

Defibrinogating therapy for peripheral circulatory disturbance in patients with vibration syndrome

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NASU Y. Defibrinogating therapy for peripheral circulatory disturbance in patients with vibration syndrome. *Scand J Work Environ Health* 12 (1986) 272–276. This study examines the effects of batroxobin (a defibrinogating drug) on the peripheral circulatory disturbance of 118 patients with vibration syndrome. In 53 cases, batroxobin was intravenously administered once a day for three successive days in the order of 20, 10, and 5 batroxobin units (BU), and 5 or 10 BU were supplemented every day or every second day, respectively, for four weeks. In these cases, the blood fibrinogen and viscosity decreased. A significant decrement in the vascular resistance of the fingers also occurred after each administration. The other 65 cases were subjected to an intravenous administration of 20 BU initially and an additional 10 BU every 2 d for four weeks. For all of the 118 cases the results of skin temperature measurement, finger plethysmography, and nail compression in conjunction with cold provocation showed statistically significant improvement after the therapy. The transcutaneous partial pressure of oxygen and finger blood flow measured in 22 and 27 cases, respectively, were also significantly improved. A sensation of warmth in the whole body appeared in 70.3 % of the 118 cases after the therapy. The results suggest that defibrinogating by batroxobin is useful for improving the peripheral circulatory disturbance of the vibration syndrome.

Key terms: batroxobin, nail compression test, peripheral vascular resistance, plethysmography, red cell aggregation, skin temperature, strain-gauge plethysmography, warm sensation, whole blood viscosity.

Raynaud's phenomenon (vibration-induced white finger), caused by a peripheral circulatory disturbance, is frequently seen in patients with vibration syndrome. In Japan such patients receive treatment in outpatient clinics or hospitals as an occupational disease. For treatment of the peripheral circulatory disturbance of the vibration syndrome, various kinds of vasodilator drugs are widely used in combination with physical therapy such as gymnastics, hot-spring baths, paraffin baths, and hot packs. Of 3 617 patients with vibration syndrome who worked in the national forest and received the aforementioned therapy, only 32 (0.9 %) were relieved of their subjective and objective symptoms after the beginning of the therapy. Most of the remaining patients were resistant to therapy, and usually hospitalization was repeated (personal communication from the Japanese Forestry Agency). Therefore it seems that the treatment of vibration syndrome has thus far been inadequate. Matoba et al (15) reported that about 85 % of patients with vibration syndrome show fair or poor improvement after discharge from the hospital. This finding indicates that the vibration syndrome, once improved by hospital treatment, reappears soon after discharge from the hospital, in spite of further continuation of treatment in an outpatient clinic. Therefore, it is necessary to find a new pharmacotherapy for the vibration syndrome.

A defibrinogating therapy has been employed for many kinds of diseases (4, 5, 6, 8, 12). Erhly (7) reported a successful therapy for patients with secondary Raynaud's phenomenon with the drug ancred. The present study examines the effects of the defibrinogating drug batroxobin on the peripheral circulatory disturbance of the vibration syndrome.

Subjects and methods

Subjects

The data in this study were collected from 118 patients with vibration syndrome. The mean age of the patients, the mean duration of use of vibrating tools, and the mean period after the cessation of vibrating tool use were 5.4 (SD 7.1), 10.7 (SD 5.5), and 6.5 (SD 3.9) years, respectively. The mean number of hospitalizations before the administration of defibrinogating therapy of the present study was 3.1 (SD 1.3). The vibrating tools used were chain saws (64.0 %), a bush cleaner (16.5 %), a rock drill (7.2 %), a grinder (4.3 %), and others. The patients were classified into 24 cases in stage II (occasional appearance of Raynaud's phenomenon in winter), and 94 cases in stage III (frequent appearance of Raynaud's phenomenon in all seasons except summer).

Administration of the defibrinogating drug

As a defibrinogating drug, batroxobin (Defibrase, DF-521, Tobishi Pharmaceutical Co, Ltd) was used in this study. To 53 of the 118 patients, batroxobin dissolved in 250 or 500 ml of normal saline was intra-

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venously administered at 24-h intervals for three successive days, in the order of 20, 10, and 5 batroxobin units (BU). For 20 of the 53 cases, 10 BU were supplemented every 2 d for four weeks. For 33 of the 53 cases, 5 BU were supplemented every day for four weeks in order to minimize the changes in the blood fibrinogen level. To the other 65 of the 118 patients, an initial dose of 20 BU was administered, and 10 BU, as a maintenance dose, was supplemented every 2 d for four weeks. As a maintenance dose 10 BU was used because an antibody against batroxobin was produced later in cases with 10-BU administration than in cases with 5-BU administration.

Laboratory examination

In a study of the acute effects of batroxobin on the digital blood flow of the first 53 cases, the blood fibrinogen concentration, whole blood viscosity, and peripheral vascular resistance of the fingers were measured at 6, 9, and 12 h after each infusion of 20, 10, and 5 BU. The blood fibrinogen concentration was measured by the thrombin method. The whole blood viscosity was measured by a cone-plate type of viscosimeter (Rheolizer Tokyo Keiki) at a shear rate of 7.5, 18.8, 37.5, 75, and 150/s at 20°C. The measured values of blood viscosity were corrected to those at 45 % of the hematocrit according to a mathematical formula obtained in another study showing the relation between hematocrit and blood viscosity (18) in patients with vibration syndrome. The peripheral vascular resistance was measured bilaterally in fingers II, III, and IV by means of strain-gauge plethysmography (SP-2, Medimatic). In 21 of the 53 cases, the erythrocyte sedimentation rate (ESR) was measured before and 12 h after the administration of 10 BU.

In order to evaluate objectively the effects of defibrinogating therapy for four weeks, we administered, (in conjunction with cold provocation) a skin temperature test (5°C, 10 min), finger plethysmography (5°C, 1 min), and a nail compression test (5°C, 10 min) to all the subjects before and after the defibrinogating therapy. In 22 of the 118 subjects the transcutaneous partial pressure of oxygen (tcPO₂) was measured at the dorsum of the middle phalanx of the middle finger before and after the therapy with a monitor for the cutaneous partial pressure of oxygen (Module 632, Kontron). The digital blood flow, vascular resistance, venous capacity, and maximal time were measured in 27 of the 118 patients before and after the therapy. The maximal time indicates the time for the volume of the finger to reach the maximal level after an instantaneous stop of venous return.

Examination of the subjective symptoms

The appearance of a warm sensation after the defibrinogating therapy was examined. The extent of the warm sensation was classified into the following four grades: grade I-a, appearance of a remarkably warm

sensation in three parts of the body (the trunk and upper and lower extremities); grade I-b, moderately warm sensation in the same three parts of the body; grade II, warm sensation in two of the three parts of the body; grade III, warm sensation in one of the three parts of the body; grade IV, no warm sensation in any part of the body.

The preceding tests were done in a room maintained at 25°C. The data were statistically analyzed with a computer (MZ-80BK, Sharp). This study was started in January 1980 and ended in May 1983.

Results

Rheological and vascular resistance examination

In the 53 patients who received 20, 10, and 5 BU at 24-h intervals, the blood fibrinogen concentration, whole blood viscosity, and peripheral vascular resistance of the fingers were changed. The results are shown in figures 1 and 2. The mean value of the fibrinogen concentration, 2.4 (SD 0.68) g/l before administration, decreased by about 0.4 g/l in 12 h after the 20-BU infusion. The fibrinogen level, around 0.4 g/l, was maintained at the same level thereafter. The maximal decrement ratio of the viscosity was 22.5 % at a shear rate of 7.5/s and 8 % at a corresponding rate of 150/s. The peripheral vascular resistance of the left-hand fingers was measured, and a significant decrease was observed 6, 9, and 12 h after each infusion. A significant difference was also observed between the values 24 h after the infusion of 20 BU and 12 h after the infusion of 10 BU. In the fingers of the right hand a significant decrease in the resistance was found only between the values before the infusion of 20 BU and 12 h after it. A tendency towards a decrement in the resistance was observed 6 h after the 20-BU infusion and 9 h after the 10-BU infusion. The erythrocyte sedimentation rate before the batroxobin therapy was 1.43 (SD 0.78) mm at 30 min, 4.19 (SD 2.86) mm at 60 min, and 13.91 (SD 10.66) mm at 120 min, the mean of the three values being 5.92 (SD 4.36) mm. Twelve hours after the 10-BU infusion the corresponding rate was 0.48 (SD 0.36) mm, 1.15 (SD 0.45) mm, and 2.21 (SD 0.89) mm at 30, 60, and 120 min, respectively, for a mean of 1.13 (SD 0.43) mm. A statistically significant difference ($p < 0.001$) was observed between the values before and after the infusion of 10 BU.

Clinical effects

Objective improvement in the peripheral circulatory disturbance was seen in the cold provocation test, the nail compression test, and the finger plethysmography of the 118 patients after the therapy (table 1). A statistically significant difference was observed for all the values. Similar results were obtained regardless of the stage of vibration syndrome (II or III) (table 2). The

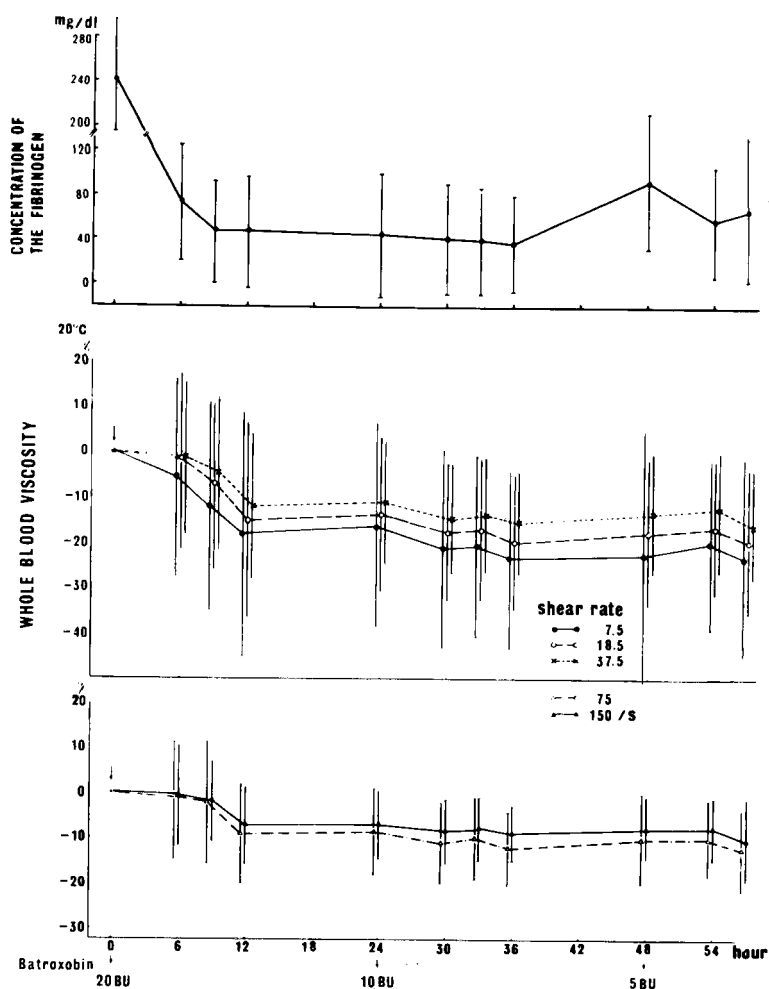


Figure 1. Changes of the blood fibrinogen concentration and whole blood viscosity in 53 patients after batroxobin therapy. Upper figure: mean and standard deviation (vertical bars) of the fibrinogen concentration. Middle and bottom figures: mean and standard deviation of the whole blood viscosity. Presented values of the blood viscosity are those corrected at 45 % of the hematocrit. Zero on the ordinate in the middle and bottom figures denotes the control value in percent before the therapy. (BU = batroxobin unit)

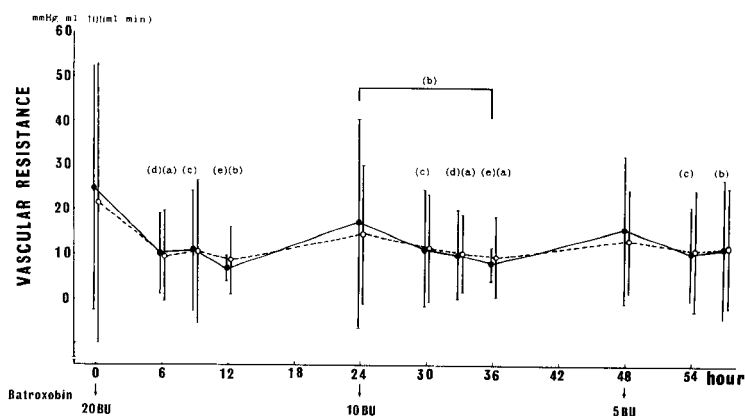


Figure 2. Changes in the peripheral vascular resistance of the fingers in patients with vibration syndrome after batroxobin therapy. The mean and standard deviation of the summed resistance of fingers II, III, and IV of the right hand are shown by open circles and those of fingers II, III, and IV of the left hand by filled circles. Significant differences between the resistances before and during batroxobin treatment were present as follows: (a): $p < 0.1$, (b): $p < 0.05$, (c): $p < 0.025$, (d): $p < 0.01$, (e): $p < 0.005$. (BU = batroxobin unit, 1 mmHg = 133.322 Pa)

Table 1. Results of tests to examine the peripheral circulatory disturbance in the 118 patients before after therapy with batroxobin.

Time in relation to immersion in cold water	Temperature in cold provocation test (°C)				Amplitude in finger plethysmography (mV/V)				Nail compression (s)			
	Before therapy		After therapy		Before therapy		After therapy		Before therapy		After therapy	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Before	31.49	3.10	32.47	2.37****	3.84	1.92	4.15	1.98**	1.18	0.37	1.13	0.33*
At end	6.54	0.98	6.82	1.43***								
5 min after	18.72	5.16	21.21	6.24****	2.71	2.05	3.09	1.99***	1.48	0.95	1.23	0.82****
10 min after	24.88	6.32	27.40	6.23****	3.00	1.90	3.50	1.88****	1.27	0.74	1.13	0.45****
Recovery rate (%)												
5 min after	49.25	18.99	56.10	20.10***								
10 min after	72.14	21.67	80.04	20.13****								

* $p < 0.05$, ** $p < 0.02$, *** $p < 0.01$, **** $p < 0.001$ between the before- and after-therapy values of the same test.

Table 2. Skin temperature in relation to the cold provocation test of patients with stage II or stage III of Raynaud's phenomenon before and after therapy with batroxobin.

Time in relation to immersion in cold water	Temperature in the cold provocation test (°C)							
	Stage II (N = 24)				Stage III (N = 94)			
	Before therapy		After therapy		Before therapy		After therapy	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Before	32.75	2.52	33.32	1.58	31.17	3.15	32.25	2.49****
At end	6.96	1.36	7.15	1.26	6.43	0.83	6.74	1.47*
5 min after	20.09	5.18	24.11	4.94****	18.37	5.10	20.47	6.32****
10 min after	26.68	5.77	30.64	4.65****	24.43	6.37	26.64	6.32****
Recovery rate (%)								
5 min after	50.78	16.89	65.00	16.61****	48.86	19.47	53.83	20.27**
10 min after	75.98	18.15	89.74	15.53****	71.16	22.38	77.56	20.41***

* $p < 0.05$, ** $p < 0.02$, *** $p < 0.01$, **** $p < 0.005$, ***** $p < 0.001$, between the before- and after-therapy values of the same stage.

bilaterally measured vascular resistance as the sum of fingers II, III, and IV was 18.11 (SD 17.60) $\text{mm Hg} \cdot \text{ml}^{-1} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$ [$2\ 414.46$ (SD $2\ 346.47$) $\text{Pa} \cdot \text{ml}^{-1} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$] before and 9.22 (SD 8.43) $\text{mm Hg} \cdot \text{ml}^{-1} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$ [$1\ 229.23$ (SD $1\ 123.90$) $\text{Pa} \cdot \text{ml}^{-1} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$] after the treatment. The maximal time was 9.36 (SD 10.23) s before therapy and 4.77 (SD 3.74) s after therapy. A significant difference ($p < 0.005$) was observed between these values before and after the therapy. However venous capacity was not changed. The mean values of tcPO_2 before treatment, 42.6 (SD 8.2) mm Hg [$5\ 679.5$ (SD $1\ 093.2$) Pa], increased significantly ($p < 0.05$) up to 49.6 (SD 12.0) mm Hg [$6\ 652.8$ (SD $1\ 599.9$) Pa] after the therapy.

According to the feeling of a warm sensation after the treatment, 47 cases were classified as grade I-a, 36 as grade I-b, 21 as grade II, 9 as grade III, and 5 as grade IV. The rate for grade I-a and I-b combined was 70.3 %.

Discussion

From the rheological point of view, the following factors are thought to be important for improving peripheral circulatory disturbance in the vibration syndrome: (i) dilation of the radius of vessels, (ii) decrease of

blood viscosity, (iii) decrease of red cell aggregation, (iv) increase of red cell deformability, and (v) decrease of the sympathetic nerve activity. According to the formula of Hagen-Poiseuille the most effective therapy is to dilate the radius of the vessels (11). Many radiographic studies have shown that pathological changes occur in the arteries of patients with vibration syndrome (14, 17). These changes are degenerative changes of the vessel wall (2, 3, 17). If they are advanced, a vasodilating drug may not produce adequate effects. There have been many cases showing a poor response of the skin temperature of the finger to heat stimulation (19). These cases also suggest that "functional" dilation of digital arteries by vasodilator drugs is not to be expected. In fact, the effects of prostaglandin E_1 , a strong vasodilator, have been examined in patients with vibration syndrome in 13 hospitals in Japan with the double-blind method. An overall statistical analysis of the data of the patients showed no significant improvement in a cold provocation test after therapy with this vasodilator (1). Turczyński et al (20, 21) reported a significant increase of serum viscosity in cases with vibration syndrome. Ikehata et al (13) and myself (18) have also observed a significant increase in whole blood viscosity at low shear rates and at low temperatures in such cases. One hypothesis (9, 10) stipulates that changes of rheological factors, such as an abnormal local increase of blood viscosity, yield

stress, and red cell aggregation in response to a fall in temperature, are important factors in the cause of Raynaud's phenomenon. Defibrinogating therapy has a close relation with blood viscosity and red cell aggregation (22). In this respect, defibrinogating is therefore considered to be a reasonable therapy for the peripheral circulatory disturbance of vibration syndrome. Indeed, the present study revealed that batroxobin decreased the blood fibrinogen and viscosity, inhibited the red cell aggregation, and increased the digital blood flow without evidence of vasodilatation. The appearance of a warm sensation in parts of the whole body after the defibrinogating therapy was considered to be compatible with other results in the present study showing a significant improvement in a cold provocation test, finger plethysmography, the nail compression test, tcPo_2 , and peripheral vascular resistance. Furthermore, in the present study, the rate of appearance of a warm sensation in the trunk and upper and lower limbs of the patients was 70.3 %. According to Matoba et al (16), who administered dl- α -tocopheryl nicotinate (Juvela Nicotinate, Eisai Co, Ltd) to 30 patients, the rate was only at 33.3 %. The effect of batroxobin, the appearance of the warm sensation, was observed even after discharge from the hospital. The time interval between relief of the vibration syndrome and its reaggravation ranged usually from several months to more than one year. Most of the patients treated successfully with batroxobin expressed changes in subjective symptoms such as sweating easily in summer, disappearance of numbness in fingers during cold seasons, and relief of Raynaud's phenomenon.

I have also treated another group with vibration syndrome with both this defibrinogating drug and an α_1 -blocker (bunazosin hydrochloride, Detantol, Eisai Co, Ltd). Rheologically the results obtained from this combined therapy were better than those from defibrinating therapy alone. Finally, no serious side effects were observed. Only a slight headache was complained of occasionally.

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