

PENTOXIFYLLINE FOR STROKE PATIENTS IN HASAN SADIKIN HOSPITAL, BANDUNG: PRELIMINARY INVESTIGATION

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During the acute phase, administration of aminophylline as a continuous infusion might improve the outcome from cerebral infarction (Oxbury, 1975), and a group of neurologists from Surabaya encouraged the continuous infusion of 120 mg aminophylline in 500cc 5% glucose solution for 8 hours duration in progressive and completed stroke (Chandra, 1976). One of the xanthine derivatives with minimal sympathetic side effects and marketed as pentoxifylline (Trental®), is reported by many studies to have a beneficial effect for the patient with stroke.

This preliminary investigation was devised to study the effectiveness and side effects of pentoxifylline in Indonesian patients with ischemic stroke compared with one of the modified treatment regimes in Hasan Sadikin Hospital, Bandung.

PHARMACOLOGY

The structural formula of pentoxifylline is 3,7-dimethyl-1-(5-oxo-hexyl)-xanthine. It is rapidly and completely absorbed from gastrointestinal tract and its metabolites are eliminated by the kidney. With single administration of drug, 98% will be eliminated from blood within 24 hours.

Pentoxifylline causes increase in the stroke volume and minute volume without increasing the heart rate; promotes relaxation of arteriole by direct action mediated through the inhibition of enzyme phosphodiesterase resulting in the accumulation of cyclic-AMP. Pentoxifylline exerts only a mild vasodilating effect and cannot thus be classified as a strong vasodilator, so unexpected hemodynamic disturbances as sudden drop of blood pressure and steal syndrome rarely happens (Mueller et al, 1975). Pentoxifylline might improve the flexibility of the erythrocyte thus allowing the cells to pass the capillary bed easily and improving oxygen supply to endangered tissue. This could happen in patients with chronic vascular disease (Ehrly AM, 1975, Schubotz and Muhlfellner, 1977) as well as in normal subjects (Grigoleit et al, 1976). This drug can also inhibit the aggregation and adhesiveness of erythrocytes (Jarrett and Browne, 1977) and platelets (Scharrer, 1971).

Side effects of pentoxifylline are minimal and seen usually as gastrointestinal disturbances and flushing. Pentoxifylline is contra-indicated in recent myocardial infarction and massive cerebral haemorrhage. Parenteral administration for patients with coronary and cerebral arteriosclerosis associated with hypertension are also contraindicated.

MATERIAL AND METHOD

This was an open comparative trial between pentoxifylline and modified stroke treatment in Hasan Sadikin Hospital. Adult patients of either sex with clinical diagnosis of ischemic stroke with duration of symptoms not more than 96 hours and not in severe coma were included. All patients underwent detailed medical and neurological examinations. Diagnosis of stroke was made with sudden onset of neurological deficits which persist for some hours or days. In case of doubt, additional examinations, electroencephalography and cerebral angiography, were performed. At the beginning and at the end of the trial, patients with pentoxifylline had ECG examination, routine blood examination plus bleeding and coagulation time, liver function test, BUN and creatinine level done.

Patients with transient ischemic attack, cerebral hemorrhage, severe renal and liver diseases, recent myocardial infarction or disturbances of cardiac output, which could alter the outcome were excluded. Patients were allocated at random to one of the treatment regimes. In the pentoxifylline treated group, the dose was two 100mg dragees three times a day for the first 2 weeks, and from week 3-6, the patients were given one dragee three times a day. The dragees were taken after meals. The patients without pentoxifylline had 500cc 10% glycerol solution as continuous infusion daily for 5 consecutive days, followed by neurotrophic vitamins alone given orally for the remaining weeks. Physiotherapy was also encouraged for both groups as there were no specific contra-indications. Subsequently, the assessment was made by evaluating the general clinical parameters, state of consciousness, subjective symptoms, neurological signs, psychological and emotional status, side effects, and results at the end of treatment period. For the first week, assessment was made before treatment started and every day for the period of 7 days. For subsequent periods, follow up assessment was made after week 1, 2, 3, 5, and 7.

All the assessments were recorded in special forms, scoring of neurological signs were added accordingly. The scoring system was designed to assess the functional status and related to the severity of stroke. Changes in the total score correlated well with changes in patients neurological status. The healthy subjects have maximum total score 78.

For quantitation of results, the following rating scale was used:

- Patients with total score more than 70: remarkably improved
- Patients with total score more than 60: improved

Patients with total score 40-59 : slightly improved
 Patients with total score less than 40: unchanged

RESULTS

Of the total 22 patients included in this trial, 12 patients (5 male and 7 female) were in the pentoxifylline treated group and mean age was 57.5 years. The remaining 10 patients (3 male and 7 female) were in the control group and had a mean age of 58 years (Table 1).

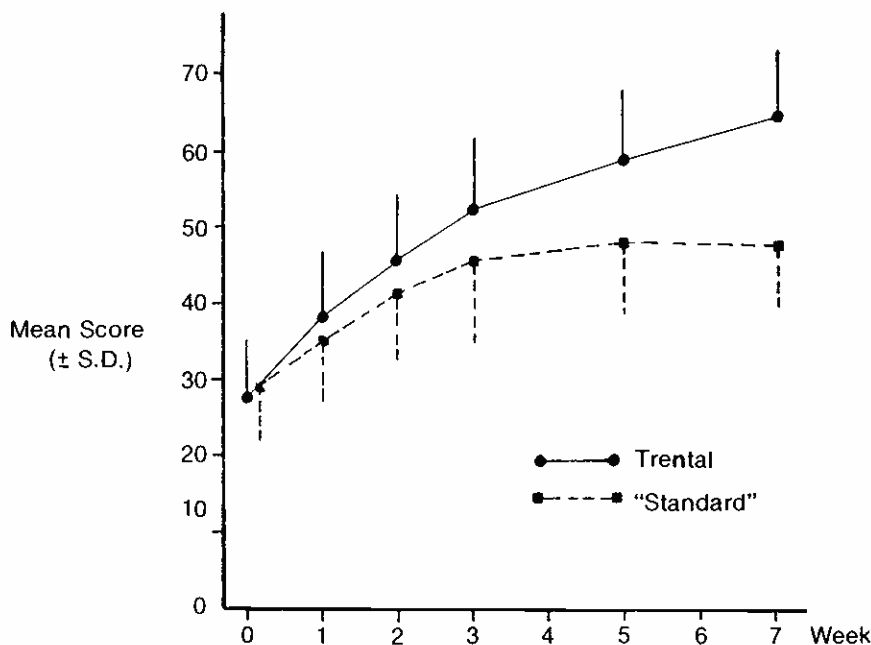
Table 1: Distribution According to Age Group and Sex

Treatment	Age Group						Sex		
	20-	30-	40-	50-	60-	70-	Male	Female	Total
Pentoxifylline	1		2	3	4	2	5	7	12
Without Pentoxifylline			3	2	4	1	3	7	10

In the pentoxifylline treated group, 10 patients could be followed up to 7 weeks, 2 patients could only be followed up to 5 weeks, while in patients without pentoxifylline treatment, 8 patients could be followed up to 7 weeks and, 2 patients were followed up to 5 weeks.

Neurological status at the beginning of trial, for the groups with and without pentoxifylline treatment was graded and a mean score of 27.27 (SD ± 8.20) and 27.90 (SD ± 8.43) obtained. After 7 weeks, the mean score for the pentoxifylline treated group became 65.10 (SD ± 10.96). This when compared with the start of treatment was statistically significant (p<0.01). For the patients without pentoxifylline, at the end of week 7, mean score was 48.75 (SD ± 13.10). This difference compared with the beginning of treatment was also statistically significant (p <0.01). If both treatment regimes were compared, in week 1 and 2, mean score of both groups were nearly equal. However, after week 3, mean score for pentoxifylline treated group was greater than that of the group without pentoxifylline treatment and the week 7, the difference between both groups was statistically significant (p<0.02). The plot of mean score for both groups is shown in Fig. 1.

FIG. 1: MEAN SCORE OF IMPROVEMENT IN PATIENTS WITH STROKE



If the motor improvement were assessed and scored by using the British Medical Research Council System (0 = paralysis and 5 = normal) the results are shown in the Table 2. This scoring system could not be used to evaluate the improvement easily. However using our scoring system (Table 3) differences are much more apparent.

Table 2: Motor Improvement Scoring by British Medical Research Council System

Treatment	Extremities	Week 1 Score				Week 5 Score				Week 7 Score			
		0	1-2	3-4	5	0	1-2	3-4	5	0	1-2	3-4	5
Pentoxifylline	Upper	8	2	2		3		5	4	1		4	5
	Lower	7	5			2		5	5			5	5
Without Pentoxifylline	Upper	7	3			2	2	6		2	2	4	
	Lower	5	5			2	1	5	2	2	1	4	1

Table 3: Mean Score of Upper and Lower muscle power from day 1 to Week 7

Treatment	Extremities	Day 1	Week I	Week II	Week III	Week V	Week VII
Pentoxifylline	Upper	1	3	4	4.8	5.5	6.9
	Lower	1.5	3.5	4.8	5.8	6.2	7.5
Without Pentoxifylline	Upper	0.9	2.4	4.2	4.2	4.2	3.7
	Lower	1.5	3.3	4.5	5.1	5.1	4.5

For the first 2 weeks, there was no difference in terms of motor improvement between the pentoxifylline treated group and control group. However after week 3, the difference in mean score between both groups became apparent and statistically significant ($p < 0.02$ for lower extremities and $p < 0.05$ for upper extremities).

3 patients from the pentoxifylline treated group and 4 patients from without pentoxifylline group had speech disturbances. 2 in each group had improved within 2-3 weeks; 1 patient from pentoxifylline treated group improved after the week 5.

No adverse effects of pentoxifylline on blood pressure and pulse rate were detected. In the 5-7 weeks, there was no sudden elevation or drop of blood pressure, cases of tachycardia or bradycardia were not seen. Various degrees of headache was found in 6 patients in pentoxifylline treated group, and 1 patient had mild vertigo. Most common side-effects were nausea and gastric irritation.

Obvious abnormal changes in blood chemistry and ECG in pentoxifylline treated group before and after the trial were not seen. The result of the trial is summarised in the Table 4.

Table 4: End Result of the Trial

Rating Scale	Pentoxifylline	Without Pentoxifylline
Remarkably improved	4	—
Improved	4	3
Slightly improved	2	4
Unchanged	2	3

DISCUSSION

Present management of the acute ischemic stroke is focused on reducing the cerebral edema, improving cerebral blood flow and promoting the general condition of the patients (Lazuardi, 1976). Thoughts concerning the benefit of various treatments are all based mainly on empirical observations in more or less controlled clinical trials, because it is not entirely clear what specific aspects of the pathophysiology should be treated (Oxbury, 1975). Effective and rational treatment have not been established yet. Reducing cerebral edema by using glycerol solution which was previously reported to exert beneficial effect for stroke patients in acute episode, was thought to exert its effect if the osmotic gradient created between the extra-cellular fluid and brain substance is great enough. This cannot be accomplished by 10% solution, so other mechanisms may play role in reducing edema. The precise rationale for treatment with glycerol has not been established.

To improve cerebral blood flow, extracranial factors such as blood pressure disturbances should as far as possible be corrected. Some workers urge the use of vasodilators to increase the cerebral blood flow through collateral channels so that more extensive cerebral infarction could be limited. The autoregulation of cerebral blood flow during episode of stroke is lost and coupled with a local acidosis secondary to ischemic infarction, this results in maximally dilated arterial vessels which offer minimum resistance to flow. As a result, flow to ischemic areas associated with stroke may be theoretically enhanced, but variably responsive to vasodilator. Some devastating effects under such condition might occur. Unfortunately clinical recovery does not seem to bear any relationship to flow changes (Yatsu, 1976).

Recently a more rational approach for effective treatment of stroke is encouraged by use of the drug pentoxifylline, which has the capability of improving the microcirculation of brain by enhancing the flexibility and reducing the rigidity of erythrocytes, to enable them to pass through the brain capillaries more easily. The drug also in some way enhances neuronal metabolism.

Previous clinical trials with pentoxifylline in stroke revealed that improvement in motor deficits were seen earlier than without pentoxifylline group (Sen SK; Sen S and Chakravarty A, 1977), and if the initial motor deficit grade was more than 2, pentoxifylline was significantly better (Janaki S).

This is rather different from our present experience. In the first 2 weeks, no clear difference was seen between the pentoxifylline group and without pentoxifylline group, either for lower or upper extremities. However after the week 3, the improvement in pentoxifylline treated group became greater than the without pentoxifylline group. The possible explanation may be in the mechanism of reducing cerebral edema by both pentoxifylline and glycerol (Ganser & Boksay, 1974), causing the mean score of both groups in the first 2 weeks nearly equal. Glycerol can maintain the cellular ultrastructure (Dodson et al, 1975), while pentoxifylline enhances the neuronal metabolism through inducing mitochondrial hypertrophy (Hartman 1977). Oxygen consumption and glucose utilization also increases. To determine whether this might explain the difference of score between 2 groups from week 3 onwards, further work seems necessary.

Previous clinical investigations reported that pentoxifylline could improve speech disturbance faster (Sen SK). Observations in the present trial gave the impression that the aphasic patients with pentoxifylline were more benefitted than the without pentoxifylline group. However, due to small sample size, no definite conclusion could be drawn. The effect of pentoxifylline in other aspects should be evaluated in a more detailed study.

The overall improvement from pentoxifylline treated group and xanthine nicotinate group were not significant (Sen SK, Janaki), but conclusive impression could not be drawn without good scoring system of neurological status. The overall results of our trial seem to favour the pentoxifylline group. Confirmation should be made by continuing the trial with larger samples of patients.

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