Mannitol Therapy in Three Cases with Severe Edema Due to Snakebite: Case Report

Yılan Isırığına Bağlı Ağır Ödem Saptanan Üç Olguda Mannitol Tedavisi

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ABSTRACT We report successful mannitol therapy in three children with severe local edema secondary to snakebites. Three female children (Case 1: 4 years old; Case 2: 10 years old; Case 3: 12 years old) with severe local edema due to Vipera Xanthina bite on the extremities admitted to our hospital. Cases 2 and 3 had received inadequate antivenin, and they were referred to our clinic 24 hours later after the snakebite. Case 1 did not apply to a medical center within 24 hours after the snakebite. The envenomation of Case 2 was graded as two, and the others were graded as three. Cases 2 and 3 exhibited clinical signs of compartment syndrome. All cases were treated with mannitol monotherapy successfully, and they were discharged without any sequelae. In late admissions, mannitol solely seems to alleviate severe local edema secondary to snakebites.

Key Words: Snake bites; mannitol

ÖZET Yılan ısırığına bağlı ağır lokal ödem gelişen ve mannitol tedavisi ile düzelen üç olguyu sunuyoruz. Vipera Xanthina tarafından ekstremitelerinden ısırılan ağır lokal ödemli üç kız çocuk (Olgu 1: 4 yaşında, olgu-2: 10 yaşında, olgu-3: 12 yaşında) hastanemize kabul edildi. Olgu 2 ve 3 yetersiz antivenin tedavisi almıştı ve hastanemize yılan ısırığından 24 saat sonra sevk edilmişlerdi. Olgu-1 yılan ısırığı sonrasındaki 24 saat içinde bir sağlık merkezine başvurmamıştı. Olgu-2'nin zehirlenme düzeyi ikinci derece diğer olguların ise üçüncü derece olarak kademelendirildi. Olgu 2 ve 3 kopartman sendromunun klinik belirtilerini göstermekteydi. Tüm olgular mannitol monoterapisi ile başarılı olarak tedavi edildiler ve sekelsiz olarak taburcu oldular.Gecikmiş olgularda, yılan ısırığına bağlı ağır lokal ödemin tedavisinde mannitol tek başına etkili olabilmektedir.

Anahtar Kelimeler: Yılan ısırıkları; mannitol

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Venomous snakebite is estimated to affect greater than 2.5 million people annually in the world, of whom more than 100 000 will die.[1] Most of the venomous snakes in Turkey are members of Viperidae family.[2,3] Envenomations by vipers are remarkable for the amount of swelling they can produce. Immobilizing the bitten extremity, transporting the patient quickly to the nearest hospital, and using antivenin according to the severity of symptoms are the general treatment approaches. If proper treatment is not established, local edema can progress and result in compartment syndrome and subsequently requires surgery.[4-6]

We, herein, report three cases of severe and moderate local envenomations resulting from Vipera Xanthina bites. Two patients had been trea-

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ted with insufficient antivenin before they were transferred to our hospital. One patient who had not received antivenin priorly admitted on third day after the snakebite. All patients were treated successfully with mannitol monotheraphy.

CASE REPORTS

CASE 1

A-4-year-old girl had been bitten by a snake on the lateral surface of her left thigh. She was brought to the emergency department 36 hours after the bite because of swelling of her thigh. On physical examination, there were visible two adjacent fang marks over the proximal third on the lateral surface of her left thigh. Bruising was noted at the thigh, and swelling and tenderness extended to the patella. Her pulses were good in the left limb. There was pain with passive movements. The circumference of the thigh was 34 cm as compared to 30 cm on the right side. We recognized the killed snake as V. xanthina. On admission, her vital signs were as follows: Blood pressure 100/60 mmHg, pulse rate 100 bpm, respiratory rate 18/min and axillary temperature 36°C. Her Glasgow Coma Score was 15/15. Baseline laboratory studies were normal, with the exception of WBC 15 600 mL and CK 890 U/L (N: 5-130 U/L). Results of coagulation studies showed that PT 17.2 sec (N: 10.8-13.9 sec), INR 1.3 (N: 0.64-1.17), aPTT 149 sec (N: 26.6-40.3 sec), fibrinogen 278 mg/dL, and D-dimer 503.7 mg/L (N: 68-494 mg/L). The envenomation profile of this case was evaluated as grade 3.[2] Intravenous fluid support (1500 mL/m^2/d) and antibiotic therapy (ampicillin/sulbactam 100 mg/kg/d and metronidazole 30 mg/kg/d, for seven days) were initiated. The wound was cleansed and tetanus toxoid was injected. Antivenin was not given because of late admission. On the 12th hour of admission, the swelling in the patient's limb increased markedly. Distal pulses of the left limb became non-palpable, and the circumference of her left thigh increased from 34 cm to 40 cm and the diagnosis of severe local edema was made. Mannitol (0.5 g/kg, 2x1, 3 days) was administered and intravenous fluid support was increased (3000 mL/m^2/d, two days). On the 60th hour of admission, the circumference of her left thigh diminished to 32 cm and mannitol therapy was stopped. The abnormal coagulation parameters normalized on third day without fresh frozen plasma therapy. The edema was completely healed on the 7th day of hospitalization. On the 10th day, she was discharged without local wound findings.

CASE 2

A-10-year-old female patient who had been bitten by a snake on her left ankle was referred to our clinic. One vial antivenin had administered at local hospital one hour after the snakebite. After 36 hours, she was transferred to our hospital due to progressive edema on her extremity. The fang marks were seen on the medial malleolus of the left ankle. There was a marked edema including tenderness, pallor and partial bruising from her toes through her knee. The distal pulses were not palpable and sensation on bitten extremity was decreased. Active and passive motion of the toes exacerbated the pain. The compartment pressure was not measured due to the lack of equipment for the measurement of intracompartment pressure (ICP). The circumference of the left leg was 29.5 cm as compared to 25 cm on the right leg. On admission, Glasgow Coma Score was 15/15. She had a body temperature of 36°C, heart rate of 118 beats per minute, blood pressure of 105/55 mm Hg, respiratory rate of 18. The severity of envenomation was graded as two.[2] We recognized the killed snake as V. Xanthina by a photograph taken by her parents. The laboratory studies were normal. Antivenin was not given due to the late admission. Antibiotic therapy (ampicillin/sulbactam 100 mg/kg/d and metronidazole 30 mg/kg/d, seven days) was initiated. Mannitol (0.5 g/kg, 2x1, three days) was administered until the difference between the circumferences of the legs reduced to 1 cm. On the fifth day, the edema disappeared completely. She was discharged on the 7th day of hospitalization without any sequelae.

CASE 3

A-12-year-old girl had been bitten by a snake on the right midfoot. Four hours after the bite, 5 vials antivenin were administered at the local hospital. Three days later, she was transferred to our hospi-

tal because of progressive swelling on her right foot. The patient complained of paresthesia and pain. The physical examination revealed fang marks over the right midfoot. The type of the snake was identified as V. xanthina with the description by her mother. There was a marked swelling, pallor and bruising up to her right lower quadrant of abdomen including tenderness. The pulses were not palpable and sensation was decreased on the whole limb. Passive flexion and extension of the toes increased the pain. The differences of circumferences were measured as 5.5 cm between her right and left thighs and 6 cm between her right and left calves. Glasgow Coma Score was 15/15. She had body temperature of 36° C, heart rate of 118 bpm, blood pressure of 110/65 mmHg, and respiratory rate of 18 per minute. Although we were unable to measure the intracranial pressure, a diagnosis of compartment syndrome following snakebite was strongly suspected based on these clinical signs (pain on passive stretching, pulselessness, pallor and paresthesia). Baseline laboratory studies were normal, with the exception of WBC 19 400 mL and CK 1004 U/L (N: 5-130 U/L). Coagulation studies were unremarkable. The severity of envenomation was graded as 3.[2] Before considering surgical intervention, mannitol (0.5 g/kg, 2x1, 3 days), intravenous fluids (3000 mL/m^2/d, 3 days) and antibiotics (ampicillin/sulbactam 100 mg/kg/d and metronidazole 30 mg/kg/d, 7 days) were instituted without antivenin. Twelve hours later, the swelling in patient's foot, calf, thigh and right lower quadrant of her abdomen diminished markedly without evidence of further progression. Twenty-four hours later, the patient showed significant improvement with diminished pain and tenderness, resolved paresthesias and pain on passive stretching, and readily palpable distal pulses. On 5th day, the circumferences of lower limbs were measured to be equal. On follow-up, after seven days, CK value returned to normal levels (84 U/L) and she was discharged without any wound findings.

DISCUSSION

The venom of the Viperidae family mainly causes local and hematotoxic effects. Venom increases local damage by elevating TNFα, phospolipase A_2, and xantine oxidase mediated inflammatory response. Local effects usually consist of pain from the bite itself, together with edema and bruising.[2,4,7-9]

Treatment is based on the clinician's overall grading of venom toxicity. Local and systemic manifestations, as well as laboratory findings, weight heavily in this judgment. Severity of envenomation is commonly graded on a four-point scale (0 to 3).[2,4,9] Severe envenomation is characterized by noteworthy local (entire extremity involvement) and systemic (hypotension, shock, bleeding diathesis, respiratory distress) clinical signs, and laboratory abnormalities (significant anemia, prolonged clotting time, metabolic acidosis).[4,9] In the present report, cases 1 and 3 were graded as severe (grade 3) due to progressive local findings on the limb entirely and prolonged clotting time for case 1, and severe local findings on entire extremity for case 3. Case 2 with local signs extended beyond wound site was graded as moderate (grade 2). It is well known that polyvalent antivenin administration is recommended for patients with moderate to severe envenomations.[2,4,9] It should also be emphasized that antivenin is most effective if delivered within 4 hours of the bite, and is of little value if administration is delayed beyond 12 hours.[2,5,6,9] In the present study, our cases did not receive antivenin because of delayed admissions (36, 36 and 72 hours after snakebite). On the other hand, inadequate antivenin administration, particularly in children, is one of the potential error in the treatment of snakebites.[10] Indeed, Case 2 had received only one vial whereas case 3 received 5 vials polyvalent antivenin in the local hospitals. These observations led us to conclude that these two patients received inadequate antivenin according to their clinical severity scores. In these cases, we were not able to clarify the reasons of low dose antivenin treatments.

The principal local effect of snakebite envenomation is edema, which usually occurs within two hours and gradually increases over the next two to three days before subsiding. The extend of observed edema ranges from a mild local reaction to involvement of entire extremity.[2,7,11] Local reaction to envenomation on an extremity may mimic compartment syndrome.[6,11] Indeed, there were noteworthy clinical signs of compartment syndrome in cases 2 and 3

as pulselessness, paresthesia, pallor, severe pain and pain on passive stretching. In medical practice, concomitant presence of these findings strongly supports the diagnosis of compartment syndrome.[12] It has been demonstrated that timely administration of antivenom mitigates the destructive local effects of the venom, thereby preventing compartment syndrome.[11,13] Furthermore, mannitol has been shown to be beneficial when used as an adjunctive therapy for compartment syndrome secondary to snakebite envenomation.[6] In addition, mannitol therapy in snakebites has been used for treatment of myoglobinuric renal failure.[14] As it is well known, mannitol is the most commonly used hyperosmalar agent. Infusion of mannitol increases serum osmolarity, which draws edema fluid from tissue by its osmotic effect.[15] Besides its osmotic diuretic properties, mannitol possesses hidroxyl radical-scavenging properties.[16] It also inhibits spontaneous aggregation of human platelets when subjected to anoxia and reoxygenation in vitro, and reduces the rate of production of H_2O_2, improving cell viability.[17] Mannitol has also demonstrated to provide neuroprotection by preventing both necrosis and apoptosis, and it protects ischemic muscles from reperfusion injury.[18,19] Although the intracranial pressure was not measured in cases 2 and 3, local signs on the limbs progressed markedly due to insufficient antivenin treatment. In these situations, fasciotomy should be considered as soon as clinically significant pressures are suspected despite the use of aggressive antivenin, as well as supportive therapies as mannitol and hyperbaric oxygen. This strategy may help to prevent the development of unwanted complications including loss of an extremity, because prevention of muscle necrosis is time-dependent when perfusion is compromised.[2,5,6] Cases 2 and 3 who had received low dose antivenin prior to admission, and Case 1 who had not admitted to a medical center before, were given mannitol. Hopefully, they well responded to this medical approachment and no additional therapy was required. It is likely that the administration of mannitol in our patients prevented the development of compartment syndrome and eliminated the need for fasciotomy.

In conclusion, varying degrees of tissue edema is common in snakebite. In cases who admitted late and in those who received low dose antivenin, mannitol monotherapy might be an effective treatment for severe local edema.

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