# Clinical and Laboratory Changes of Patients with Various Diseases Treated by SVATE-3.

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## Abstrak

*Snake Venom Anti Thrombus Enzyme-3 (SVATE-3) telah dipakai secara luas dalam klinik pada berbagai penyakit, dan dikatakan memiliki efek samping yang ringan. Telah dilakukan penilaian efek SVATE-3 pada gejala klinik, hemoreologi, kadar lemak darah dan fungsi hati pada 12 penderita (11 laki-laki dan 1 wanita) yang semuanya memiliki gejala penyakit dan hemodinamik stabil, umur 42-70 tahun, semua mendapat pengobatan SVATE-3 selama 21 hari sesuai protokol. Selama pengobatan dengan SVATE-3 tidak ada perubahan obat-obatan yang sedang digunakan oleh penderita. Hasil yang diperoleh menunjukkan bahwa efektivitas SVATE-3 berdasarkan perbaikan gejala klinik adalah 89.5%. Tidak terdapat perbedaan yang bermakna secara statistik sebelum dan sesudah pengobatan dengan SVATE-3 pada : hemoglobin (14±1.3 vs 13.9±1.3), trombosit (303±83 vs 301±85), fibrinogen (379±86 vs 353±85), asam urat (5.9±2.3 vs 5.6±1.9), kadar lemak dan agregasi darah. Terdapat satu penderita dengan peningkatan agregasi trombosit sebelum pengobatan yang menjadi normal setelah pemberian SVATE-3. Terdapat penurunan bermakna pada kadar SGOT (20.5±3 vs 13.7±2) dan SGPT (25±4 vs 15.7±4) sebelum dan sesudah pengobatan dengan SVATE-3. Selama pemberian SVATE-3, seorang penderita mengalami gejala alergi yang dapat diatasi dengan pemberian antihistamin. Tidak ditemukan tanda-tanda perdarahan. Sehingga disimpulkan bahwa pengobatan dengan SVATE-3 pada penderita yang kondisi penyakitnya stabil dapat memperbaiki gejala penyakit tanpa menimbulkan efek samping yang berarti.*

## Abstract

*Snake Venom Anti Thrombus Enzyme-3 (SVATE-3) has already been widely used in the clinic for various diseases, and has been claimed to have less side-effects. We investigated the effect of SVATE-3 on the clinical symptoms, hemorrheology, lipid profile and liver function. Twelve patients (11 male and 1 female) who were symptomatically and hemodynamically stable, aged 42-70 years, all of whom received a 21-day SVATE-3 treatment according to the protocol, were studied. During the treatment, there were no alteration of medication which had been used by these patients. The result showed that the effectiveness of SVATE-3 treatment based on the improvement of symptom is 89,5%. There were no statistically difference before and after SVATE-3 treatment on haemoglobin (14±1.3 vs 13.9±1.3), thrombocyte (303±83 vs 301±85), fibrinogen (379±86 vs 353±85), uric acid (5.9±2.3 vs 5.6±1.9), lipid profile and aggregation. In fact, one patient who had an increased thrombocyte aggregation before treatment, which become normal after treatment. There were significant reduction of SGOT (20.5±3 vs 13.7±2) and SGPT (25±4 vs 15.7±4) level before and after treatment. During treatment, one patient suffered from allergy that was controlled by antihistamin. There were no sign of bleeding reported. We concluded that SVATE-3 treatment in patients with stable condition may improve clinical symptoms without serious side effects.*


***Key words:*** *Snake Venom Anti Thrombus Enzyme, hemorhoelogy, lipid profile, liver function.*

## INTRODUCTION

The purified enzyme extracted from snake venom (Ancrod) had been used clinically to tread thrombotic disease since 1968, and has been included in the British Pharmacopea published in 1973.[1]

The Snake Venom Anti Thrombus Enzyme (SVATE) was later developed in China by Hao Wen-Xue et al.[2] This drug has been shown to possess many functions such as: anticoagulation, thrombolysis, dilating blood vessels, lowering blood fat, promoting nerve growth, and anti senility. And has been reported successful in treating cerebral thrombosis, acute myocardial infarction, unstable angina, hypercholesterolaemia, diabetes mellitus, Raynaud disease and senile diseases.[3] The major side effect of SVATE is bleeding

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because of its thrombolytic effect, and because it contains neurotoxin, it therefore can also cause dizziness, fever, numbness etc.

SVATE-3 is a new refined product of SVATE extracted from Agkistrodon Hyals by a better technological process, of which the factory has claimed to have less side-effect or adverse reaction for the majority of patients.

Since SVATE-3 has gained popularity in our community, and has been frequently used by doctors in Jakarta in treating various diseases, we therefore would like to investigate the effectiveness of SVATE-3 treatment, and more importantly if there are any side-effects of SVATE-3 occuring in patients.

## MATERIALS AND METHODS

SVATE-3: The frozen-dry venine powder of Agkistrodon Hyals was provided by the Research Center of Prevention and Treatment of Senile Diseases of China Medical University. Each ampule containing 100 usp/ml (0.25 unit) of arginine esterase activity.

Subjects: Patients who came to the Preventive Cardiology Unit, National Cardiac Center, Jakarta, seeking for SVATE-3 treatment, had either heard from their friend, or sent by doctors will be selected. The diagnoses were based on history taking, physical and laboratory examinations, or data presented by patients themselve. The inclusion criteria was : the patiens had to be in a stable condition, which meant that they were symptomatically and hemodynamically stable (no one critically ill).

Sample selection: Twelve patiens were randomly selected from a total of 43 patient who finished a 21-day course of SVATE-3 treatment during 1st-November-1993 to 31st-December-1993. Because the study was designed to compare means in paired group, in which subjects were measured or observed twice, the formula used to estimate sample size was based on Dawson-Saunders and Trapp (1990); for a study with a P-value of 0.05, and experiment will have a 90% chance of detecting an actual difference between the two groups, the sample of 12 patients should be sufficient.[4]

Study procedure: All patiens should maintain their medication until the end of the SVATE-3 treatment. Blood sample for examination of hemorrheology, lipid profile, liver and kidney functions were taken at the begining and at the end of SVATE-3 treatment. Before SVATE-3 treatment, informed consent will be sought after the anticipated benefit and potential hazards of the treatment and discomfort it may entail were explained to the patiens by the doctor. The questionaire was given to every patient for answering about their health status, symptoms and activity before, during and after SVATE-3 treatment.

The effect of treatment was judged by the alteration of symptoms, which is devided into four groups, that are : worse, no change, improve and marked improve.

The SVATE-3 treatment: SVATE-3 was given as recommended, that was 4 ampules a day for patients weight under 60 Kg, and 8 ampules a day for patients heavier than 60 Kg. The drug was disolved in normal saline, that are 4 ampules in 10 ml administered intravenously directly, and another 4 ampules in 250 ml of normal saline and administered intravenously with the rate of 45 drops/minute. All patients received a 21-day course of SVATE-3 treatment.

Statistics: The data were presented as mean and standard deviation of the mean. The statistical significance of difference between pairs of means was determined by paired Student's t-test. The analyses were performed using the computer programe CSS (Statsoft, Tulsa, ESA) run under the MS-DOS 3.3 operating system. In all cases, level of probability (P) of less than 0,05 were taken to indicate significance.

## RESULTS

Twelve patients (28%) of a total of 43 patient were enrolled in this study. Baseline characteristic of patients was shown in table 1. Most patients suffered from coronary artery disease with the addition of other diseases.

After a 21-day course of Svate-3 treatment, the therapeutic effects based on clinical symptoms were determined. The overall effectiveness rate was 89,5% (Table 2).

SVATE-3 treatment did not result in any alteration of the principle biochemical and hematological data, in particular the haemoglobin level, the platelet count, haemotocrit, and the kidney function test. The SGOT and SGPT level were lower after SVATE-3 treatment (Table 3).

Table 4 summarizes the result of platelets aggregation; there were no statistically difference in the extent of ADP-induced aggregation before and after SVATE-3 treatment. One patient who had an increased thrombocyte aggregation before treatment become normal after treatment.

There were not any changes on the lipid profile before and after SVATE-3 treatment (Table 5).

No patients withheld a 21-day course of SVATE-treatment because of side-effects.

During treatment, there were no any spontaneous bleeding or neurological symptoms reported, except one patients who had a rash and itch after the injection that can be controlled by antihistamin.

Table 1. Demographic and clinical characteristic (n=12)

| Variable | | Number | Mean ± | SD |
|---|---|---|---|---|
| Age (years) | | | 59,5 | 9 |
| Sex | Male | 11 | | |
| | Female | 1 | | |
| HR (x/min) | | | 74 | 11 |
| BP | Systolic (mmHg) | | 132 | 17 |
| | Diastolic (mmHg) | | 83 | 10 |
| Coronary Artery Disease | | 10 | | |
| Non-haemorhagic Stroke | | 1 | | |
| Stenosis a. Carotic Communis | | 1 | | |
| Parkinsonism | | 1 | | |
| History of Hypertension | | 4 | | |
| Diabetes Mellitus | | 2 | | |

Table 2. Comparison of symptoms before & after SVATE-3 treatment (n=12)
Note : some patients have more than 1 symptom

| Item | no. of case | changes after treatment | | | | effective |
|---|---|---|---|---|---|---|
| | | worse | no change | improve | market improve | rate |
| Angina | 9 | 0 | 1 | 7 | 1 | 88.8% |
| Paresthesia | 4 | 0 | 1 | 2 | 1 | 75% |
| Insomnia | 2 | 0 | 0 | 2 | 0 | 100% |
| Dyzzyness | 1 | 0 | 0 | 1 | 0 | 100% |
| Short of breath | 2 | 0 | 0 | 2 | 0 | 100% |
| Tremor | 1 | 0 | 0 | 1 | 0 | 100% |
| Total | 19 | 0 | 2 | 15 | 2 | 89.5% |

Table 3. Comparison of haematological data before and after treatment of SVATE-3 (n=12)

| | Before | | After | | P-Value |
|---|---|---|---|---|---|
| | Mean ± | SD | Mean ± | SD | |
| Haemaglobin | 14 | 1,3 | 13,9 | 1,3 | NS |
| Leucocyte | 6370 | 1086 | 6500 | 975 | NS |
| Haematocrite | 44 | 4,1 | 42 | 3,7 | NS |
| S G P T | 20,5 | 3 | 13,7 | 2 | < 0,05 |
| S G O T | 25 | 4 | 15,7 | 4 | < 0,05 |
| Ureum | 33,3 | 13 | 33,9 | 12 | NS |
| Creatinine | 1,38 | 0,3 | 1,42 | 0,3 | NS |
| Uric Acid | 5,9 | 2,3 | 5,6 | 1,9 | NS |

Table 4. Comparison of platelet aggregation in whole blood (n=12) before and after the SVATE-3 treatment

| | Before | | After | | P-Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Thrombocyte | 302,7 | 83 | 301,1 | 85 | > 0,05 |
| Fibrinogen | 379,2 | 86 | 353,6 | 85 | > 0,05 |
| Platelet Aggregation | | | | | |
| Agg. max ADP 5 mm | 30,4 | 17,6 | 29,4 | 13,5 | > 0,05 |
| Time | 1'17" | 0'34" | 1'38" | 0'07" | > 0,05 |
| Agg. max ADP 10 mm | 38,1 | 18,5 | 35,6 | 14,5 | > 0,05 |
| Time | 1'14" | 0'51" | 1'19" | 0'23" | > 0,05 |
| Reversibilitas | 29,2 | 12 | 27,3 | 10,9 | > 0,05 |

Table 5. Comparison of lipid profile before and after the SVATE-3 treatment

| | Before | | After | | P-Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Cholesterol total | 215,8 | 44 | 211,1 | 42 | > 0,05 |
| H D L | 37,6 | 13 | 39,6 | 14 | > 0,05 |
| L D L | 148,2 | 38 | 145 | 41 | > 0,05 |
| Total cholesterol/HDL | 6,3 | 2 | 5,8 | 1,8 | > 0,05 |
| Triglyceride | 143,6 | 65 | 125,2 | 50 | > 0,05 |

## DISCUSSION

Platelet mediated thrombus is a main patho-genetic mechanism that limits the efficacy of thrombolytic agents such as streptokinase or tissue plaminogen activator, because these agents also stimulate coagulation.[5] Attempts to isolate the more effective anti thrombotic agent to treat or to prevent platelet-mediated thromboembolism is therefore developed, including the use of aspirin, protagladin E, selective thromboxame A2 receptor antagonsts, hirudin and the latest, SVATE-3.

Svate-3 has been widely used in the treatment of thromboembolic diseases in China. It possesses several anti thromboembolic functions such as anticoagulation, thrombolysis, and dilating blood vessels.[2,6] It has been shown that Kistrin obtained from the venom of Agkistrodon Rhodostroma is the specific human platelet $GP_{IIb/IIIa}$ receptor antagonist that inhibit platelet aggregation.[7] SVATE-3 which is also isolated from the venom of Agkistrodon may have platelet $GP_{IIb/IIIa}$ antagonist activity; on top of the thrombolytic effect, especially for old thrombus,[8] SVATE-3 may accelerate the lysis as well as prevent

the reocclusion of thromboembolism. Thus, it seems reasonable to use SVATE-3 in treating thromboembolic diseases.

The clinical presentation of thromboembolic disease is dependent on where the target organ is affected; cramps or muscle pain in the limb may indicate the occlution of arterial circulation in the extremities. Intermitten neurological dysfunction usually associate with cerebral thrombus. Seventeen percent patients with coronary artery disease had been demonstrated to have thrombus around the atherosclerotic plaque.[9] These patients are therefore selected for SVATE-3 treatment in our clinic.

Because SVATE-3 is a relatively new agent in Indonesia, in order to avoid untoward effects, the patients chosen in this study were all in stable condition.

It has been reported that hemorrheology and lipid profile of patients with cerebrothrombosis dropped significantly after the SVATE-3 treatment.[10] In this study, we found no alteration of the hemorrheology (Table 4) and lipid profile (Table 5) in patients who received a 21-day course of SVATE-3 treatment. This discrepancy may be due to the differebce in population selection; In this study, the patients were all in the stable condition, while previous studies investigated with ill patients. In the acute or subacute disease stage, the aggregation process or others blood biochemistry are more activated,[11] therefore the inhibitory effect of SVATE-3 may become more pronounce compared to a stable condition. Previous study has shown that the intravenous (I.V) and intraperitoneal (I.P) $LD_{50}$ of SVATE-3 for mouse were 1930 $\pm$ 177 usp/KgBw, and 825 $\pm$ 73 usp/KgBw, respectively. By using 20 usp/KgBw/day of SVATE-3 to treat rabbits for a-3-month period showed no differences on the ability of movement, the rate of gaining weight, the last survival rate and the hepatic function compared to control group.[12] The dosage of SVATE-3 recommended for clinical use is 2-10 usp/KgBw each time which is 200 times lower than $LD_{50}$. It has been reported that there were no untoward reaction found in patients treated with large dose of SVATE-3, that was 1 u (4 ampules) on first day, then continued by 2 u (8 ampules) every day for one and half months.[10] Based on this result and clinical findings, SVATE-3 seems to be a safe agent. This is in accord with the present study that no one of our patients had complained of side effect, no spontanous bleeding or neurological symptoms occured.

The haemoglobin, platelet count, kidney function were unchanged before and after SVATE-3 treatment (Table 3).

The decreased SGOT and SGPT level is interesting, further research should be carried out to see whether SVATE-3 would decrease the SGOT and SGPT level in patients with hepatic disease.

Nevertheless, present study showed that SVATE-3 treatment at the recommended dosage in patients with stable condition of thromboembolic diseases may improve symptom and without any serious side effect. Further large scale experiments are needed to comfirm this preliminary result.

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