	-	
P3		10.0	1.00	1.00	1.00	1.00	1.00	1.00		
Bruising	Single-dose	2 (0.7)	1	1	0	0	0	0	0.09	<0.001
	Multiple-dose	22 (40)	12	11	9	6	4	2	<0.001	
P3		<0.001	0.04	0.10	0.16	0.25	1.00	1.00		
Blister	Single-dose	0	0	0	0	0	0	0	-	0.07
	Multiple-dose	5 (9.1)	0	0	0	0	0	0	-	
P3		0.06	0.42	1.00	1.00	1.00	1.00	1.00		
P1: At the 5% level of the Cochran test										
P2: At the 5% level of Chi-square test										
P3: At the 5% level of the Mann-Whitney test										

Table 2: Frequency distribution of systemic symptoms of snakebite after single or multiple dose administration of anti-inflammatory drugs during the study.

Variables N (%)	Type of treatment	On admission	1 st day	2 nd day	3 rd day	4 th day	5 th day	6 th day	P1	P2
Bradypnea	Single-dose	0	0	0	0	0	0	0	-	0.42
	Multiple-dose	1 (1.8)	0	0	0	0	0	0	0.31	
Tachycardia	Single-dose	1 (2.9)	0	0	0	0	0	0	<0.001	0.20
	Multiple-dose	0	0	0	0	0	0	0	-	
Bradycardia	Single-dose	1 (2.9)	0	0	0	0	0	0	<0.001	0.20
	Multiple-dose	0	0	0	0	0	0	0	-	
Loss of consciousness	Single-dose	0	0	0	0	0	0	0	-	0.16
	Multiple-dose	3 (5.5)	2	1	1	0	0	0	<0.001	
Local bleeding	Single-dose	0	0	0	0	0	0	0	-	0.16
	Multiple-dose	3 (5.5)	0	0	0	0	0	0	<0.001	
Rhabdomyolysis	Single-dose	1 (2.9)	1	0	0	0	0	0	0.31	0.56
	Multiple-dose	3 (5.5)	2	2	0	0	0	0	<0.001	
DIC	Single-dose	1 (2.9)	0	0	0	0	0	0	<0.001	0.20
	Multiple-dose	0	0	0	0	0	0	0	-	
Renal failure	Single-dose	1 (2.9)	0	0	0	0	0	0	<0.001	0.20
	Multiple-dose	0	0	0	0	0	0	0	-	
P1: At the 5% level of the Cochran test										
P2: At the 5% level of Chi-square test										

Table 3: Evaluation of the recovery rate and mean length of hospitalization of patients by type of treatment.

Patients Outcomes	Single dose (N=35)	Multiple doses (N=55)	p-value
Uncomplicated Recovery N (%)	14 (15%)	22 (24%)	0.53
Complicated Recovery N (%)	15 (16%)	15 (16%)	
Death N (%)	0	1 (1%)	
Discharge with patient consent N (%)	6 (6%)	7 (7%)	
Average length of hospitalization (Mean±SD)	3.01±1.56	1.10±0.71	<0.001

symptoms (Watt, 1985). For example, a study in Brazil in 2017 compared the effects of antivenom treatment alone or with dexamethasone on the symptoms of snake-bitten mice, and showed that mice that received anti-venom with dexamethasone, edema and inflammation experienced a faster and better healing process. Also, samples which received antivenom with dexamethasone showed faster recovery of muscle necrosis (Barreto et al, 2017). On the other hand, venom and anti-venom complex can have mild to severe inflammatory effects (Nelson et al, 2019). A study in Sri Lanka on the prevention of antivenom side effects showed that treatment with only antihistamines can not prevent mild local anti-venom allergic symptoms (such as itching, fever, facial edema and urticaria) (de Silva et al, 2011).

Another study also showed that the use of hydrocortisone alone was not effective in reducing symptoms such as nausea, vomiting, bronchospasm and abdominal pain due to antivenom. However, concomitant use with chlorpheniramine has been shown to reduce the above symptoms (Gawarammana et al, 2004). Similar to the results of our study, according to a study, the effects of snakebites are due to the synergistic effects of different parts of the snake venom complex, and the use of drugs such as diphenhydramine and dexamethasone alone can prevent some complications such as edema, but these drugs can not prevent systemic and serious complications such as shock and death (Selistre et al, 1990).

Abnormal laboratory parameters were observed infrequently and only on the first day. There was no significant difference in any of the laboratory parameters of snakebite victims between the recipients of the single dose and multiple doses of anti-inflammatory drugs on admission and in the following days ($p>0.05$). An Australian study found that early (less than 6hr after the bite) and late (more than 6hr after the bite), injections of anti-venom had the same results in improving coagulation parameters (Churchman et al, 2010). Compared to the study in Australia, a study in Africa by Mion and colleagues found that in *Echis* snakebites, coagulation test levels improved much faster in people who received antivenom than in those who did not receive anti-venom (Mion et al, 2013).

Evaluation of the recovery rate and mean length of hospitalization of patients by type of treatment was presented in Table 3. There was no significant difference in the outcome between the two groups ($p=0.53$). However,

the mean duration of hospitalization was significantly lower in the multiple-dose group ($p<0.001$).

In summary, the results of our study showed that administration of multiple doses of anti-inflammatory drugs had a greater effect on reducing local symptoms of snakebite including inflammatory manifestations. We suggest a randomized clinical trial to compare the effects of single dose versus multiple doses of anti-inflammatory drugs on clinical manifestations of snakebite patients.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

This article is the result of the dissertation No. 397407 of Isfahan University of Medical Sciences. We would like to thank The Toxicology Department Personnel for their encouragement throughout this work.

REFERENCES

- Ahmed SM, Ahmed M, Nadeem A, et.al. 2008. Emergency treatment of a snake bite: Pearls from literature. *J Emerg Trauma Shock*, 1, 97-105.
- Araújo SD, De Souza A, Nunes F, et.al. Effect of dexamethasone associated with serum therapy on treatment of Bothrops jararaca venom-induced paw edema in mice. 2007. *Inflamm Res*, 56, 409-13.
- Barnes PJ, Adcock I, Spedding M, et.al. 1993. Anti-inflammatory actions of steroids: molecular mechanisms. *Trends Pharmacol Sci*, 14, 436-41.
- Barreto GNLS, de Oliveira SS, Dos Anjos IV, et.al. 2017. Experimental Bothrops atrox envenomation: Efficacy of antivenom therapy and the combination of Bothrops antivenom with dexamethasone. *PLoS Negl Trop Dis*, 11, e0005458.
- Chafiq F, Hami H, Mokhtari A, et.al. 2018. Geographical distribution of health indicators related to snake bites and envenomation in Morocco between 1999 and 2013. *Epidemiol Health*, 40, e2018024.
- Churchman A, O'Leary MA, Buckley NA, et.al. 2010. Clinical effects of red-bellied black snake (*Pseudechis porphyriacus*) envenoming and correlation with venom concentrations: Australian Snakebite Project (ASP-11). *Med J Aust*, 193, 696-700.
- De Faria L, Antunes E, Bon C, et.al. 2001. Pharmacological characterization of the rat paw edema induced by Bothrops lanceolatus (Fer de lance) venom. *Toxicon*, 39, 825-830.
- de Silva HA, Pathmeswaran A, Ranasinha CD, et.al. 2011. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS Med*, 8, e1000435.

- Di Nicola MR, Pontara A, Kass GE, et al. 2021. Vipers of Major clinical relevance in Europe: Taxonomy, venom composition, toxicology and clinical management of human bites. *Toxicology*, 453, 152724.
- Gawarammana IB, Kularatne SAM, Kumarasiri RP, et.al. 2004. Parallel infusion of hydrocortisone±chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites. *Med J Aust*, 180, 20-23.
- Mion G, Larréché S, Benois A, et.al. 2013. Hemostasis dynamics during coagulopathy resulting from Echis envenomation. *Toxicon*, 76, 103-109.
- Nelson LS, Howland MA and Lewin NA. 2019. *Goldfrank's toxicologic emergencies*, McGraw-Hill Education.
- Olivo RdA, Teixeira CF and Wallace JL. 2007. Role of cyclooxygenases in oedema-forming activity of bothropic venoms. *Toxicon*, 49, 670-677.
- Selistre H, Queiroz L, Cunha O, et.al. 1990. Isolation and characterization of hemorrhagic, myonecrotic and edema-inducing toxins from *Bothrops insularis* (jararaca ilhoa) snake venom. *Toxicon*, 28, 261-273.
- Strauch MA, Tomaz MA, Monteiro-Machado M, et al. 2019. Lapa-chol and synthetic derivatives: in vitro and in vivo activities against *Bothrops* snake venoms. *Plos one*, 14, e0211229.
- Watt Jr C. 1985. Treatment of poisonous snakebite with emphasis on digit dermatomy. *South Med J*, 78, 694-699.