

Antivenom therapy in the green pit viper bite.

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This presentation is a study in ten green pit viper bite children who were admitted to Chulalongkorn Hospital. Three patients who either had low platelet counts or low plasma fibrinogen levels manifested no abnormal systemic signs or symptoms. While the remained 7 cases who had very low levels of both platelet counts and plasma fibrinogen, all except one had significant systemic bleedings. Since green pit viper bite generally dose not cause serious problem but death from hemorrhage had however occasionally occurred. Criteria for selection patients who are at risk for severe hemorrhage were therefore suggested. Specific antivenom for green pit viper manufactured by the Thai Red Cross Society was shown, in this study, to have potent effect in correcting the abnormal hemostasis, both clinical and laboratory derangements, in these patients.

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รายงานนี้เป็นการศึกษาเด็กถุงงูเขียวหางไหม้ 10 ราย ที่ถูกรับไว้รักษาในโรงพยาบาลจุฬาลงกรณ์ 3 ราย ที่ผลการตรวจทางห้องปฏิบัติการพบมีเกร็ดเลือดหรือไฟบริโนเจนอย่างใดอย่างหนึ่งต่ำ ผู้ป่วยเหล่านี้ไม่มีอาการทางคลินิกของระบบหัวใจอื่น ๆ เลย นอกจากอาการเปลี่ยนแปลงของเนื้อเยื่อรอบ ๆ แผลกัด (ซึ่งต้องการรักษาทางศัลยกรรมช่วยด้วย) เทียบกับผู้ป่วย 7 ราย ที่มีทั้งจำนวนเกร็ดเลือดและระดับไฟบริโนเจนในน้ำเหลืองต่ำมาก 6 ใน 7 รายมีอาการเลือดออกจากระบบต่าง ๆ มากอย่างชัดเจน เนื่องจากโดยทั่วไปเด็กป่วยที่ถุงงูเขียวหางไหม้กัดมักไม่เกิดอาการที่รุนแรง แต่ก็มีรายงานว่าทำให้เลือดออกมากจนถึงตายได้ ผู้รายงานจึงได้เสนอข้อสังเกตที่จะช่วยป้องกันเด็กป่วยถุงงูเขียวหางไหม้กัดกำลังอยู่ในภาวะที่เสี่ยงต่อการมีเลือดออกอย่างรุนแรงได้ไว้ และศึกษาและแสดงประสิทธิภาพของซีรัมแก่พิษงูเขียวหางไหม้ ซึ่งผลิตโดยสถานเสาวภาสภากาชาดไทยในการรักษาผู้ป่วยเหล่านี้

The green pit viper (*Trimeresurus*) is the most common cause of snakebite in Bangkok. In 1982 there were 1621 snakebite patients visits to the Emergency Room of Chulalongkorn Hospital. Among the 1003 patients where the biting snakes were identified 644 cases or 64.21% were due to green pit vipers (Table 1).⁽¹⁾ The majority of green pit vipers found in Bangkok and neighbouring townships are *Trimeresurus albolabris* and

trimeresurus macrops.^(2,3) Their venoms are known to induce hypofibrinogenemia as well as thrombocytopenia. The bleeding diathesis seen in these patients is generally of mild to moderate degree, but has caused occasional deaths.^(3,4) This presentation described the clinical manifestations in green pit viper bite children seen at Chulalongkorn University Hospital and their response to specific antivenom therapy.

Table 1. Snakebite cases seen in the Emergency Room of Chulalongkorn Hospital, (during 1982).⁽¹⁾

Snake	Cases
Non-poisonous	285
Poisonous	718
Cobra	66
Green pit viper	644
Malayan pit viper	2
Russell's viper	6
Unidentified	618
Total	1621

Materials and methods

Between October 1986 and March 1990 there were ten children with snakebite admitted to the Pediatric Ward of Chulalongkorn Hospital, who received specific antivenom for green pit viper. There were 8 boys and 2 girl. Their ages ranged from 1 8/12 to 14 years (mean of 6.2 years) Nine patients lived in Bangkok and one in Samutprakarn. The snakes were definitely identified as green pit viper in 6 children. The snakes were not definitely identified in 4. Clinical manifestations however were similar to those usually seen in green pit viper bites.^(3,4)

Laboratory investigations performed in these patients included a complete blood count and coagulogram. Platelet count and plasma fibrinogen levels⁽⁵⁾ were also performed before and after antivenom therapy.

Indications for the use of antivenom in these patients included cases who had significant systemic bleeding with thrombocytopenia and/or hypofibrinogenemia; or cases who had combination of severe thrombocytopenia (platelet count less than 20,000/c.mm) and severe hypofibrinogenemia (fibrinogen less than 50 mg/dl)

even without significant systemic bleeding.

The green pit viper antivenom was manufactured by the Science Division of the Thai Red Cross Society. The lyophilized powder in each vial was reconstituted with 10 ml distilled water. Each dose of 20-40 ml antivenom was then further diluted in 50 to 100 ml of half strength normal saline. The mixture was given by intravenous drip in half an hour to one hour duration.

For prevention of hypersensitivity to horse serum in the antivenom, skin test was performed prior to the administration and the intermittent doses of intravenous corticosteroids were concomitantly given with the antivenom.

Results

Table 2 show local changes around the bite wounds. Fang marks were clearly seen in all cases. Three patients were bitten on fingers, 6 on the foot and one case at the calf. Swelling involved the whole extremity in four cases and in three of these the swelling extended to the trunk. The swelling reached a maximum within 24

to 48 hours. Ecchymoses accompanied the swelling in all cases. Hemorrhagic blisters (numbered 1-4) occurred in 7 cases. Case 2, developed gangrene of a finger which required amputation. A skin graft was required in case 10. Debridement only was performed in four cases. The remaining case, who also had a blister, needed only supportive treatment. Table 3, demonstrates systemic

signs and symptoms in these patients. Cases 1-4 had no abnormal systemic manifestations. Specific antivenom for green pit viper was nevertheless given because surgery was required in three cases (No.1-3), who either had a very low platelet count (case 1) or a markedly low plasma fibrinogen level (cases 2 and 3). Case 4 had very low levels of platelets and plasma fibrinogen, (Table 4).

Table 2. Local changes in green pit viper bitten patients.

Case No. Age-yr. Sex	Site of bite	Snake iden- tified	Maximum swelling time after /up to bite	Ecchy- mosis	Blister*	Necrosis	Local treatment
1. WS 3½, F	finger	no	9 hr/shoulder	+	++++	0	debridement
2. SC 14, M	finger	no	2 d/upper arm	+	+	+	amputation
3. SK 5, M	finger	yes	1 d/trunk, nipple line	+	+	0	0
4. AL 5, M	foot	yes	1 d/mid leg	+	0	0	0
5. TP 10, M	foot	yes	20 hr/trunk, waist line	+	+++ (sized 4×4 cm. ² each)	0	debridement
6. SS 3, M	calf	yes	2 d/upper thigh to lower leg	+	0	0	debridement
7. KS 2, F	foot	yes	1 hr/knee	+ and petichiae	0	0	0
8. JK 7, M	foot	no	2 d/mid thigh	+	+	0	debridement
9. KK 11, M	foot	no	14 hr/knee	+	+	0	0
10. ES 1 8/12, M	foot	yes	36 hr/trunk, subcostal level	+	+	+	skin graft

* + = one hemorrhagic blister

Table 3. Systemic manifestations of green pit viper bite patients.

Case No.	General*	Bleeding*	Hosp. stay (day)	Remarks
1. WS	irritable from pain	none	11	- urticaria ½ hr. after 4th dose of AV - mumps on day 4 after bite
2. SC	none	none	25	-
3. SK	none	none	8	-
4. AL	none	none	2	-
5. TP	5 hr-vomited many times	24 hr-bleeding puncture site 70 hr-microscopic hematuria	3	-
6. SS	12 hr-vomited once	18 hr-epistaxis	4	-
7. KS	1 hr-vomited 3 times	9 hr-bleeding gums	3	-
8. JK	36 hr-vomited once	30 hr-melena, blood streak in sputum 60 hr-bleeding gums	8	-
9. KK	½ hr-vomited 2 times -unconscious for half an hour 1 hr-puffy eye lids, swelling lips & face	½ hr-blood in vomitus 1 hr-subconjunctival hemorrhage both sides, bleeding from puncture sites and abrasion on toes 2 hr-vomited blood 14 hr-increased subconjunctival hemorrhage, epistaxis	4	-

* hr = hour after bite

Table 4. Laboratory tests and antivenom therapy in green pit viper bite patients.

Case No.	Time after bite	Hb gm/dl	Plt $\times 10^3/c.mm$	FI mg/dl	Treatment for bleeding diathesis
1. WS	8 hr	13.6	65	303.75	
	15 hr	-	-	-	AV 20 ml q 6 hr, 4 doses
	55 hr	9.7	133	-	
2. SC	36 hr	11.0	255	15.75	AV 20 ml, one dose*
	84 hr	10.2	320	106.75	
	day 6	-	-	209.25	
	day 11	11.5	235	321.75	
3. SK	63 hr	12.5	100	31.5	
	88 hr	-	-	-	AV 20 ml q 6 hr, 4 doses
	day 6	-	250	235.0	
4. AL	36 hr	12.8	51	15.75	
	39 hr	-	-	-	AV 20 ml q 6 hr, 4 doses
	55 hr	11.7	150	67.5	
	79 hr	-	138	94.5	
5. TP	72 hr	10.7	8	27	AV 40 ml*
	78 hr	-	-	(VCT 5')	
	91 hr	-	240	184.5	
	day 6	8.0	250	321.75	
6. SS	24 hr	9.6	adq	prolonged PT	AV 10 ml*
	37 hr	10.0	9	22.5	
	40 hr	-	-	-	AV 40 ml
	43 hr	-	133	60.75	
	44 hr	-	-	-	AV 40 ml
	71 hr	-	172	123.75	
7. KS	9 hr	11.9	21	38.25	AV 20 ml. FFP 140 ml*
	14 hr	11.0	4/HPF	(VCT 7')	
	33 hr	-	121	159.75	
	39 hr	7.9	165	191.25	
	57 hr	-	136	218	
8. JK	2 hr	11.7	adq	-	
	67 hr	10.0	decreased	31.5	AV 40 ml*
	74 hr	-	-	109	
	87 hr	9.4	33	229	
	day 5	8.4	56	400	
	day 6	9.7	109	495	
	day 11	9.0	420	364	
9. KK	2 hr	17.7	markedly decreased	(PT-no clot)	FFP 240 ml
	12 hr	-	-	35.75	
	16 hr	9.7	12	109	AV 40 ml.*
	20 hr	-	235	139	AV 40 ml q 6 hr, 2 doses*
	39 hr	8.8	91	180	
	day 5	9.8	224	351	

AV = Antivenom for green pit viper, *given after lab results were reported

FFP = Fresh frozen plasma

Plt = Platelet

FI = Fibrinogen

VCT = Venous clotting time

PT = Prothrombin time

Cases 5-9 vomited 1-3 time during the first two days after the bite and also had mild to moderate systemic bleeding (e.g., epistaxis, bleeding from gums, blood streaked sputum and melen). All these five cases had a severe depression of platelet and the fibrinogen level. Antivenom was therefore infused and a good response was obtained in all (Tables 3, 4 and Figure 1.)

Case 9, KK, a 14 year-old boy, was bitten at left foot by an unidentified snake while playing football (Tables 2,3 and 4 and Figure 1). He complained of severe pain at the bite site and oozing of blood soon after the bite. Half and hour later en route to the hospital, he became unconscious and vomited food which was blood tinged. On admission, about one hour after the bite, he appeared alert and had a swelling of the face, particularly around eyes and lips. He also had subconjunctival hemorrhages and bled from abrasions on his toes. Laboratory investigation on admission revealed a Hb 17.7 gm/dl, markedly decreased platelets and markedly prolonged prothrombin time. Transfusion of 250 ml FFP was given at three hours after the bite. Eleven hours later he had epistaxis and the subconjunctival hemorrhage worsened. The Hb was 9.7 gm/dl, reticulocyte 0.3%, WBC 16,600/c. mm, PMN 87%, L 13%, platelet 12,000/c.mm, PT-no clot and the plasma fibrinogen was 109 mg/dl. 40 ml of antivenom was given at 16 1/2 hours after the bite. Two to three hours after that, all bleeding stopped. Twenty hours after the bite, laboratory tests revealed a platelet count of 235,000/c.mm., PT-19.6" (Control 13.6") and a fibrinogen of 139 mg/dl. Intravenous antivenom administration was repeated for two more doses of 40 ml at 6 hour intervals. The boy then recovered rapidly and was discharged after four days of hospitalization.

Case 10, ES,⁽⁶⁾ a 18/12 year old boy, was bitten on back of left foot by a green pit viper. One hour after bite, on admission three fang marks were noted surrounded by mild swelling of soft tissues. Local changes reached their maximum at 36 hours after the bite. The swelling plus ecchymoses involved his whole left lower extremity as well as the scrotum and extended to subcostal level of the trunk. The pulse of the left dorsalis pedis artery was not palpable and a hemorrhagic blister developed at the back of left foot.

On admission he was stable until 10 hours later when he started to breathe rapidly, appeared pale, become semiconscious and restless. Laboratory investigations on admission revealed a Hct of 39%, WBC 39,150/c.mm, platelets were adequate, PMN 31% L 68% E 1%. Venous blood was noted to clot readily. Nine hours later the Hct was 26%, WBC 15,800/c.mm, platelets 22,000/c.mm, APTT-no clot, PT - no clot and the plasma fibrinogen

was 6.75 mg/dl. Infusions of packed red cells 150 ml, FFP 100 ml, fresh whole blood 200 ml and antivenom 40 ml were given during the following 10-20 hours. The boy, however, developed hypertension (B.P. 150/100 mm Hg) and the bleeding diathesis became worse. Exchange transfusion with fresh whole blood (double of his calculated blood volume) followed by cryoprecipitate (2-3 units) and platelet concentrate (2-3 units) was then performed. The child responded well to this treatment. The procedure, however, had to be repeated twice at 36 and 39 hour intervals respectively in order maintain his good clinical response.

Discussion

Two significant clinical manifestations of green pit viper (*Trimeresurus*) bite patients are local changes around the bite-site and a bleeding diathesis. Swelling, around the bite wound, the hallmark of envenomization, which sometimes is very severe and involves the whole extremity as well as the adjacent part of the trunk, usually causes no compartmental syndrome. Hemorrhagic blisters and necrosis, not uncommon local changes, usually do not end in serious sequelae like those seen in Malayan pit viper bites.⁽⁷⁾ Hemostatic defects are mainly the result of low plasma fibrinogen level and thrombocytopenia. Only few green pit viper bite victims have these hemostatic derangements and even fewer have systemic bleeding. Death from bleeding has however been reported.^(3,4) Cases with significant systemic bleeding usually have abnormal hemostasis tests, i.e., low plasma fibrinogen (or prolonged venous blood clotting time) and/or thrombocytopenia. Caution and close observation is therefore indicated for patients who have signs of systemic bleedings as well as for those who have a combination of very low plasma fibrinogen and marked thrombocytopenia (such as cases 4-10, as shown in Tables 2-4).

Replacement using various blood components has been shown to be ineffective in green pit viper bite patients.⁽⁴⁾ Neutralization of venom, e.g., by using antivenom, is the treatment of choice in such symptomatic snake bite patients.

However, because of the low mortality and low morbidity among green pit viper bite victims,^(4,8) and metabolism of the venom usually within a week and the poor potency of the antivenom previously available, there have been no reports of use of antivenom therapy with controlled laboratory tests in green pit viper bites in Thailand. The Thai Red Cross Society, however, has recently produced specific antivenom against *Trimeresurus albolabris*.⁽²⁾ During October 1986 to March 1990

there were 10 children bitten by green pit viper admitted to Chulalongkorn Hospital who required intravenous antivenom (Tables 2-4). Seven cases, No. 4-10, have very low levels of fibrinogen and platelets. All, except case No. 4 had signs of systemic bleedings. The other 3 cases (No. 1-3) had low levels of platelets or fibrinogen, had no signs of systemic bleeding but surgical wound care was required. The bleeding diathesis of these children, except

case No. 10, responded well to green pit viper antivenom. After the first 20-40 ml of antivenom, both abnormal hemostatic tests as well as clinical bleedings were usually corrected within 4-6 hours (Figure 1. and Table 3.). A difference in the clinical course was clearly seen when one compares the progress of previously reported patients who did not receive antivenom therapy, to those who did in this presentation. An average one week after the bite was required for the self eradication, Figure 2. (4)

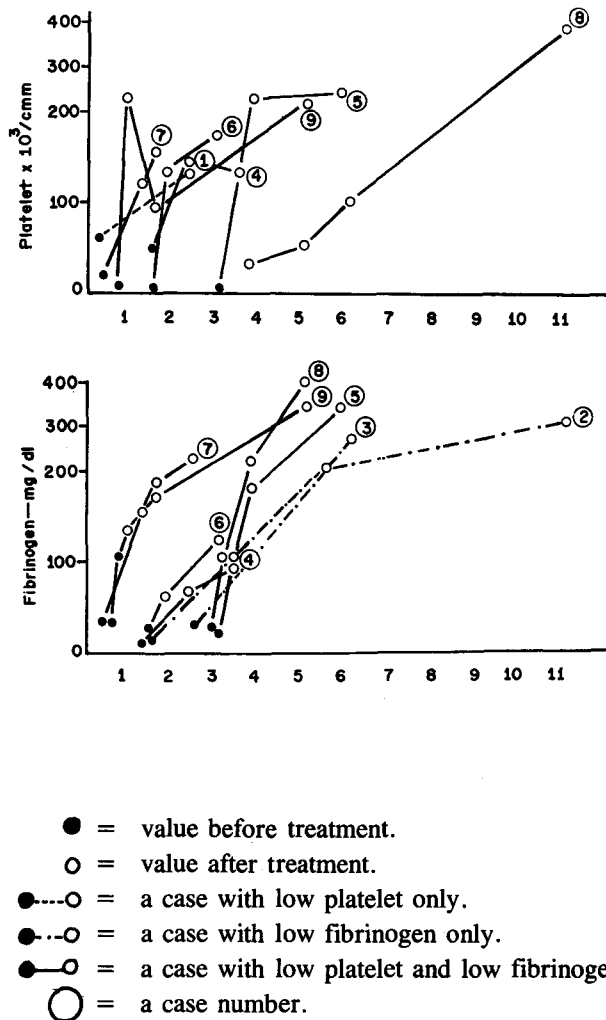


Figure 1. Response of platelet and plasma fibrinogen in green pit viper bite patients to the antivenom therapy.

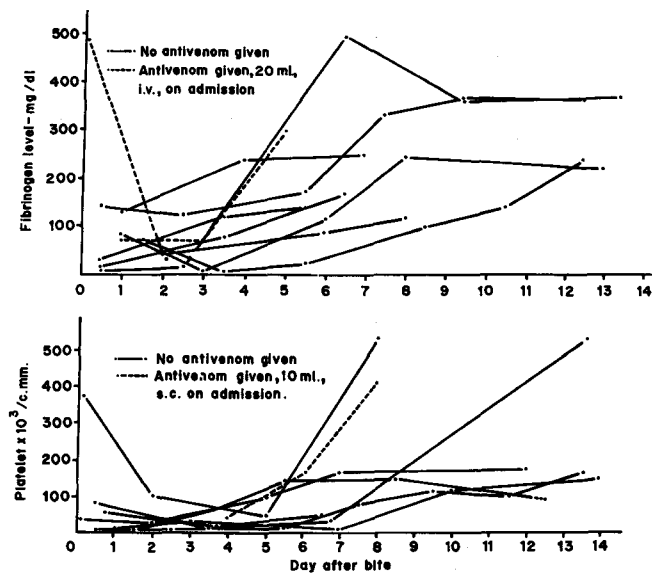


Figure 2. Follow-up studies of fibrinogen and platelet levels in 10 cases of green pit viper bite.⁽⁴⁾

Continuous absorption of venom from tissues around the bite wound lasts about one week in green pit viper bite victims.^(4,6,9) In some cases a few more doses of the antivenom may be therefore required to neutralize the circulating venom.

Case No. 10,⁽⁶⁾ a 1 8/12 year old boy, was severely ill, from probable internal bleedings which occurred within 10 hours of being bitten by a green pit viper. Since no response was observed after the first dose of antivenom (40 ml intravenously together with FFP 100 ml and PRC 150 ml), exchange transfusion was performed to eliminate circulating venom and replace blood components. The boy was cured after three attempts of the procedure.

We conclude that green pit viper bite patients in Central Thailand, who have signs of systemic bleeding with derangement of hemostatic tests as well as those who have a combination of severe hypofibrinogenemia

(fibrinogen less than 50 mg/dl) and severe thrombocytopenia (platelet counts of less than 20,000/c.mm) even with out bleeding, are at risk for hemorrhage. This study demonstrated that signs of bleedings and the abnormal hemostatic tests in these green pit viper bite patients were corrected by administration of green pit viper antivenom produced by the Queen Saovabha Memorial Institute of the Thai Red Cross Society. Most children required only 1-3 doses of 20-40 ml given intravenously every 4 to 6 hours.

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